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Featured Article

Mnemonic strategy training of the elderly at risk for dementia enhances integration of information processing via cross-frequency coupling

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Abstract

Introduction: We sought to identify whether intensive 10-week mobile health mnemonic strategy training (MST) could shift the resting-state brain network more toward cortical-level integration, which has recently been proven to reflect the reorganization of the brain networks compensating the cognitive decline.

Methods: One hundred fifty-eight patients with mild cognitive impairment (MCI) were selected and participated in 10-week training lasting 90 min/d of memory training. They benefited from an initial and a follow-up neuropsychological evaluation and resting-state electroencephalography (EEG).

Results: At follow-up, MST revealed an extensive significant training effect that changed the network with an increase of synchronization between parietotemporal and frontal areas; frontal$^{\theta}$-parietal$^{\alpha 2}$ causal strengthening as part of top-down inhibitory control; enhancement of sensorimotor connections in β band; and a general increase of cortical-level integration. More precisely, MST induced gain as an increase of the global cost efficiency (GCE) of the whole cortical network and a neuropsychological performance improvement, which was correlated with it ($r = 0.32$, $P = .0001$). The present study unfolded intervention changes based on EEG source activity via novel neuroinformatic tools for revealing intrinsic coupling modes in both amplitude-phase representations and in the mixed spectrospatiotemporal domain.

Discussion: Further work should identify whether the GCE enhancement of the functional cortical brain networks is a compensation mechanism to the brain network dysfunction or a more permanent neuroplasticity effect.

Keywords: Older adults; Cognitive training; Cognitive function; Physical activity; Augmented reality; Brain plasticity; Intrinsic coupling modes

1. Introduction

Over the last few years, an increasing number of studies report on cases of older people who showed extensive pathology of Alzheimer's disease (AD) during brain autopsy but did not clinically manifest cognitive impairment at their late life [1,2]. This ability to tolerate the pathology of the

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disease, independent of disease biomarkers, and to moderate its clinical consequences is referred to as cognitive reserve [3]. Both the cognitive and the neural reserve seem to make independent and synergistic contributions to an individual's clinical resilience, and the mechanisms that underlie both reserves are currently under investigation [4]. However, it is the interaction between the concept of the reserve and life experiences that might have important implications for disease prevention [5]. For instance, participation in cognitively enriching and socially stimulating environments has been suggested to increase the neural reserve [6] and slow the rate of hippocampal atrophy in normal aging [7].

Recently, changes in the cortex functionality while at rest have been found to be particularly relevant to aging and neurodegeneration [8]. More specifically, the disruption of default-mode network's (DMN's) functionality is correlated with working memory performance [9], verbal and visual memory performance [10], autobiographical memory performance [11], and a general lower reaction time as a function of task demands [12]. In terms of DMN power, resting-state electroencephalographic (EEG) rhythms in mild cognitive impairment (MCI)/AD show a power increase in low frequencies (0.5–8 Hz), that is, δ and θ band, and a decrease in higher frequencies (8–30 Hz), that is, α and β [13]. Moreover, inefficient cross-frequency synchronization at the posterior sources of δ and dominant α rhythms is related to global cognitive status and may lead to age-related short-term memory decline [14].

This is the very first study that uses resting-state DMN's cross-frequency synchronization enhancement to evaluate the hypothesis of far transfer [15] in mobile health (mHealth) intervention, which combines physical and cognitive training components. Compared with an active and passive control group, the experimental group was expected to have a significantly greater spatial improvement in functional connectivity among brain regions and especially in the increased cortical-level integration of neuronal oscillations and it was expected that this activation will be correlated with neuropsychological performance.

We hypothesized that ICNs will be affected by the "active" intervention based on both physical and cognitive training compared with the baseline passive protocol followed by a control group. The evaluation of this intervention will be realized via functional brain network analysis using various estimators [16–22]. In this study, sample size was calculated a priori to achieve a power of 80% on the neuropsychological performance at 3 months, after adjusting for an expected dropout rate of 10% to 15%. All analyses were performed using intent-to-treat principles, and the power calculations were based on previous studies in 140 patients with MCI [23–28].

See Section 2 for details of the sample, experimental paradigm, and analysis methods.

2. Methods

2.1. Participants

For this study, 200 patients were randomly approached from a hospital-based cohort. From this cohort, 42 adults were excluded and 158 adults were deemed eligible to participate in the trial, excluding a diagnosis of AD according to guidelines by Dubois [29].

This project was conducted in accordance with the Helsinki Declaration for Human Rights. The ethics committee of Greek Association for Alzheimer's Disease and Related Disorders approved the study protocol, and all participants provided an written informed consent. Group characteristics were matched on age, male-to-female ratio, and general cognitive status and are summarized in S. Table 1 (see Supplementary Material).

3. Materials

Participants underwent a comprehensive cognitive assessment (see Suppplementary Material for further details).

3.1. Interventions

The mnemonic strategy training (MST) program is a method of loci intervention delivered by mHealth to users in their natural environments. A demo showing the MST sequence is shown in S. Fig. 1, and in Supplementary Material, there is a detailed description of the task.

The whole protocol was computerized. Randomization was undertaken in blocks of 10 to 16, according to a random list of computer-generated numbers, with five to eight individuals allocated to each group. Owing to the nature of the intervention, participants were not blinded to group membership; however, research assistants undertaking the follow-up assessments were.

3.2. EEG data acquisition

We chose EEG data for our study, which were recorded using a Nihon Kohden JE-207A equipped with active electrodes attached on a cap fitted to the scalp. The device recorded brain signals through 57 electrodes, 2 reference electrodes attached to the earlobes, and a ground electrode placed at a left anterior position. We also recorded both vertical and horizontal electrooculograms and electrocardiographic activity using bipolar electrodes. Electrode impedances were kept lower than 2 kΩs, and the sampling rate was set at 500 Hz. Participants were instructed to sit in a comfortable armed chair, to close their eyes, and to stay calm for 5 minutes.

3.3. EEG data source connectivity analysis

We base our neuroimaging data analysis in this work and extend it by investigating the synchronous firing of cortical