The effectiveness of adaptive working memory training on EEG and cognitive performance in Alzheimer disease

Pegah Dehghan¹, S. M. Hossein Mousavi Nasab¹*, HosseinAli Ebrahimi²*

¹ Department of Psychology, Faculty of literature and humanities, Shahid Bahonar University of Kerman, Iran
² Neurology Research Center, Kerman University of Medical Sciences, Kerman, Iran

Abstract

Due to the progressive aging of population, the prevalence of dementia and age-related cognitive impairment, and in particular Alzheimer’s disease, is highly increasing, and becoming one of the important problems bearing on the health system. Recently, the diagnostic tools and pharmacological treatments have shown a rising potential. Yet, non-pharmacological interventions have attracted significant interest. However, the effectiveness of such interventions has remained controversial. The aim of this study was to investigate whether working memory training changes the EEG and cognitive performance at resting state in patients with Alzheimer’s disease. Twenty patients with mild to moderate Alzheimer's disease were recruited and randomly divided into training and control groups. The training group received twenty-five sessions of adaptive n-back training. Mini Mental Status Examination (MMSE), digit span, and EEG were assessed before and after the intervention period. Working memory training led to a significant increase in MMSE score and alpha power over the frontal and parietal-occipital regions. Non-significant increase of the log EEG power was shown for beta, theta, and delta concerning the entire regions. Adaptive n-back training is effective on quantitative EEG in patients with mild to moderate Alzheimer’s disease.

Keywords: Dementia, Alzheimer disease, Cognitive training, EEG, resting state

The elderly population is on the rise globally which will undoubtedly cause consequences including increased old age-related pathologies like dementia and, especially, Alzheimer’s disease (AD), in which the cognitive competence of the patient is progressively lost. Such pathologies also impose immense medical and economic burden on the society. According to Nichols and colleagues, dementia will increase from approximately 57.4 million patients worldwide in 2019 to around 152.8 million in 2050 (Alzheimer's Association, 2021).

* Corresponding authors:
E-mail: hossein.mousavi-nasab@uk.ac.ir, hebrahimi@kmu.ac.ir
Major advancements in pharmacological treatments and diagnostic tools in recent years have shown great potentials. However, due to the adverse effects of such medications (Cholinesterase inhibitors and Memantine, for instance), in addition to their moderate treatment effects, and the fact that the disease continues to progress even while the medication is administered, non-pharmacological treatments have received considerable attention (Doody et al., 2001).

In dementia, the core of the disease is cognitive impairment, including working memory, indicated through loss of independent functions. Working memory (WM) is a key factor and important concept in some cognitive activities. Since the definition of working memory is based on a theory for figuring this concept, it is difficult to provide a unitary definition. Cowan examining the relevant studies, presented about nine various definitions for working memory as life planning WM, multicomponent WM, computer working memory, recent event working memory, processing WM and storage, generic WM, and long-term WM (Cowan, 2017). Such differences in theories can be rooted in their underlying assumptions about WM like the extent to which WM includes long term memory or multiple storage modules (Oberauer, 2019). For instance, in generic WM view (Cowan et al., 1998), WM is the collaborative of mind components temporarily holding information in an availability heightened state for using in processing the ongoing information. In the multicomponent theory, WM is conceptualized as a multicomponent system temporarily maintaining information and mediating its use in current mental activities (Baddeley, Hitch, & Bower, 1974). In Storage-and-processing WM theory (Daneman & Carpenter, 1980) the inclusion of processing component or storage process alone is not regarded as WM contrary to the multicomponent theory. In fact, WM is the integration of temporary storage and processing the activities with a restricted capacity for the summing up the processing activities and storage. Moreover, there is close relation between working memory, fluid intelligence and attention. Thus, providing independent definition is difficult. Engle (2018) revealed that working memory tasks represent the capability of temporarily maintaining the information. Furthermore, the individuals' ability is illustrated by intelligence tests for disengaging from the present information, which is not useful anymore. According to Oberauer (2019), by holding a chosen subset of all accessible representations in memory, WM is a kind of attention by definition (attention and working memory). Hence, it is not simple to provide a general agreed definition about WM. Working memory (WM) enables the procedure of temporary storage and manipulating the information essential for higher level cognitive tasks like learning, comprehension, and reasoning. Furthermore, normally shortages in WM are related to the several neuropsychiatric disorders such as Alzheimer disease (Gilmour et al., 2019; Hampstead, Sathian, Bikson, & Stringer, 2017; Jiang, Abiri, & Zhao, 2017).

