

# Transcranial direct current stimulation in mild cognitive impairment: Behavioral effects and neural mechanisms

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## Abstract

**Introduction:** The long preclinical phase of Alzheimer's disease provides opportunities for potential disease-modifying interventions in prodromal stages such as mild cognitive impairment (MCI). Anodal transcranial direct current stimulation (anodal-tDCS), with its potential to enhance neuroplasticity, may allow improving cognition in MCI.

**Methods:** In a double-blind, cross-over, sham-controlled study, anodal-tDCS was administered to the left inferior frontal cortex during task-related and resting-state functional magnetic resonance imaging (fMRI) to assess its impact on cognition and brain functions in MCI.

**Results:** During sham stimulation, MCI patients produced fewer correct semantic-word-retrieval responses than matched healthy controls, which was associated with hyperactivity in bilateral prefrontal regions. Anodal-tDCS significantly improved performance to the level of controls, reduced task-related prefrontal hyperactivity and resulted in "normalization" of abnormal network configuration during resting-state fMRI.

**Discussion:** Anodal-tDCS exerts beneficial effects on cognition and brain functions in MCI, thereby providing a framework to test whether repeated stimulation sessions may yield sustained reversal of cognitive deficits.

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## Keywords:

Transcranial direct current stimulation; Mild cognitive impairment; Functional magnetic resonance imaging; Resting-state fMRI; Language; Aging

## 1. Introduction

Increasing global life expectancy will put more individuals at risk for developing Alzheimer's disease (AD) [1]. Given that brain damage in AD may be too severe to be treated [2], research focuses on transitional stages between normal aging and dementia, such as mild cognitive impairment (MCI) [3]. Pharmacological interventions showed little positive impact in MCI trials [4]. Therefore, nonpharmacological interventions to treat MCI received increasing attention [5]. Of these, anodal transcranial direct current stimulation (anodal-tDCS) may offer an exciting novel treatment option [6]. Anodal-tDCS facilitates neural plasticity by

delivering weak electrical currents to the scalp to enhance excitability of underlying brain regions [7]. In healthy individuals, anodal-tDCS improved motor and cognitive functions, including learning [8], and ameliorated age-associated cognitive deficits [9]. Functional imaging studies revealed that large-scale neural network modulations mediate these behavioral improvements [9–11]. Anodal-tDCS also improved cognitive functions in neurological and psychiatric diseases, including studies in patients diagnosed with AD [6]. However, the impact of anodal-tDCS on cognition in MCI and the underlying neural mechanisms have not yet been explored.

Goals of this study were threefold: First, we assessed the impact of anodal-tDCS administered to the left inferior frontal gyrus (IFG) on semantic word-retrieval in MCI in a double-blind, cross-over, sham-stimulation controlled

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(sham-tDCS), within-subjects design. Impaired semantic word-retrieval is an early marker of MCI, resulting in substantially impaired daily functioning in AD [12] and anodal-tDCS has been shown to improve semantic word-retrieval in healthy older adults [9]. Therefore, this task is particularly well suited to test the impact of anodal-tDCS on cognition in MCI. The second goal was to elucidate the neural mechanisms underlying stimulation effects using simultaneous functional magnetic resonance imaging (fMRI). Task-related activity modulations were assessed during overt semantic word-retrieval. Performance-independent resting-state (RS) fMRI assessed stimulation effects on large-scale functional networks. A number of RS-networks are affected in MCI, including the default mode, dorsal attention, control, salience and sensory-motor networks [13]. Importantly, most of these networks are connected directly [14] or indirectly [15] with the stimulated IFG. Moreover, this montage has previously been shown to exert beneficial effects on semantic word-retrieval, task-related brain activity and RS-network configuration in healthy individuals [9,11]. The third goal was to assess whether anodal-tDCS would counteract pathological alterations of task-related activation and RS-networks in MCI and induce a more “normal” pattern of brain functions. For this purpose, data of patients were compared with matched healthy controls.

## 2. Methods

In two identical fMRI sessions, patients were scanned either with concurrent anodal-tDCS or sham-tDCS. Stimulation order was randomized and counterbalanced between patients. Sessions were scheduled 1 week apart to prevent carry-over effects. Data of healthy controls were acquired using the same fMRI protocols and cross-over designs reported previously [9,10]. Here, only data acquired during sham-tDCS was used, given our aim to determine differences between patients and controls in their “native states” (sham-tDCS) and to explore whether anodal-tDCS would induce a more “normal” pattern of performance and brain functions in patients by comparison with controls scanned during sham-tDCS. However, we also report an explorative comparison of stimulation effects using data from a previous study [9] that administered anodal-tDCS to the left IFG in the [Supplementary Material](#). Written informed consent was obtained from all participants. The study was approved by the local ethics committee, conducted in accordance with the Helsinki declaration and registered under [ClinicalTrials.gov](#) (NCT01771211).

