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Alzheimer's & Dementia: Translational Research & Clinical Interventions ■ (2017) 1-12

Alzheimer's & Dementia

Featured Article

Combined mnemonic strategy training and high-definition transcranial direct current stimulation for memory deficits in mild cognitive impairment

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Abstract

Introduction: Memory deficits characterize Alzheimer's dementia and the clinical precursor stage known as mild cognitive impairment. Nonpharmacologic interventions hold promise for enhancing functioning in these patients, potentially delaying functional impairment that denotes transition to dementia. Previous findings revealed that mnemonic strategy training (MST) enhances long-term retention of trained stimuli and is accompanied by increased blood oxygen level–dependent signal in the lateral frontal and parietal cortices as well as in the hippocampus. The present study was designed to enhance MST generalization, and the range of patients who benefit, via concurrent delivery of transcranial direct current stimulation (tDCS).

Methods: This protocol describes a prospective, randomized controlled, four-arm, double-blind study targeting memory deficits in those with mild cognitive impairment. Once randomized, participants complete five consecutive daily sessions in which they receive either active or sham high definition tDCS over the left lateral prefrontal cortex, a region known to be important for successful memory encoding and that has been engaged by MST. High definition tDCS (active or sham) will be combined with either MST or autobiographical memory recall (comparable to reminiscence therapy). Participants undergo memory testing using ecologically relevant measures and functional magnetic resonance imaging before and after these treatment sessions as well as at a 3-month follow-up. Primary outcome measures include face-name and object-location association tasks. Secondary outcome measures include self-report of memory abilities as well as a spatial navigation task (near transfer) and prose memory (medication instructions; far transfer). Changes in functional magnetic resonance imaging will be evaluated during both task performance and the resting-state using activation and connectivity analyses.

Discussion: The results will provide important information about the efficacy of cognitive and neuromodulatory techniques as well as the synergistic interaction between these promising approaches. Exploratory results will examine patient characteristics that affect treatment efficacy, thereby identifying those most appropriate for intervention.

Trial status: The study is actively enrolling participants.

Trial Registration: www.clinicaltrials.gov: NCT02155946 (Registered on May 29, 2014).

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http://dx.doi.org/10.1016/j.trci.2017.04.008

Keywords: Aging; Dementia; Alzheimer's disease; Learning; Memory; Cognitive rehabilitation; Cognitive training; Neurorehabilitation; fMRI; tDCS; Neurostimulation; Neuromodulation

1. Background

It is well known that the proportion of older adults is increasing within both the United States and globally. Alzheimer's disease is the most common cause of dementia (i.e., Alzheimer's dementia—AD) with a rate of about 9.5% in those for more than age 70 years; this rate is expected to increase twofold to threefold in the coming decades [1,2]. Delaying conversion to AD will not only improve patient quality of life but may also reduce the financial costs of the disease. The diagnosis of mild cognitive impairment (MCI) captures those who are cognitively symptomatic and at high risk of conversion to AD, yet demonstrate relatively preserved everyday functioning [3–5]. Learning and memory deficits are the most common presenting problem [3,5] and are associated with medial temporal lobe atrophy and dysfunction [5–7]. Associative memory paradigms may be especially sensitive to early decline given their reliance on medial temporal lobe structures [8]. In fact, patients with MCI demonstrate deficits on ecologically relevant associative tasks such as face-name [9] and object-location associations [10], which are accompanied by hypoactivation of key lateral frontoparietal and medial temporal regions relative to control subjects [10]. The lateral frontoparietal network (i.e., middle and inferior frontal gyri, inferior frontal sulcus, and intraparietal sulcus) is known to be important in successful memory formation [11], possibly because of its role in mediating working memory [12–14]. We further supported the importance of this network using effective connectivity analyses, which revealed that cognitively intact older adults engaged the left frontoparietal network during the successful encoding of new object-location associations [15]. In contrast, MCI patients engaged the right frontal eye field, a region known to mediate basic attentional saccades. Together, these findings suggest that memory deficits in patients with MCI may emerge through a combined "loss" of medial temporal and frontoparietal functioning.

The critical question is how to enhance or otherwise maximize memory in those with MCI, especially considering the limited cognitive effects of existing pharmacologic agents [16–18]. The current, ongoing, double-blind, randomized controlled trial addresses this question using two promising nonpharmacologic approaches: mnemonic strategy training (MST) and transcranial direct current stimulation (tDCS).

As we previously described [19,20], MST teaches participants to use cognitive "tools" that enhance the organization of information while also requiring patients to process information more deeply, factors known to enhance memory [21,22]. We demonstrated that MST enhances memory for face-name [23] and object-location associations [19] and others have found comparable benefits for tasks such as word lists [24]. These behavioral improvements were accompanied by increased activation in regions of the lateral frontoparietal network [24,25] and the hippocampus [26]. Together, these findings suggest that MST may enhance memory by re-engaging these previously dysfunctional brain regions/networks. However, our prior data indicate two potential limitations. First, MST appears less effective in patients with "late" MCI (i.e., those closer to developing AD) than "early" MCI (i.e., those closer to "normal") [19,23]. Second, patients have difficulty spontaneously transferring MST to novel types of information, a common problem in this area of research.

We selected tDCS as a potential method for overcoming these limitations. tDCS modulates neuronal excitability by passing a weak electric current between electrodes that are placed on the scalp. Traditionally, tDCS uses two electrodes (usually 25–35 cm^2): an anode that "introduces" the electrical current and a cathode that "collects" the current. Evidence suggests that neuronal somata under the anode become depolarized [27]. Thus, tDCS does not directly induce neuronal firing but, rather, produces conditions that make firing more or less likely to occur. To enhance focality, we are using high definition (HD) tDCS. This method uses a 4 × 1 ring configuration in which the central electrode is surrounded by four electrodes of the opposite polarity [28,29]. Practically, this means that the "ring" electrodes each use about ¼ of the electrical current, whereas the central electrode uses the full amount. This approach limits the cortical modulation effects to the area of the four-electrode ring (see [29]) and presumably minimizes the confounding physiological effects of the ring electrodes. Applied to the motor cortex, HD-tDCS induces greater and more persistent neuromodulatory effects than the traditional approach [30] while remaining well tolerated and without significant side effects (see [28,31]).

We believe the combined use of MST and HD-tDCS is especially appropriate because there is evidence that concurrent tDCS and training enhances consolidation of the trained skill (see [32]). We target the left lateral prefrontal cortex (PFC) given its importance in successful learning and in mnemonic strategy use (as described previously). Thus, we are particularly interested in the synergistic effects of combined MST and HD-tDCS. The current trial randomizes participants to one of four treatment groups that consist of MST or an autobiographical memory recall (ABR) in combination with active or sham HD-tDCS.