Hopefully, there is growing indication on brain plasticity demonstrating the memory performance enhancement through memory training (Hampstead, Stringer, Stilla, & Sathian, 2020; Nguyen, Murphy, & Andrews, 2019; Salminen, Mårtensson, Schubert, & Kühn, 2016; Teixeira-Santos et al., 2019). There are two main memory
training methods including process-oriented memory training as well as strategy-oriented memory training (Legge, Madan, Ng, & Caplan, 2012; Peeters & Segundo-Ortin, 2019). Strategy-oriented memory training represents the enhancement memory performance through mnemonic strategies to information retrieval and encoding (Li et al., 2016). Among the effective mnemonic strategies are method of loci, imagery, associations, rehearsal, categorization. The second memory training type is Process-oriented training which is used in the present work. In training the process-oriented memory, it is mostly focused on improvement of the capacities associated with operations like executive functions and processing speed (Li et al., 2016; Nouchi, Saito, Nouchi, & Kawashima, 2016). The dual n-back task as one of the most experimental paradigms frequently used for process-oriented training (Owen, McMillan, Laird, & Bullmore, 2005) includes simultaneous serial exhibition of visual and auditory stimuli needing participants for a specific response on the location or identity. This is when there is consistency between the present stimulus and the one provided inn trials (Jaeggi, Buschkuehl, Jonides, & Perrig, 2008; Shipstead, Redick, & Engle, 2012). N-back training was connected by several studies to enhance the WM capacity (Heinzell, Lorenz, et al., 2014; Jaeggi et al., 2010), near transfer to perform similar WM tasks structurally (Olesen, Westerberg, & Klingberg, 2004), as well as far transfer to fluid intelligence (Jaeggi et al., 2010; Olesen et al., 2004). Near transfer represents the improved a task performance intended for measuring the trained cognitive domain. However, far transfer denotes the enhancement in another cognitive domain like WM training resulting in better performance in an intelligence measuring the task (Von Bastian & Oberauer, 2014).

Also, many studies have been conducted to find out whether cognitive training triggers any improvements in patients with Alzheimer’s disease (Herrera, Chambon, Michel, Paban, & Alescio-Lautier, 2012; Huntley, Hampshire, Bor, Owen, & Howard, 2017; Lai, Mok, & Lin, 2011). As indicated by some of these findings, n-back training is effective in helping the elderly, both healthy and with Alzheimer’s disease (Heinzell, Lorenz, et al., 2014; Heinzell, Riemer, et al., 2014; Heinzell, Schulte, et al., 2014; Huntley et al., 2017). On the other hand, some studies do not find any improvement in cognitive ability, near or far transfer resulting from cognitive training. More specifically, there are several studies investigating the effectiveness of n-back training in adults, the elderly, mild cognitive impairment, and the Alzheimer's disease population. Nevertheless, they did not reach a consistent result.

For example, Rip (2021) found that n-back training does not change FMRI activity in patients with Alzheimer's but can improve cognition in some tasks. Li and colleagues (2021) showed that n-back training improves the general cognition domain in both trained and untrained tasks (near and far transfer) in adults. However, Lawlor-Savage and Goghari (2016) found no improvement in working memory and fluid intelligence resulting from applying n-back training in healthy adults. Therefore, the effectiveness of cognitive training is controversial, and more evidence is needed to support the extent to which n-back training can be effective.
(Melby-Lervåg, Redick, & Hulme, 2016; Redick et al., 2013), especially in populations vulnerable to WM deficit.