### 2.1. Participants

Eighteen MCI patients were referred to the study from the local memory clinic. They fulfilled core clinical criteria for the diagnosis of “MCI due to AD” [16] ([Table 1](#)). All reported subjective memory complaints which were confirmed

by standardized testing using the Consortium to Establish a Registry for Alzheimer’s disease test battery (CERAD; [www.memoryclinic.ch](#)). All maintained independence and reported no impairment of function in daily life. A clinical interview, neurological examination and structural MRI revealed no systemic or brain diseases accounting for declined cognition. Patients were diagnosed with either amnesic (N = 11) or multiple domain MCI with memory complaints (N = 7). These subtypes show the highest conversion rates to AD [3].

18 matched healthy older subjects served as controls. They did not report memory problems, scored within normal age-adjusted norms on all CERAD subtests, reported no history of previous or current neurological or psychiatric diseases and presented with age-appropriate structural imaging parameters [9,10]. None of the participants received drugs other than lipid- or blood pressure lowering (patients and controls N = 8/7), anti-platelet (N = 2/1) and thyroid hormone replacement medication (N = 3/4). All scored within normal ranges on the Beck Depression Inventory.

### 2.2. Transcranial direct current stimulation

A constant direct current (1 mA, 20 minutes) was administered by an MRI-compatible stimulator (DC-Stimulator Plus<sup>®</sup>, NeuroConn) using an established set-up during fMRI [9–11,17]. The anode was attached over the left ventral IFG (vIFG), the cathode was positioned over the right supraorbital region as in previous studies of our group [9,11]. The current was ramped-up over 10 seconds before the start of the functional sequences and remained stable until completion of the semantic task (anodal-tDCS) or was turned off after 30 seconds (sham-tDCS; for details of the tDCS methods see [Supplementary Material](#) and [11]). Self-report scales assessed mood and affect of participants, a post-study questionnaire assessed effectiveness of blinding.

### 2.3. Magnetic resonance imaging

MRI data were acquired using a 3-Tesla Siemens Trio MRI-system. T1-weighted images were subjected to voxel-based morphometry analysis (VBM) and compared between groups ([Supplementary Material](#)). Functional sequences were acquired using identical set-ups in both groups: During RS-fMRI (~5 minutes) participants were instructed to keep their eyes closed and think of nothing particular. Afterwards, participants performed an overt semantic word-retrieval task (~11 minutes) that has previously been described in detail [9,11]. In short, six different categories were visually presented in blocks of 10 consecutive trials of the same category (trial = 3.8 seconds). Participants were instructed to overtly produce one exemplar during each trial without repeating exemplars or to say “next” in case they could not come up with a response. Task blocks alternated with baseline blocks (saying “rest”; five trials). In between

Table 1  
Demographic and clinical characteristics of healthy older participants and MCI patients

	Healthy controls		MCI patients		Sign
Age (yrs)	69.56 ± 5.56		67.44 ± 7.27		0.335
Education (yrs)	14.81 ± 3.0		14.33 ± 2.0		0.582
Sex (females/males)	7/11		7/11		
CERAD raw score (age-corrected z-score)					
Mini-Mental State Examination	29.22 ± 1.22	(0.33 ± 0.83)	27.17 ± 1.34	(−1.61 ± 0.79)	0.000*
Verbal fluency (# exemplars produced in 1 minute)					
Semantic fluency	24.0 ± 5.92	(0.29 ± 1.26)	18.06 ± 5.41	(−0.74 ± 0.88)	0.007*
Phonemic fluency	16.94 ± 4.11	(0.76 ± 0.97)	14.67 ± 3.74	(0.48 ± 0.71)	0.322
Boston naming test	14.67 ± 0.59	(0.51 ± 0.64)	14.39 ± 1.14	(0.37 ± 1.23)	0.663
Verbal learning and memory test (# correct)					
Learning success (runs 1–3)	21.83 ± 3.19	(0.4 ± 0.98)	16.28 ± 3.92	(−1.49 ± 1.11)	0.000*
Delayed recall	8.06 ± 1.26	(0.56 ± 0.98)	5.28 ± 1.84	(−1.07 ± 0.88)	0.000*
Intrusions	0.44 ± 1.15	(0.24 ± 0.87)	1.06 ± 1.7	(−0.32 ± 1.16)	0.115
Savings (%)	95.0 ± 0.15	(0.49 ± 1.19)	83.59 ± 0.17	(−0.36 ± 1.43)	0.065
Discriminability (%)	98.06 ± 0.04	(0.19 ± 0.85)	93.61 ± 0.05	(−0.90 ± 0.95)	0.001*
Visual spatial items (sum score)					
Copy	10.39 ± 1.29	(0.05 ± 1.21)	10.0 ± 1.28	(−0.43 ± 1.05)	0.212
Delayed recall	9.33 ± 1.68	(0.18 ± 0.96)	8.0 ± 2.57	(−0.58 ± 1.06)	0.031*
Trail making test A	38.17 ± 9.87	(0.57 ± 1.04)	43.72 ± 15.63	(0.16 ± 1.1)	0.253
Trail making test B	75.89 ± 17.59	(0.9 ± 0.78)	104.89 ± 59.86	(0.33 ± 1.41)	0.148

