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 sensori-motor 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.

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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

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but did not clinically manifest cognitive impairment at their late life [1,2]. This ability to tolerate the pathology of the 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 intrinsic connectivity networks 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 Supplementary Table 1 (see Supplementary Material).

3. Materials

Participants underwent a comprehensive cognitive assessment (see Supplementary 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 Supplementary 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 (Nihon-Kohden S. A., Tokyo, Japan) 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 regions and the dynamic organization of the functional networks within the concept of phase-amplitude coupling (PAC) interactions [21]. Cortical activity was obtained from 57 scalp EEG signals in each experiment through the high-resolution EEG technique, involving realistic models to characterize the effects of the different electrical conductivities of the head structures and linear inverse solutions. In the present study, we considered an average head model from the reconstruction of 152 normal magnetic resonance imaging (MRI) scans (MNI template, http://www-nlb.loni.ucla.edu/ICBM/). Scalp, outer-skull, inner-skull, and cortex structures were extracted through the boundary element method (BEM) [30]. The BEM approximates the different compartments of volume conductor models by closed triangle meshes with a limited number of nodes. In the present study, each structure consisted of 305 nodes, being enough to model the smooth surfaces of the average head model. Thus, the cortex model consisted of 305 equivalent electrical dipoles representing the cortical sources.

Connectivity analysis was applied to six conventionally defined frequency bands: δ, 1 to 4 Hz; θ, 4 to 8 Hz; α_1, 8 to 10 Hz; α_2, 10 to 13 Hz; β, 13 to 30 Hz; and γ, 30 to 45 Hz. Band-limited brain activity was derived by applying third-order Butterworth filter (in zero-phase mode). We quantified the brain source network using four types of interactions and adopting properly defined connectivity estimators: (1) intrafrequency phase coupling within each of the six frequencies was estimated using the imaginary part of phase locking value (iPLV); (2) cross-frequency coupling (CFC) namely PAC between 15 possible pairs of frequencies was defined with the PAC estimator [21]; (3) cross-frequency causal interactions between every possible pair of frequencies were quantified using a novel estimator based on delay symbolic transfer entropy (dSTE) where we can detect both the strength and the delay lag of significant causal interactions [22]; and (4) the correlation of the orthogonalized envelopes *corr* within each frequency band [31]. The adopted three estimators (iPLV/PAC/dSTE) ranging from 0 to 1 while *corr* ranges from −1 to 1. The derived quantities are tabulated in an [305 $\times$ 305] matrix, called hereafter the functional connectivity graph (FCG), in which an entry conveys the strength of iPLV/PAC/dSTE/*corr* for each pair of cortical sources. The aforementioned procedure produced 6 + 15 + 15 + 6 = 42 FCGs for each subject and pre/post condition. (For surrogate analysis, see Supplementary Material.)

4. Results

4.1. Neuropsychological performance

Demographics, baseline cognitive test scores, and the effects of the intervention in the three different groups are summarized in Supplementary Material (Supplementary Table 2). On average, study participants had moderate to high levels of cognitive function at baseline, consistent with their age and education levels. When we examined individual cognitive tests, there were significant main effects ($P < .0001$) for the California Verbal Learning Test (CVLT), perseveration and intrusion errors; CVLT immediate and delayed recall; Trail-Making Test, part A; Trail-Making Test, part B (TMT-B); and Geriatric Depression Scale (GDS; see Supplementary Material, Supplementary Table 2). In contrary, the active control (AC) group showed a significant increment ($P = .01$) in Mini-Mental State Examination and GDS scores and significant decrement ($P = .001$) in CVLT immediate and delayed recall, CVLT perseveration errors, and TMT-B time of completion after the intervention. Waiting-list control group did not show any significant difference (see Supplementary Material, Supplementary Table 2).

4.2. Brain connectivity effects

Statistical analysis revealed an increment/decrement of PAC values within anterior-middle/posterior brain sites correspondingly due to intervention for the MST group in three PAC pairs. We demonstrate the cortical functional networks for PAC pairs θ:β, α1:γ, α2:γ, and β:γ in Fig. 1. In general, a significantly more extended functional subnetwork was revealed for the MST group compared to AC in the three out of the four frequency pairs. The density of intervention-induced significant functional cortical networks for each PAC pair and for both MST and AC groups is demonstrated in Fig. 2.

