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Research Article

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

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Abstract

Background: 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.

Conclusions: 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.

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

1. Background

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 Information. Written informed consent was obtained from all participats. 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 amnestic (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®, 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 Information 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 Information). 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