Abbreviations: MCI, mild cognitive impairment; CERAD Consortium to Establish a Registry for Alzheimer's disease; mean ± standard deviation (SD) are reported.

\*Significant differences between groups are based on unpaired t-tests and age-corrected z-scores.

trials, a black screen was displayed (2.2 seconds) and a single functional whole-brain volume was acquired. This design allowed assessing overt verbal responses during a scanner off-phase thereby avoiding articulation-related artifacts (see [Supplementary Material](#) and [9,11]).

#### 2.4. Task-related fMRI data analysis

Statistical Parametric Mapping (SPM5) was used for data analysis. Pre-processing and statistical analyses were identical as in our previous studies [9,11]. In short, after image pre-processing, statistical maps were generated for each participant representing activity elicited by the semantic word-retrieval task during both stimulation conditions (see [Supplementary Material](#) for details). To assess the impact of the stimulation on task-related activity and activity differences between patients and controls, an a priori region-of-interest (ROI) analysis was conducted that focussed on bilateral prefrontal areas using the contrast-of-interest (correct semantic word-retrieval vs. baseline trials): Previous studies that employed the same task in healthy participants revealed two main findings: (a) The task elicited activity mainly in bilateral frontal regions where enhanced activity was associated with reduced performance [9,11,18–20], (b) anodal-tDCS induced performance improvements were associated with left-lateralized or bilateral prefrontal activity reductions [9,11]. Prefrontal activity changes have also been linked to impaired executive functions, attention and working memory in MCI [21–23]. Therefore, to allow for comparisons of stimulation effects with previous studies

[9,11], the a priori analysis focussed on four task-relevant prefrontal ROIs. Left vIFG, specifically implicated with semantic retrieval processes [24] and right vIFG and middle frontal gyrus (MFG) were selected because enhanced activity in these areas was associated with semantic word-retrieval impairment in healthy older adults [9,19,20]. These regions also showed decreased activity in older adults during anodal-tDCS compared with sham-tDCS [9]. Left dorsal IFG (dIFG), associated with phonological retrieval [24], served as a control region. This area was not upregulated in older adults during semantic word-retrieval [9] and not affected by anodal-tDCS in healthy individuals [9,11]. This region also assessed whether early damage to medial temporal regions associated with semantic retrieval [25,26] may result in unspecific upregulation in MCI (see [Supplementary Material](#) and [9,11] for details of ROI-analysis). Repeated measures analyses of variances (ANOVAs) quantified the impact of anodal-tDCS on task-related brain activity in ROIs compared with sham-tDCS in the patients and differences between patients (anodal-tDCS; sham-tDCS) and controls (sham-tDCS). Post hoc tests were corrected for multiple-comparisons using the false-discovery-rate [27]. Associations between performance and activity changes induced by anodal-tDCS were explored using Pearson's correlation coefficients. We also conducted a whole-brain random-effects analysis to assure that ROIs were located in areas activated by the task (sham-tDCS) and an exploratory comparison that directly compared data acquired during both stimulation conditions in the patients (paired t-test) to gain additional information on the distribution of

stimulation effects (cluster threshold  $P < .05$  family-wise error-corrected; voxel threshold  $P < .001$ ).

### 2.5. Resting-state fMRI

Data preprocessing was carried out using Leipzig Image Processing and Statistical Inference Algorithms and Eigenvector Centrality Mapping (ECM [28]). ECM is a graph-based approach that has previously been used to characterize functional network changes in AD [29] and network modulations induced by anodal-tDCS in healthy individuals [9-11]. Higher ECM-values indicate that a voxel is more strongly connected to other voxels central within networks [30]. ECM offers several advantages over alternative RS-data analysis approaches: Specifically, previous studies demonstrated changes in several RS-networks in preclinical AD [13,31], possibly explained by altered interactions between different networks rather than changes in a single network [32]. Moreover, stimulation-induced network modulations may extend to interconnected networks [9-11] which may not be captured by approaches focusing on a single network. ECM allows characterizing complex network structures across the entire functional connectome without requiring a priori assumptions [28,33] and its inherently "exploratory" nature [34] rendered it an ideal tool for this study. Spectral-ECM of low frequency bands was applied [9]. Data pre-processing included motion and slice time correction, spatial normalization, band-pass filtering (1/90 sec), and smoothing ( $6 \times 6 \times 6 \text{ mm}^3$ ). Voxel-wise spectral coherence analysis was conducted for patients (anodal-tDCS; sham-tDCS) and controls (sham-tDCS). After z-transformation, data of patients and controls were compared using whole-brain unpaired or paired t-tests. Results were thresholded at  $P < .05$ , corrected for multiple comparisons using Monte-Carlo simulation [28].