Fig. 3 summarizes the statistically significant increment of connectivity strength between causal CFCs estimated with dSTE between frontal[θ] brain areas and parietal[α2]. Fig. 4 demonstrates intervention-induced significant cortical networks of correlations *corr* over orthogonalized envelopes of β frequency between left frontal and temporal brain areas. Additionally, no lag difference was detected for every significant identified interaction based on dSTE in the MST group.

We have to mention that we did not detect any significant intervention change on the topology of both groups based on intrafrequency FCG[iPLV].

4.3. Correlation of cortical functional network properties with neuropsychological measures

Table 1 summarizes global cost efficiency (GCE) for the four PAC frequency pairs in both groups. GE and C did not show any significant trend in both groups. Differences between preintervention and postintervention period were detected with Wilcoxon rank-sum test ($P < .0001$). The whole procedure revealed significant intervention-induced changes of the relationships between neuropsychological measures and the balance between GE and cost (GCE) only in the MST group (Table 2).
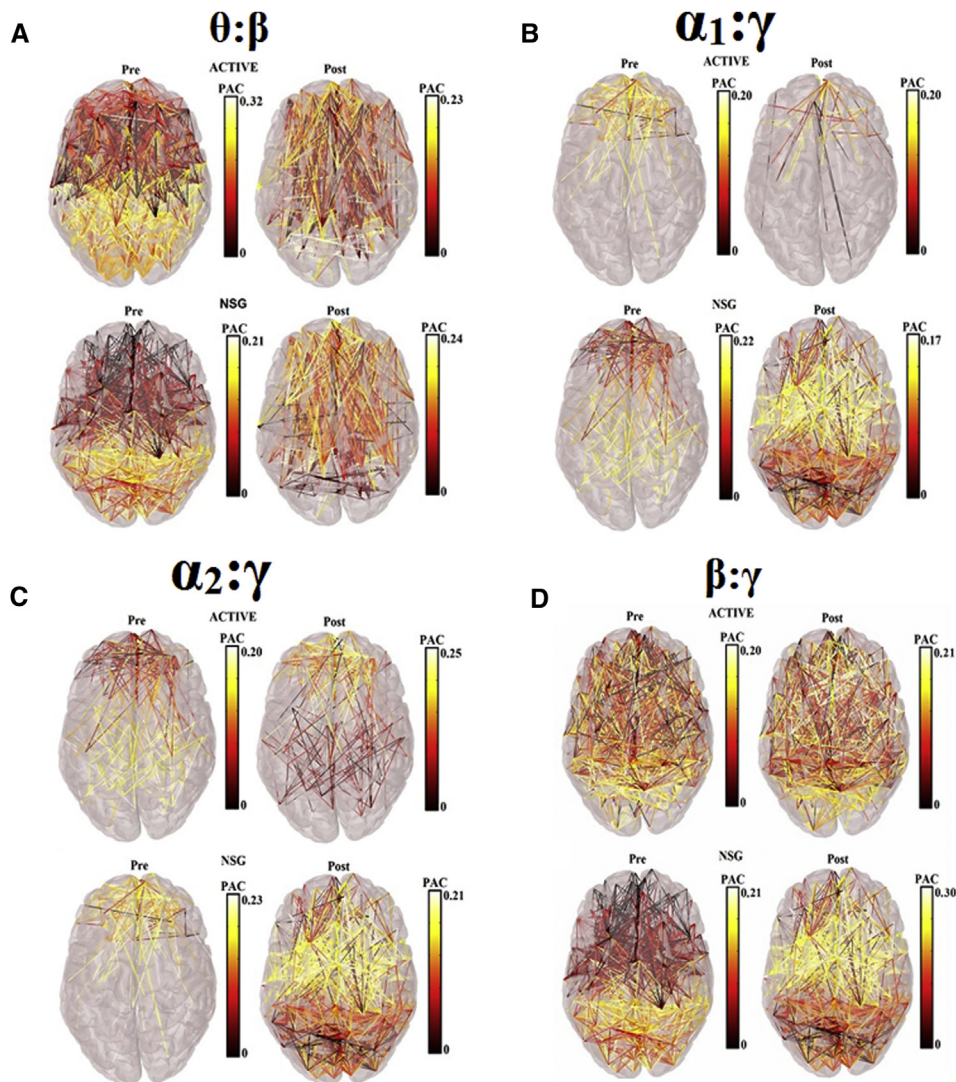
Fig. 1. Topographies of intervention-induced significant cortical networks of cross-frequency coupling (CFC) at resting state by adopting a phase-amplitude coupling (PAC) estimator. We found a significant increase at the frontal, medial temporal, and inferior parietal cortex synchronization for the MST group after the intervention for the pairs $\alpha 1:\gamma$, $\alpha 2:\gamma$, and $\beta:\gamma$. NSG, novel serious game.