Furthermore, EEG, known as the biomarker of Alzheimer’s disease, has been employed to evaluate the severity of dementia as well as efficacy of medicinal treatments (Horvath et al., 2018). EEG rhythm at resting state of AD patients is manifested in the forms of decreased power in higher frequencies, Alpha and Beta (8-30 hertz) and increased power in lower frequencies, delta, and theta (1-8 hertz) (Hort et al., 2010). Recording and studying EEG data while performing no specific tasks at resting state, will provide valuable information for examining human brain’s functional organization, and can be utilized for studying the default activities of the brain’s functional network (Raichle et al., 2001; Schlee et al., 2012). Studies which have investigated resting state EEG power changes have mostly targeted healthy elderly subjects (Heinzel et al., 2016; Vlahou, Thurm, Kolassa, & Schlee, 2014), population at risk of dementia (Styliadis, Kartsidis, Paraskievopoulos, Ioannides, & Bamidis, 2015), or patients with minor pathologies (Gandelman-Marton, Aichenbaum, Dobronevsky, Khainrekht, & Rabey, 2017). Moreover, the tried out interventions have either been a combination of sport exercises and cognitive interventions (Horvath et al., 2018), which though effective, disrupts the accurate separate assessment of the cognitive intervention’s effect, or the intervention is non-cognitive, like Repetitive transcranial magnetic stimulation (rTMS) (Hogrefe, Studer-Luethi, Kodzhabashev, & Perrig, 2017).

However, a limited number of studies have measured the effects of cognitive interventions on EEG bands' power - one of the significant indices of the disease. Studies on Alzheimer’s disease take the patients through various evaluations while performing the task to evaluate brain activity while involved with cognitive tasks. Yet, very few studies have adopted a cognitive training for this disease in which the brain changes have been examined at resting state. In addition, there are few reports on the efficacy of working memory trainings which have adopted controlled interventions, an absolute necessity for clinical trials (Huntley et al., 2017). Therefore, in the present study we aimed to fill this gap.

In this study, our goal was to study: 1- whether n-back training can enhance general cognitive domain (by increasing MMSE score); 2- whether n-back training changes brain activity manifested by electroencephalography; 3- whether visual WM training task can improve an untrained module task (verbal digit span). We hypothesized that if cognitive training were effective, it would be observable by 1: changes induced in EEG bands power resulted from Alzheimer’s disease. 2: improvement in cognitive measurements (in trained or untrained tasks).
METHOD

Participants and procedure

A total of 20 patients diagnosed with mild to moderate Alzheimer’s disease were recruited at the Neurology Research Center, Kerman University of Medical Sciences, Kerman, Iran, based on the criteria set forth by the diagnostic and statistical manual of Mental Disorder (DSM-V), and with a Mini-Mental State Examination score between 15 and 24, GDS < 15 and age ≥ 60. The Geriatric Depression Scale (GDS-30) is a 30-item self-rating scale developed to screen for depression in elderly population, typically over the age of 65 years (Yesavage et al., 1983). The Geriatric Depression Scale GDS is applied to assess Depressive symptomology in which participants answer to “yes/no” self-report questions. This scale is applied to make sure participants cognitive decline is not due to the depression.

Mini-Mental State Examination ± (MMSE) as a brief cognitive test is utilized for screening and monitoring the progression of dementing illnesses like Alzheimer’s disease (AD). There are various questions in the MMSE with a maximum score of 30 points, which should be managed within 5-10 min ordinarily. Typically, the questions are classified into seven classes each rationally presenting a various cognitive function or domain (Orientation to place (5 points); Attention and Calculation (5 points); Orientation to time (5 points); Registering words (3 points); Language (8 points) and Visual Construction (1 point); and Recall of three words (3 points). Generally, a score of 23 or less represents the existence of cognitive impairment (0-17 = severe cognitive impairment; 18-23 = mild cognitive impairment; 24-30 = no cognitive impairment) (Tombaugh & McIntyre, 1992).

All patients were right handed and generally healthy based on their medical history, as well as general and neurological examinations. Patients were excluded if they reported a history of brain stroke, seizure or epilepsy, taking of any psychiatric medications, and alcohol and/or drug abuse. None of the patients had received any types of cholinesterase inhibitors, memantine, NMDA antagonists, and ACHE-I, at least 1 month prior to the study, and no changes were made concerning the medications taken by the patients for hypertension, diabetes mellitus, or heart stroke and heart diseases. They all had the capacity to provide written informed consent to participate in the study which was approved by the research ethics committee of the Research Deputy, Kerman University of Medical sciences (REC reference number IR.KMU.REC.1398.279) and Iranian Registry of clinical trial (IRCT) with IRCT Id of IRCT20190616043901N1.