## 3. Results

### 3.1. Baseline cognitive characteristics

MCI patients performed significantly worse than controls on the semantic fluency test, three verbal-learning subtests, and delayed recall of visual-spatial information. Naming, phonemic fluency and trail making test were comparable between groups (Table 1). Selectively impaired semantic fluency is in line with previous studies [12], possibly explained by impairment of medial temporal structures [25,26].

### 3.2. Structural MRI

VBM analysis revealed significantly reduced grey matter volume in the left hippocampus in patients compared with controls (peak voxel  $x/y/z = -20/-7/-23$ , cluster extent  $k = 113$  voxels,  $Z = 3.7$ ). The whole brain comparison demonstrated additional grey matter volume reductions bilaterally in the brain stem and left parahippocampal gyrus and thalamus ( $2/-25/-6$ ,  $k = 1582$ ,  $Z = 4.6$ ).

### 3.3. Performance, mood and affect

Patients produced significantly more errors than controls (sham-tDCS  $t(34) = 2.65$ ,  $P = .012$ ). Anodal-tDCS significantly improved semantic word-retrieval performance in the patients ( $t(17) = 3.08$ ,  $P = .007$ ) to the level of controls (nonsignificant group-difference  $t(34) = 0.94$ ,  $P = .34$ ; Fig. 1). Patients tolerated the stimulation well, no adverse effects were reported and mood and affect were not affected by anodal-tDCS (Supplementary Material).

### 3.4. fMRI ROI-analysis

Fig. 2 illustrates activity differences between patients and controls (sham-tDCS) and stimulation-effects in the patients (anodal-tDCS vs. sham-tDCS). ROIs were located in areas active during the task (Fig. 3A). Repeated measures ANOVA revealed a significant effect of GROUP during sham-tDCS ( $F(1,34) = 19.18$ ,  $P < .0001$ ). Patients exhibited significantly enhanced activity in all ROIs compared with controls (left vIFG  $t(34) = 2.14$ ,  $P = .043$ ; left dIFG  $t(34) = 2.09$ ,  $P = .043$ ; right vIFG  $t(34) = 2.61$ ,  $P = .017$ , right MFG  $t(34) = 2.14$ ,  $P = .043$ ).

Repeated measures ANOVA that assessed atDCS-induced changes in the patients revealed a significant main effect of STIMULATION ( $F(1,17) = 14.23$ ,  $P = .001$ ). Post hoc paired t-tests confirmed significantly reduced activity in all ROIs during anodal-tDCS (left vIFG  $t(17) = 3.15$ ,  $P = .012$ ; left dIFG  $t(17) = 2.58$ ,  $P = .025$ ; right vIFG  $t(17) = 2.36$ ,  $P = .030$ ; right MFG  $t(17) = 4.32$ ,

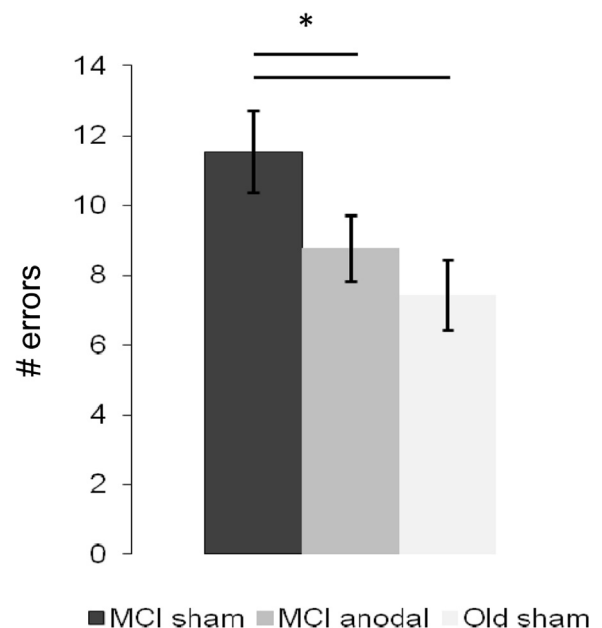


Fig. 1. Illustrates behavioral performance during the semantic word-generation task: performance is depicted as # of errors (max. 60) in the mild cognitive impairment (MCI) group (sham-tDCS [transcranial direct current stimulation] and anodal-tDCS) and healthy controls (sham-tDCS). Data show mean  $\pm$  standard error of the mean,  $*P < .05$ .