5. Discussion

In this study examining the neural correlates of an intervention program integrating both physical and mental activity for older adults with cognitive impairment due to dementia, we found a significantly more extended functional connectivity pattern at the intervention group over the course of 10 weeks. In addition, we also found that cognitive scores improved significantly, and our findings are consistent with prior studies, which have found that an intensive computer training program improves cognitive function more than educational DVDs in healthy and cognitively impaired older adults [32,33]. This study aimed to extend our knowledge about the plasticity of functional brain networks in older adults with cognitive impairment due to dementia. We were particularly interested in examining whether intensive 10-week training could shift the resting-state EEG brain network more toward a higher functional integration. Such changes are important as they have recently been proven to reflect

the reorganization of the brain networks accompanied with the cognitive decline that may lead to AD [34]. This notion is in line with a recent piece of work by Mantini et al. [35] in which process-based novelty elderly training interventions provided enhanced effects on specific cognitive functions and small effects on unspecific cognitive abilities.

Coordination of neuronal oscillations generated at different frequencies has been hypothesized to be an important feature of integrative brain functions. A recent study on 42 healthy older adults highlighted the link between cognitive training and a "top-down control of sensory processing by the dorsal attention network" and emphasized that altered brain connectivity may also serve as a marker for evaluating the success of training [36]. As argued in that and similar studies, the resting state can be regarded as the starting point for subsequent task-related cognitive processes [37].

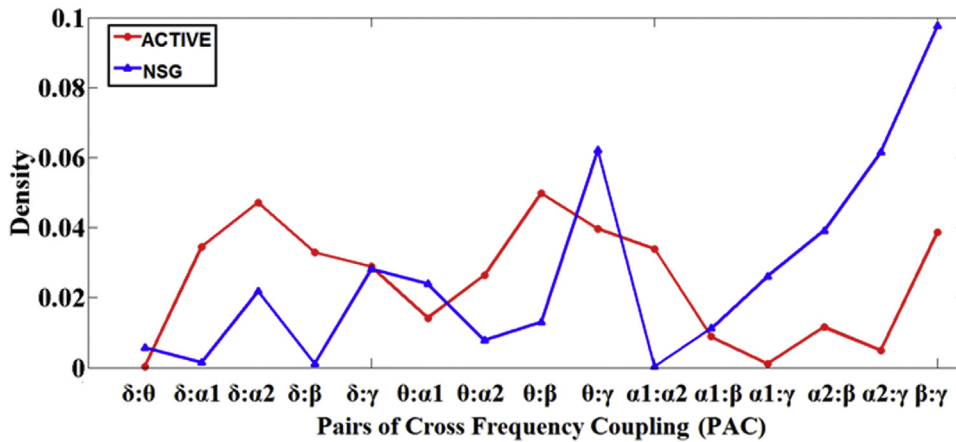Several intrinsic connectivity networks such as the somatomotor network (SMN), the DMN, and the dorsal attention

Fig. 2. Density of intervention-induced significant functional cortical networks for each PAC pair and for both groups. The results represent the group values before and after intervention. Density is defined as the number of surviving connections divided by the total number of possible connections among 305 cortical sources. NSG, novel serious game.

network are thought to be crucial for the maintenance of cognitive function in normal levels [38]. For example, a correlation of DMN's disruption with amnestic MCI and also with AD has already been reported [39], and for that reason is closely related to progression of the abnormal neurophysiology profile in progressive MCI [40].