Following informed consent and baseline EEG and MMSE assessment, the participants were randomized to either the training (n = 10) or the control group (n = 10), using an online block randomization program. Demographic data is shown in Table 1.
Table 1
Demographic data of the two group (control and experimental AD patients).

<table>
<thead>
<tr>
<th></th>
<th>Training group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Age, years</td>
<td>66.5(5.91)</td>
<td>68.60(5.8)</td>
</tr>
<tr>
<td>Sex, female</td>
<td>40 (%)</td>
<td>40 (%)</td>
</tr>
<tr>
<td>Years of education</td>
<td>5.6(1.43)</td>
<td>5.8(1.32)</td>
</tr>
<tr>
<td>Disease duration</td>
<td>4.3(1.8)</td>
<td>3.8(2.3)</td>
</tr>
</tbody>
</table>

Note. The data is represented as mean (SD) or number (percentage)

Measures

Adaptive single n-back training

The adaptive single n-back training employed in this study was programmed using MATLAB. The blue squares were presented sequentially in one of nine locations, in a 3 × 3 matrix at a rate of 3-second (stimulus length, 500 ms; interstimulus interval, 2500 ms). One training session comprised 20 blocks, each consisting of 20+n trials (Jaeggi et al., 2008). Participants were instructed to answer with a keyboard whenever the current stimuli matched the target stimuli, presented N trials back. The difficulty level was adjusted based on the level of n (Jonides et al., 1997). The N-back level was fixed at \( N = 2 \) for the first block, after which if the subject’s score was more than 75%, the difficulty would be increased to the next n-back level. If the score was between 50%-75% the participant remained at the current level, and if the score fell less than 50%, the difficulty would be decreased one level. Participants in the training group attended twenty-five sessions, held five days a week for five weeks in a row (Goghari & Lawlor-Savage, 2017). Pretest and post-test were assessed 3 days before and three days after the total intervention.

EEG Examination and Spectrum Analysis

The EEG was recorded by a set made under the license of NegroSain Company, Canada, in a laboratory, by technicians who were instructed to keep the patients awake. Patients sat in a comfortable reclined chair, with their eyes closed. The EEG recording was done with 21 electrodes in 3 regions: frontal (FP1, FP2, F3, F4, F7,F8,Fz), temporal (A1, A2, T3, T4, C4, C3, Cz), and parieto-occipital (T5, Pz, O1, O2, T6, P3, P4) at the 10-20 system 1positions, with a sample frequency of 500 Hz and the electrode impedance of below 5KΩ. The reference was placed on the forehead. The lower and upper bandpass filters were set at 0.5 and 40, respectively and Notch filter at 50 Hz to remove the interference, and twenty minutes of the subject’s awake state was recorded for additional processing. Subsequent 1 to baseline correction and visual inspection of artifacts caused by eye blinks, eye movements or muscle tension were marked and excluded from further analyses; the
Power spectra were computed using the fast Fourier transform algorithm. The absolute power values were calculated using fixed frequency band delta (1 to < 4 Hz), theta (4 to < 8 Hz), alpha (8 to < 13 Hz), and beta (13 to < 30 Hz) for each and every 21 derivations. The false-discovery rate was used to control multiple comparisons. Electroencephalogram data collection was carried out 3 days before training (n = 10) and 3 days after the training protocol was done (n = 10). The MMSE was evaluated before EEG recording.

**Cognitive Examination**

In addition to the electrophysiological examination, the patients’ verbal working memory was also tested by means of the Digit Span subtest of the Wechsler Adult Intelligence Scale-IV (Carlozzi, Grech, & Tulsky, 2013). Subjects repeated a series of verbally presented digits verbatim, forward, and backward. The patients were trained to recite the digit orders with increasing lengths either in the presented order (forward digit span) or in reverse order (digits backward). Two trials exist for each sequence length. For the standard administration, the test should be discontinued by errors made by the patient on both trials with identical spans. The summation of the points before failure on two trials with the equal span length determines the total score (Green, 2000).

Briefly, we evaluated the cognitive examinations (MMSE, backward and forward digit span) after choosing the participants based on our criteria. At the same day, we also recorded their EEG, 3 days before initiating the protocol. Then, the participants with matched MMSE scores were randomized into training and passive control groups. Twenty-five sessions of adaptive n-back training were provided for the training group for 5 weeks. The participants' cognitive measurements and EEG were evaluated 3 days after the last session.