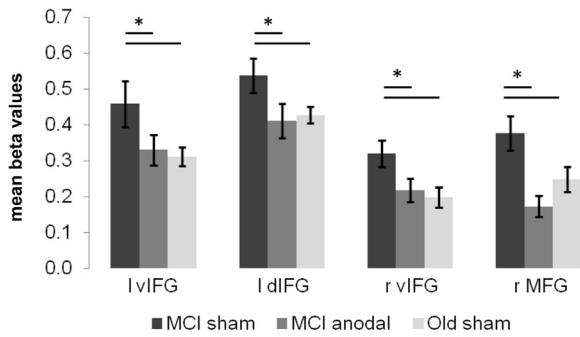


Fig. 2. Results of the a priori region of interest (ROI) analysis: compared with healthy older adults, mild cognitive impairment (MCI) patients showed enhanced activity in all four ROIs during sham-tDCS (transcranial direct current stimulation). Significantly reduced activity in all four ROIs during anodal-tDCS in the MCI group resulted in comparable activity between patients and healthy controls. Data show mean  $\pm$  standard error of the mean,  $*P < .05$ .

$P = .002$ ). Activity levels in all ROIs were comparable when patients received anodal-tDCS compared with controls scanned during sham-tDCS (nonsignificant GROUP-effect,  $F[1,34] = 0.31$ ,  $P = .57$ ; post hoc tests all  $P > .44$ ). No linear correlations between performance and activity changes were found (all  $P > .2$ ).

### 3.5. Task-related whole brain analysis

The exploratory voxel-wise analysis revealed reduced activity during anodal-tDCS compared with sham-tDCS in bilateral prefrontal areas, right middle temporal gyrus, left basal ganglia and thalamus. Therefore, the stimulation did not induce generalized activity reductions across the

entire brain. No activity increases were found (Fig. 3B; Supplementary Tables 1 and 2).

### 3.6. Resting-state ECM analysis

The comparison of patients and controls during sham-tDCS revealed enhanced connectivity in the patients bilaterally in the cerebellum, middle and superior temporal and fusiform gyri, and left parietal regions (Fig. 4 and Supplementary Table 3). A large cluster that comprised bilateral medial frontal and sensory-motor regions and extended into the left superior and middle frontal gyri showed reduced connectivity in the patients (Fig. 4, left column).

Within patients, anodal-tDCS compared with sham-tDCS resulted in increased connectivity bilaterally in lateral and medial frontal and sensorimotor cortices and left occipito-temporal regions (Fig. 4, middle column). Reduced connectivity was observed in the right cerebellum, left middle and right superior temporal gyri and right insula. Stimulation-induced connectivity modulations overlapped substantially with areas that exhibited connectivity differences in the two groups during sham-tDCS in fronto-temporal and also posterior brain regions. This more “normal” connectivity pattern is illustrated by the comparison of patients during anodal-tDCS and controls during sham-tDCS (Fig. 4, right column): While some connectivity differences still remained (e.g., in bilateral occipito-temporal and parietal regions and the cerebellum), others were greatly diminished in regions that showed major connectivity differences between the two groups during sham-tDCS. In addition, while there were no group differences in bilateral anterior fronto-temporal perisylvian areas during sham-tDCS, anodal-