Overall, our analysis demonstrated a significant increment of the causal strength between frontal$^\theta$ brain areas and parietal$^{\alpha2}$, supporting an improvement of the attention profile in individuals following the intervention protocol. In addition, we uncovered significant enhancement of the strength between areas of SMN on the left hemisphere within the beta frequency after intervention. This effect could be the positive outcome of the physical activity [41].

A well-documented distributed brain network that is known to support inhibitory control includes the inferior frontal gyrus (IFG), the anterior cingulate cortex (ACC), the dorsolateral prefrontal cortex (DLPFC), the frontal eye field, the posterior parietal cortex, the cerebellum, and the striatum [42]. The ACC encapsulates specialized subdivisions that subserve a variety of emotional, executive, cogni-

tive, visuospatial, and nociceptive functions [43,44]. The dorsal part of the ACC (Brodmann area [BA] 32) is implicated in modulation of attention, which is part of the distributed attentional network [43].

The posterior parietal superior (PSP) plays a key role in a large number of visuospatial tasks including orienting of attention, with or without the involvement of working memory [45]. This suggests that the activation of PSP cortex reflects the processing of attended items. The right middle frontal gyrus (MFG) has been found to be involved in working memory processes [46] and attentional control [47].

Functional changes in the MFG have been associated with age-related declines in episodic memory retrieval [48]. The supramarginal gyrus is a portion of the parietal lobe (BA 40). An important function of the DLPFC (BA 9) is the executive functions, such as cognitive flexibility, working memory, inhibition, and abstract reasoning [49]. DLPFC is also the highest cortical area that is involved in motor planning, organization, and regulation. These top-down connections originated from the ACC, the right MFG, and the right IFG.
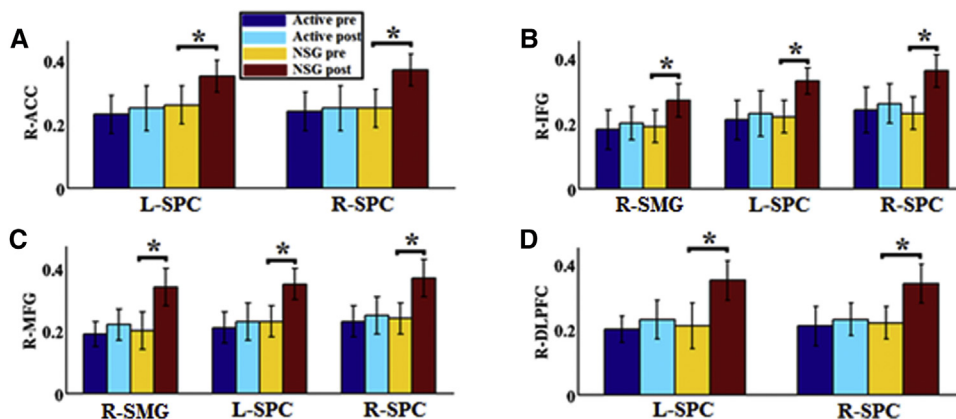

Fig. 3. Intervention-induced significant cortical networks of causal cross-frequency couplings estimated with dSTE between frontal$^\theta$ brain areas and parietal$^{\alpha2}$. R, right; ACC, anterior cingulate cortex; L, left; SPC, superior parietal cortex; IFG, inferior frontal gyrus; SMG, supramarginal gyrus; MFG, medial frontal gyrus; DLPFC, dorsolateral prefrontal cortex. *$P < .001$ with Wilcoxon rank sum test.
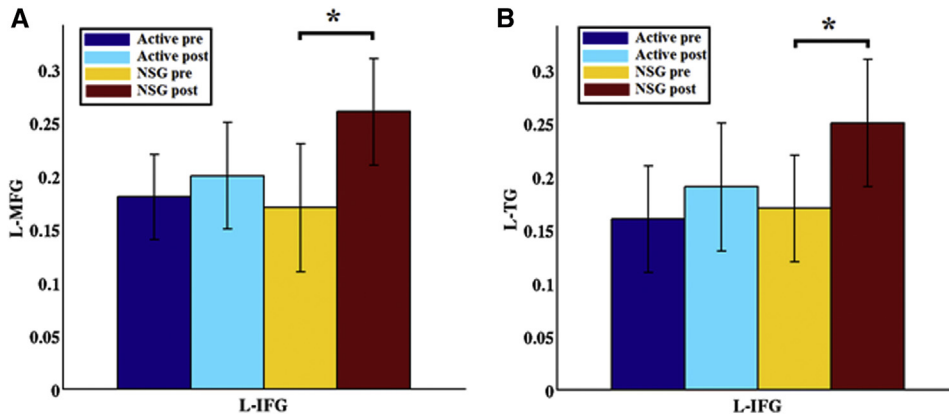
Fig. 4. Intervention-induced significant cortical networks of correlations *corr* over orthogonalized envelopes of β frequency between (A) L-MFG and L-IFG and (B) L-TG and L-IFG. L, left; MFG, middle frontal gyrus; IFG, inferior frontal gyrus; TG, temporal gyrus. *$P < .001$ with Wilcoxon rank sum test.