**Statistical analysis**

Aiming at the computation of each absolute power value, firstly, the log transformation was applied to the electroencephalogram data to normalize them, and then averaged in each region. The statistical analysis was carried out by SPSS 22 and the variables were analyzed using ANCOVA to analyze the differences between changes in the training and control groups after 25 sessions of adaptive n-back training. The independent variables in each analysis were the groups (control and training). The dependent variables consist of post-test measurements (including EEG bands power, MMSE score, digit span scores) and pretests measurements stand as covariates. The Leven test was applied to analyze the homogeneity between control and experimental groups. P values less than 0.05 were regarded as significant.
Cognition, Brain, Behavior. An Interdisciplinary Journal
26 (2022) 19-36

Figure 1. Log mean and SDs of power in the delta, theta, alpha and beta electroencephalogram (EEG) frequency over the frontal, temporal, parieto-occipital regions before and after 25 sessions of n-back training in both the training and the control groups.

RESULTS

As evident in Table 2, the ANCOVA revealed that the training group had a significant increase in absolute alpha power over frontal ($F(1,19) = 5.20; \eta^2 = 0.23$) and parietal occipital ($F(1,19) = 5.84; \eta^2 = 0.27$). There was a non-significant increase over the following bands: alpha over the temporal ($F(1,19) = 1.83; \eta^2 = 0.10$); beta over frontal ($F(1,19) = 2.37; \eta^2 = 0.12$), temporal ($F(1,19) = 2.00; \eta^2 = 0.10$), and decrease in parieto-occipital ($F(1,19) = 1.47; \eta^2 = 0.08$); increase in theta over frontal ($F(1,19) = 3.00; \eta^2 = 0.15$), temporal ($F(1,19) = 1.98; \eta^2 = 0.10$), and parieto-occipital ($F(1,19) = 1.32; \eta^2 = 0.07$); decrease in delta over frontal ($F(1,19) = 2.13; \eta^2 = 0.11$) and temporal ($F(1,19) = 0.64; \eta^2 = 0.04$), and increase in parieto-occipital ($F(1,19) = 0.88; \eta^2 = 0.05$) (Figure 1). Also, the training group showed significant increases in MMSE scores ($F(1,19) = 34.17; \eta^2 = 0.50$) (Figure 2) and non-significant increases in the forward digit span ($F(1,18) = 2.22; \eta^2 = 0.12$) as well as the backward digit span ($F(1,19) = 1.79; \eta^2 = 0.10$), after the training (Figure 3).
Table 2
The comparison of resting EEG power and MMSE score differences between the control and the training group after 25 sessions of adaptive single n-back training

<table>
<thead>
<tr>
<th>Measure</th>
<th>Control group</th>
<th>Experimental group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pretest</td>
<td>posttest</td>
<td>pretest</td>
</tr>
<tr>
<td>MMSE</td>
<td>18.90 (3.34)</td>
<td>19.20 (3.15)</td>
<td>18.4 (2.72)</td>
</tr>
<tr>
<td>Forward digit span</td>
<td>3.90 (0.87)</td>
<td>4.40 (1.00)</td>
<td>4.10 (0.87)</td>
</tr>
<tr>
<td>Backward digit span</td>
<td>2.50 (0.85)</td>
<td>2.40 (1.00)</td>
<td>2.60 (1.00)</td>
</tr>
<tr>
<td>Frontal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha power</td>
<td>2.65 (0.27)</td>
<td>2.59 (0.23)</td>
<td>2.32 (0.28)</td>
</tr>
<tr>
<td>Beta power</td>
<td>2.82 (0.30)</td>
<td>2.74 (0.26)</td>
<td>2.63 (0.55)</td>
</tr>
<tr>
<td>Theta power</td>
<td>2.71 (0.30)</td>
<td>3.00 (0.20)</td>
<td>2.67 (0.29)</td>
</tr>
<tr>
<td>Delta power</td>
<td>3.43 (0.41)</td>
<td>3.39 (0.42)</td>
<td>3.51 (0.44)</td>
</tr>
<tr>
<td>Temporal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha power</td>
<td>3.00 (0.26)</td>
<td>2.89 (0.21)</td>
<td>2.70 (0.22)</td>
</tr>
<tr>
<td>Beta power</td>
<td>3.07 (0.26)</td>
<td>2.93 (0.13)</td>
<td>2.78 (0.34)</td>
</tr>
<tr>
<td>Theta Power</td>
<td>3.22 (0.28)</td>
<td>3.22 (0.45)</td>
<td>2.80 (0.29)</td>
</tr>
<tr>
<td>Delta power</td>
<td>3.73 (0.35)</td>
<td>3.67 (0.38)</td>
<td>3.66 (0.37)</td>
</tr>
<tr>
<td>Parietal occipital</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha power</td>
<td>3.18 (0.35)</td>
<td>3.09 (0.28)</td>
<td>2.77 (0.29)</td>
</tr>
<tr>
<td>Beta power</td>
<td>3.01 (0.26)</td>
<td>2.94 (0.36)</td>
<td>2.96 (0.20)</td>
</tr>
<tr>
<td>Theta Power</td>
<td>3.22 (0.32)</td>
<td>3.32 (0.39)</td>
<td>2.86 (0.24)</td>
</tr>
<tr>
<td>Delta power</td>
<td>3.62 (0.45)</td>
<td>3.69 (0.43)</td>
<td>3.32 (0.25)</td>
</tr>
</tbody>
</table>