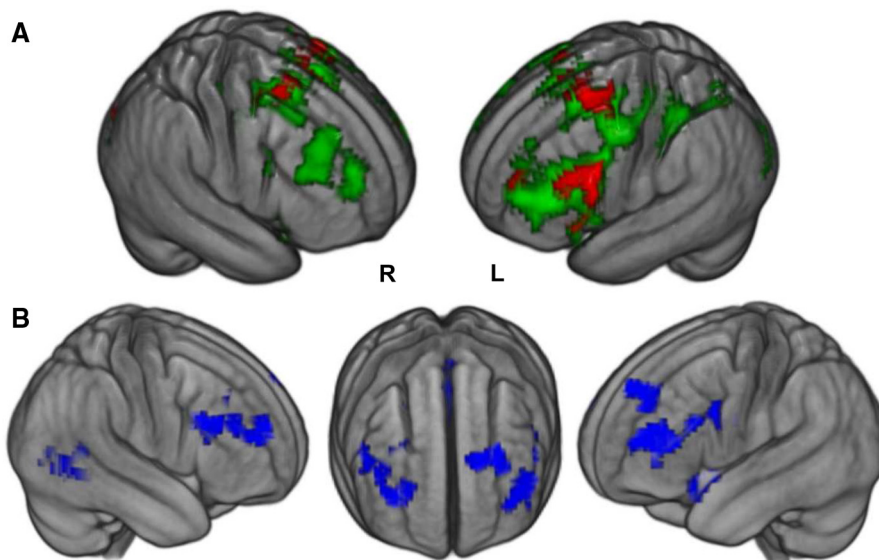


Fig. 3. (A) Illustrates activity patterns associated with the two stimulation conditions in the patients. Results of the contrast semantic word-retrieval  $>$  baseline are shown as surface rendering separately for sham-tDCS (transcranial direct current stimulation, green) or anodal-tDCS (red) overlaid on normalized mean grey matter image of the patient group. (B) Shows results of the voxel-wise comparison between the two stimulation conditions: Location of areas with reduced task-related activity during sham-tDCS compared with anodal-tDCS is depicted in blue. R/L = right/left hemisphere, middle image = front view. The same statistical threshold is used for all images (voxel level  $P < .001$  uncorrected, cluster level  $P < .05$  family-wise error corrected).