The primary function of the inferior temporal gyrus is associated with processing of visual stimuli, namely visual object recognition, and has been suggested by recent experimental results as the final location of the ventral cortical visual system [50]. The left IFG (BA 44) has been implicated in go–no-go [51] tasks. The left IFG has been suggested to play a role in inhibition, including the tendency to inhibit learning from undesirable information. For example, TMS to the left IFG has been shown to release such inhibition, increasing the ability to learn from undesirable information [52].

In studies of effective connectivity in the frontoparietal network, endogenous effective connectivity has been reported as bidirectional between frontal and parietal areas, with top-down control-specific modulation in frontal-to-parietal direction [53]. A functional MRI study showed a disconnected profile of frontoparietal junctions, supporting an impaired attention profile in very early stages of AD [54].

Whether enhancement of such integration of the functional brain networks is a compensation mechanism to the brain network dysfunction remains to be seen according to models of connectivity and data from other stages of the disease [55].

5.1. Methodological considerations

Our study had several key strengths, including the use of a large sample, a novel intervention, and an AC condition, which enabled us to control for factors such as social interaction during the group mental stimulation associated with using a computer. However, there were also several limitations. The first is that the EEG data were obtained only in the resting condition. Obtaining a more precise understanding of functional brain activity and its association with synchronization requires EEG data obtained during resting and task-performing states to be compared. In addition, the degree of change in EEG data between resting and task-performing state seems to be different in cognitively impaired patients compared with normal controls. Another limitation is the fact that the study was not conducted in a blinded fashion.

Second, our graph-theoretical analysis on the basis of intracerebral activity could be improved by referring to the individual brain anatomy. This enables improved estimations for inverse modeling compared with the average brain by taking head size and cortical folding into account. In addition, one of the unsolved problems in EEG data connectivity analysis is the volume conduction. This problem is especially

Table 1
GCE for the four PAC frequency pairs in both groups before and after intervention

GCE/PAC frequency pairs	NSG		AC	
	M0	M3	M0	M3
θ:β	0.02 ± 0.07	0.05 ± 0.29***	0.10 ± 0.06	0.20 ± 0.07***
γ:α1	0.06 ± 0.23	0.12 ± 0.62***	0.29 ± 0.09	0.35 ± 0.14
γ:α2	0.07 ± 0.26	0.14 ± 0.66***	0.31 ± 0.12	0.37 ± 0.13
γ:β	0.09 ± 0.42	0.13 ± 0.61***	0.01 ± 0.51	0.09 ± 0.61

Abbreviations: GCE, global cost efficiency; PAC, phase-amplitude coupling; NSG, novel serious game; AC, active control.
***$P < .0001$.

Table 2
Correlation r of the most significant neuropsychological measurements for the NSG group before and after intervention with GCE presented for PAC frequency pairs where an improvement was detected