Note. ANCOVA was used to analyze group differences between changes in the control and training groups after 25 sessions program. Values are presented as mean (SD). * Significant difference (p < 0.05) in MMSE score, digit span and absolute alpha power value.

Figure 2. MMSE score before and after 25 sessions of n-back training in both the training and control groups
Figure 3. Digit span score before and after 25 sessions of n-back training in both the training and control groups

DISCUSSION

The aim of the present study was to investigate whether cognitive training has any effects on cognitive performance and EEG spectrum at resting state in different regions of the brain. The resting state can be regarded as the starting point for subsequent task-related cognitive processes (Bragin et al., 2015). Therefore, our hypothesis was that intensive working memory training would modify this starting point and be beneficial for subsequent working memory performance.

Considering the methodological shortcomings reported in several controversial results of previous studies, we aimed to state some of these shortcomings. The studies had the main shortcomings including using a no-matched control group, not randomly allocating participants to the groups, utilizing only a single task for measuring a given cognitive ability and small sample sizes (Melby-Lervåg & Hulme, 2013; Melby-Lervåg et al., 2016; Shipstead, Redick, & Engle, 2010). Thus, we assigned the participants randomly to experimental and control groups based on the age, severity of the disease (MMSE score) and education level.

Moreover, a great deal of attention has been recently attracted by the information rooted in resting EEG. Resting state (RS) on a behavioral level represents a state of the subject with no motor task or explicit cognition related to mind-wandering, on a neurophysiological level. It has the characteristics of complex neuronal interactions spatio-temporal patterns in the brain (Bazanova & Vernon, 2014; Raichle, 2010). Simultaneously, test-retest reproducibility and heritability are represented by RS neuronal dynamics (Diaz et al., 2013; Linkenkaer-Hansen et al., 2007). According to former, there are similarities between task-related activity and RS neuronal dynamics: Functional networks including fronto-parietal networks,
interact continuously in patterns corresponding to those expressed while doing the task performance (Becker, Van De Ville, & Kleinschmidt, 2018; Mahjoory, Cesnaite, Hohlfeld, Villringer, & Nikulin, 2019). Indeed, topography of neuronal activity at rest is resembled during task. Hence, the present study aimed to study Alzheimer disease using resting state method.

After training for twenty-five sessions, the findings indicated a significant increase in MMSE that is in line with most of the previous studies on the effects of cognitive training on dementia (Bragin et al., 2015; Buschert, Bokde, & Hampel, 2010; Heinzel et al., 2016; Huntley, Gould, Liu, Smith, & Howard, 2015; Huntley et al., 2017). Although the training led to improvements in the MMSE (clinical measure of general cognitive function) of the training group compared with the control group, there was no transfer of benefit from spatial working memory task to verbal working memory task.

The lack of transference to verbal working memory could be due to the fact that as participants were trained only on their visual WM ability (updating and maintaining visual stimuli). This cognitive intervention did not transfer to their ability to store targeted exclusively by the training paradigm. Especially as there was an increase in verbal WM score, though not significantly, it is possible that by increasing the number of sessions this increase may reach the threshold of becoming significant. Furthermore, since the participants have low level of education, they may not feel confident enough to deal with numbers.