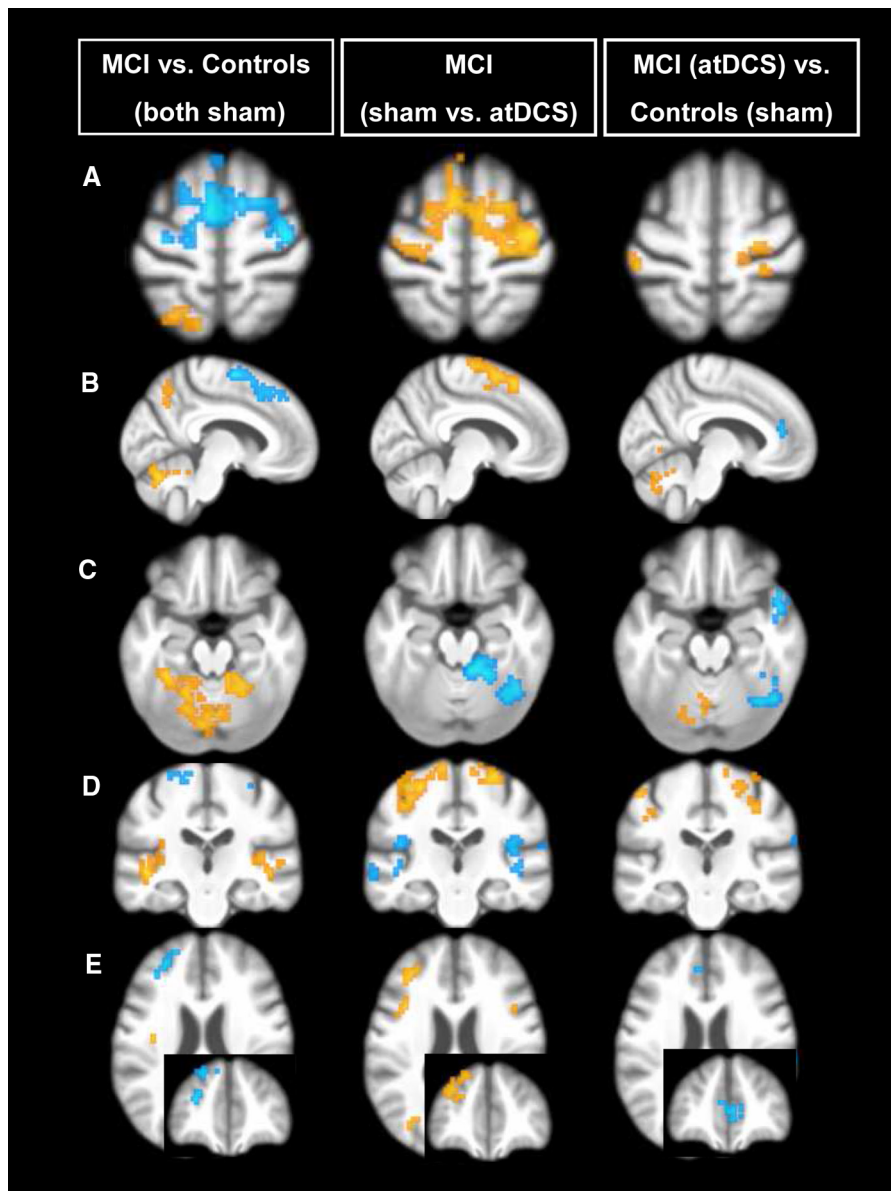


Fig. 4. Results of the resting-state data analysis overlaid on an averaged and normalized brain template of the entire group. Left panel illustrates the comparison between mild cognitive impairment (MCI) patients and controls during sham-tDCS (transcranial direct current stimulation); right panel illustrates the comparison of the patient group during anodal-tDCS and controls during sham-tDCS. Orange blobs indicate areas where patients exhibited higher Eigenvector Centrality Mapping (ECM) values than controls; blue blobs indicate regions with lower ECM values in the patient group. The middle panel shows the within group difference between both stimulation conditions (orange/blue = increased/decreased ECM values during anodal-tDCS). Left, middle and right panels display the same slices and are thresholded identically ( $P < .05$  Monte-Carlo corrected). (A) Bilateral sensorimotor regions ( $y = 62$ ); (B) left supplementary and presupplementary areas ( $x = -8$ ); (C) bilateral cerebellum ( $x = -20$ ); (D) bilateral insula and superior temporal cortex ( $y = -22$ ); (E) left frontal gyrus ( $z = 21$ ;  $y = 42$ ); left side of images = left hemisphere on axial and coronal slices.

tDCS resulted in reduced connectivity of right fronto-temporal regions.

#### 4. Discussion

This double-blind, cross-over, sham-controlled study demonstrated that anodal-tDCS can improve impaired cognition in MCI, a condition at high risk for developing AD [3]. Simultaneous fMRI enabled insights into the neural

mechanisms underlying these stimulation effects. Carefully matched healthy controls served as a reference for the degree of improvement and brain activity modulations. This proof-of-concept study assessed acute stimulation effects, thereby providing a framework to explore whether more sustained stimulation protocols may induce long-lasting improvements of performance and brain functions. Given the low effectiveness of pharmaceutical interventions in MCI [2] and extended intervention periods associated with

behavioral training or lifestyle interventions [5], anodal-tDCS may offer a novel, neuroscientifically grounded and cost-effective approach to improve cognition in MCI [6].

#### 4.1. Impact on performance

Numerous studies demonstrated that anodal-tDCS administered before or during cognitive or motor tasks can improve performance in healthy young individuals [8] and ameliorate age-associated cognitive decline [9,35,36]. These studies suggested that anodal-tDCS may be suited to address cognitive impairment in dementia and its precursors. Indeed, next to encouraging results in a number of psychiatric and neurological conditions, previous studies demonstrated beneficial effects of anodal-tDCS on memory functions in AD [6]. However, potential stimulation effects had not been explored in MCI, a stage that may be more promising for early interventions than AD, where major brain pathology is already present. This study demonstrated that anodal-tDCS can enhance cognition in MCI to the level of healthy controls, using a task known to deteriorate early in the course of dementia [12,37].

Behavioral improvements in this study were likely mediated by short-term facilitation of neural firing due to modulation of resting-membrane potentials [7]. However, previous studies in healthy individuals and also vulnerable populations like stroke patients have demonstrated that 5 to 10 days of stimulation not only yielded sustained behavioral improvements up to 9 months, but were also safe and well tolerated by the participants [6,38]. These effects were possibly explained by stimulation effects on protein synthesis resulting in persistent modification of post-synaptic connections [7]. Therefore, our results justify future clinical trials employing more sustained stimulation protocols to explore whether anodal-tDCS can induce long-lasting improvement of cognition in MCI. Moreover, given that the stimulated IFG is a major hub for cognition and executive control [39], our results provide a rationale to explore potential beneficial effects of this montage on other cognitive functions affected in MCI as well.

#### 4.2. Impact on task-related activity

fMRI during semantic word-retrieval yielded unprecedented insights into the neural mechanisms underlying behavioral improvements due to anodal-tDCS. Previous studies that used word-retrieval tasks in healthy older adults linked upregulated activity in prefrontal cortices to reduced performance [9,19,40]. Similar findings have been described in other cognitive domains and explained by enhanced top-down demands or reduced processing efficiency [41]. In the present study, impaired word-retrieval in MCI was accompanied by even more pronounced prefrontal activity increases than previously shown in healthy older controls in bilateral vIFG and right MFG [9]. Over-recruitment was also evident in dIFG, an area that has been implicated with phonological retrieval (dIFG [24]), and that was not upregu-

lated in healthy older adults in a previous study [9]. This may represent an attempt to compensate for early structural impairment of left medial temporal lobe structures implicated with semantic retrieval [25,26].