	NSG	
	M0	M3
MMSE		
Global	$r = 0.07^{\alpha1-\gamma***}$	$r = 0.33^{\alpha1-\gamma***}$
CVLT		
Immediate recall	$r = 0.10^{\theta-\beta***}$	$r = 0.34^{\theta-\beta***}$
Delayed recall	$r = 0.06^{\alpha1-\gamma***}$	$r = 0.36^{\alpha1-\gamma***}$
Perseveration errors	$r = -0.09^{\theta-\beta***}$	$r = -0.23^{\theta-\beta***}$
	$r = -0.06^{\alpha2-\gamma}$	$r = -0.30^{\alpha2-\gamma}$
Executive functions		
TMT-B	$r = -0.05^{\alpha1-\gamma***}$	$r = -0.31^{\alpha1-\gamma**}$
Attention		
Direct span	$r = 0.05^{\alpha1-\gamma**}$	$r = 0.32^{\alpha2-\gamma***}$
Reverse span	$r = 0.06^{\alpha1-\gamma***}$	$r = 0.26^{\alpha1-\gamma***}$
Total score	$r = 0.05^{\beta-\gamma***}$	$r = 0.32^{\beta-\gamma***}$

Abbreviations: NSG, novel serious game; GCE, global cost efficiency; PAC, phase-amplitude coupling; MMSE, Mini-Mental State Examination; CVLT, California Verbal Learning Test; TMT-B, Trail-Making Test, part B.
**$P < .001$; ***$P < .0001$.

critical with analyses at sensor level and to a lesser extent in the intracortical space, as was done in the present study. Third, this study did not have a 6-month follow-up EEG connectivity data analysis after the intervention. The follow-up would enable us to be able to answer whether the integration enhancement of neuronal oscillations at the functional brain networks is a compensation mechanism to the brain network dysfunction or a more permanent neuroplasticity effect or even an adequate measure to decelerate or prevent conversion to AD. Nevertheless, these limitations could be addressed at a future study design as our present results showed that 10 weeks of the intervention was associated with significant improvements in global cognitive function, with evidence of neuroplasticity in older adults with cognitive impairment due to dementia. These findings may reflect practice effects or may suggest that the type of activity is more important than the amount in this subject population.

6. Conclusion

To our knowledge, this is the first study that has investigated the capacity of functional intrinsic brain networks to adapt to a mHealth intervention by using graph-theoretical network analyses and appropriate neuroinformatic tools. Our approach for the very first time integrates spectrospatiotemporal properties of brain activity for evaluating intervention. Spectral and spatiotemporal brain properties are reconciled under the framework of metastability. With our approach, we manipulated the source of brain complexity which is the spatiotemporal forming and dissolution of brain subsystems on prominent frequencies. To conclude, there were four main findings in the present study: (1) the better the neuropsychological performance correlated positively/negatively with GCE for the functional networks in the θ:β, α1:γ, α2:γ, and β:γ band pairs using PAC; (2) GCE for the four CFC pairs was significantly improved for the MST group while the density of significant connections was also higher for the MST group, exhibiting higher integration of distributed information over local and global brain regions; (3) statistically significant increment of causal connectivity strength between frontal[θ] and parietal[α2] brain areas diminishes the impairments of the top-down attentional control; (4) statistically significant increment between left frontal and temporal brain areas related to somatomotor cortical network accessed with correlations *corr* over orthogonalized envelopes of β frequency. Finally, we suggested an extension of BAs to include also prominent coupling modes including both intrafrequency and interfrequency coupling, amplitude/phase, and connectivity.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.trci.2016.08.004.

RESEARCH IN CONTEXT

1. Systematic review: This is the first reported study of a targeted mnemonic strategy training (MST) protocol based on a mobile application of elderly at risk for dementia. Resting-state functional connectivity patterns are an index of the "reflex" of each functional independent brain subnetwork. To reveal and evaluate the benefits of the proposed intervention scheme, we adopted appropriate neuroinformatic tools that deal simultaneously with spectrospatiotemporal attributes of brain activity. To demonstrate the effectiveness of the suggested intervention protocol, we used a second group where a different protocol was followed.

2. Interpretation: The suggested MST protocol enhanced integration of information processing via cross-frequency coupling. Particularly, we observed an enhancement of top-down inhibitory control with an increase of synchronization between parietal-temporal and frontal areas; frontal[θ]-parietal[α2] causal strengthening; enhancement of sensorimotor connections in β band; and a general increase of cortical-level integration, which was correlated with neuropsychological performance improvement.

3. Future directions: Further work should identify whether the enhancement of information flow of the functional cortical brain networks is a compensation mechanism to the brain network dysfunction or a more permanent neuroplasticity effect.

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