**Interpretation of EEG results**

Analysis of the EEG background activity showed a significantly increased alpha power over the frontal and the parieto-occipital. The decreased rhythm observed in the Alzheimer’s disease has been correlated with hippocampal atrophy, which is indicative of disease progression (Babiloni et al., 2006). Resting state EEG analyses indicate a decline in alpha power in the early stages of 10 Alzheimer’s disease, along with reduced alpha rhythm and a rise in the presence of low- frequency bands (Jeong, 2004). Alpha band is the dominant rhythm during the eyes- closed resting and waking states in healthy adults, which starts in the thalamo-cortical neurons, projecting into the occipital cortex (Lőrincz, Kékesi, Juhász, Crunelli, & Hughes, 2009). Previous studies that have employed the computational model (Bhattacharya, Cakir, Serap-Sengor, Maguire, & Coyle, 2013) and FMRI functional connectivity, have shown that Alzheimer’s disease disrupts the projection route (Zhou et al., 2013). The exact function of alpha power has remained as a challenging research topic and not fully comprehended as of yet (Mahjoory et al., 2019). Alpha power are connected to cognitive tasks, a connection which can be observed and measured not only during task performance but also while resting (Sadaghiani & Kleinschmidt, 2016). In the present study, regions with significant alpha power overlap with those defined for cognitive control in the working memory: frontal region (i.e., middle frontal gyrus near the precentral sulcus, right inferior frontal junction) and parietal region (e.g., the right intraparietal sulcus) (Gazzaley & D'Esposito, 2007). The working memory, in
charge of temporary storage and manipulation of information, is a system with a limited capacity (Baddeley, 2000), entailing the two components of maintenance and executive control, both of which are involved in the participant’s functioning while doing n-back (Heinzel, Schulte, et al., 2014). Maintenance of spatial rather than verbal information is referred to as the dorsal posterior lateral frontal cortex and most of the posterior regions of the brain, rather than ventral regions and executive control involves the dorsolateral prefrontal regions (Baddeley, 2003).

Moreover, the area of the dorsal attention system which gets involved in n-back task is located at the lateral premotor cortex (LPMC)/caudal superior frontal sulcus (cSFS), in the posterior parietal cortex (Linden, 2007) and subcortical regions (Frank, Loughry, & O’Reilly, 2001), thus it can be a possible explanation as to why the significant changes were manifested in the frontal and posterior areas. Alpha activity, furthermore, shows functional inhibition at the neuronal level, involved in rhythmic updating (Chakravarthi & VanRullen, 2012), gating of information (Jensen & Mazaheri, 2010), and information coding (Jensen, Bonnefond, & VanRullen, 2012). It can be stated that alpha plays a role, both in the inhibition of task-irrelevant networks, and the scheduling of relevant ones. It also is an important player in attention via intervention in the brain’s processing, focusing attention and blocking attention-irrelevant process (Klimesch, 2012). It is possible to say that n-back as a working memory training improved working memory in patients with early stage of Alzheimer disease But in order to determine whether the improvement in working memory was caused by or mediated by improvement in attention or/and inhibition, it should be investigated in further study in which wide range of cognitive and neurophysiological assessments are applied.

Limitations of the present study include the small number of participants and their low education levels, as well as not having a follow up in the experimental design. Not having used other neurophysiological tools such as event related potential (ERPs) is next the limitation. In light of data derived from ERP many aspects of human brain can be studied. For example, it helps to study anterior and posterior cortical regions and contribution of dopaminergic and adrenergic (NE) pathways in cognition and in the development of the resting state network.

Overall, our study indicated that visual n-back training improves general cognition or, to say, reduces the cognition decline severity of Alzheimer's disease at an early stage; however, this improvement is not seen in the verbal working memory area. Therefore, the present study is in line with those papers showing that n-back training can enhance general cognition, and those findings that illustrate n-back training gains poor transference. The improvement in working memory or cognitive domain can also be seen through an increase in alpha power at frontal and parietal occipital regions, which are related to the maintenance of spatial information. Further study on long term effects of working memory training is required to extent our research.
REFERENCES