In line with previous studies in healthy individuals [9,11,42] improved performance during anodal-tDCS in the patients was accompanied by reduced hyperactivity in bilateral prefrontal cortex (including left dIFG), so that activity levels during anodal-tDCS were comparable to those of controls. Given that we found reduced activity in all four a priori ROIs, it is important to note that this finding did not generalize to the entire brain. Rather, the whole brain analysis showed that activity reductions were restricted to bilateral frontal cortices and two additional regions (left basal ganglia/thalamus; right middle temporal gyrus) that have been implicated with mediating prefrontal top-down control processes and semantic retrieval [43]. Reduced activity in these areas may represent more efficient or less effortful processing at different levels [44] due to neural facilitation induced by anodal-tDCS [9,11]. Such an assumption would be in line with the neural efficiency hypothesis [45] that proposes a reduction in cortical metabolic rates in individuals with increased cognitive ability. However, it also needs to be acknowledged that no correlations were found between reduced activity and improved performance in this study.

#### 4.3. Impact on RS-fMRI

While task-related fMRI allowed assessing the neural underpinnings of improved performance due to anodal-tDCS, it is difficult to disentangle performance effects from pure stimulation effects [46]. Therefore, the analysis was complemented by task-independent RS-fMRI. Previous studies demonstrated RS-network changes in MCI, however, these studies typically focused on a small number of networks, and results have been inconsistent [31]. As the degree of network changes in MCI depends on disease progression [13], differences between studies are likely explained by sample heterogeneities. Instead of focusing on arbitrarily selected networks, we employed ECM that has been shown to be sensitive to reveal differences between groups of participants (old vs. young adults [9]; healthy adults vs. AD [29]) and also functional network modulations induced by anodal-tDCS [9,10]. The comparison of patients with healthy controls allowed assessing whether anodal-tDCS would result in "normalization" of RS-connectivity.

The present data analysis approach was justified by our results of widespread connectivity changes in patients compared with controls including hubs associated with previously described attention, executive control, salience and sensorimotor RS-networks [46,47]. Most importantly, anodal-tDCS resulted in reversal of this abnormal pattern in several of these regions, including medial frontal and lateral fronto-temporal cortices, bilateral sensorimotor regions, and the right cerebellum. These findings are in line

with previous studies demonstrating large-scale functional RS-network modulations after prefrontal cortex anodal tDCS within and beyond stimulated networks [9–11]. For example, anodal-tDCS of the left IFG altered connectivity in distinct networks associated with stimulated ventral and dorsal IFG, including lateral and medial frontal and sensorimotor regions [9,11]. Similarly, network modulations in the present study overlapped with areas functionally connected to the stimulated IFG [14] and also interconnected networks like the cerebellum [15]. Therefore, anodal-tDCS exerts beneficial effects on functional connectivity beyond the stimulated area by modulations of specific network nodes connected to the stimulation site.

Surprisingly, ECM analysis did not reveal major group differences or stimulation-induced differences in the posterior default mode network (DMN). DMN disruptions have been reported in MCI and AD and linked to early  $\beta$ -amyloid deposition [31], a finding also confirmed by studies that used graph-theoretical methods (degree centrality, DC [48]). While DC measures direct connections between nodes, ECM provides a more “layered” network approach by considering the importance (centrality) of neighboring nodes as well. Therefore, methodological differences may explain the lack of stimulation effects in the posterior DMN. This finding is also in line with a previous study that did not detect differences between healthy individuals and AD patients using ECM in posterior DMN [29]. However, irrespective of these methodological considerations, ECM revealed a number of network abnormalities between controls and patients, and also that these differences can be ameliorated using anodal-tDCS.

## 5. Conclusions

This study provides evidence that anodal-tDCS can ameliorate cognitive dysfunction in MCI and temporarily reverse pathological brain activity. Notably, the comparison of stimulation effects in the patients with those reported previously by our group [9] in healthy older adults (Supplementary Material) revealed no evidence of diminished stimulation effects, which highlights the potential of anodal-tDCS to improve cognition in MCI. Strengths of the study include parallel assessment of performance, task-related activity and network effects and inclusion of carefully matched controls. This study provides a strong rationale to explore whether repeated stimulation sessions can induce long-lasting beneficial effects on cognition in MCI.

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## Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.jalz.2014.07.159>.

## RESEARCH IN CONTEXT

1. Systematic review: We searched all reports in PubMed with the terms mild cognitive impairment/MCI; transcranial direct current stimulation/tDCS; functional magnetic resonance imaging/fMRI. For all terms, we also explored alternative names and included several references from previous articles. However, not a single study so far explored potential beneficial effects of tDCS on cognition and brain functions in MCI.
2. Interpretation: This study provides first time evidence that tDCS (1) can ameliorate cognitive dysfunction in MCI and (2) reverse pathological brain activity and connectivity patterns.
3. Future directions: Our results provides a strong rationale to explore effects of repeated stimulation sessions to assess potential disease modifying effects that may result in delayed progression of disease in MCI.

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