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Quantitative EEG Neurometric Analysis–Guided Neurofeedback Treatment in Dementia: 20 Cases. How Neurometric Analysis Is Important for the Treatment of Dementia and as a Biomarker?

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Abstract

Dementia is a debilitating degenerative disorder where the sufferer's cognitive abilities decline over time, depending on the type of dementia. The more common types of dementia include Alzheimer's disease and vascular or multi-infarct dementia. In this study, 20 subjects with dementia (9 of Alzheimer's type, and 11 with vascular dementia) were treated using qEEG-guided neurofeedback training. The Mini Mental Status Examination (MMSE) was used as the primary outcome measure. The results showed an increase of the MMSE scores for all subjects regardless of dementia type with an average MMSE score increase of 6 points, which was found to be significant. To our knowledge this is the first time the same modality was shown to be beneficial in both dementia groups.

Keywords

dementia, neurofeedback, qEEG, neurometrics, Alzheimer's disease, vascular dementia, multi-infarct dementia, NxLink database, EEG, MMSE

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Introduction

According to *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*),[1] dementia requires the development of multiple cognitive deficits manifested by both (*a*) memory impairment (impaired ability to learn new information or to recall previously learned information) and (*b*) one or more of the cognitive disturbances such as aphasia, apraxia, agnosia, and disturbance in executive functioning. It is a degenerative disorder where the sufferers cognitive abilities decline over time. The speed of the decline depends on the type of dementia and on the individual. Currently, dementias are believed to be irreversible. The more common types of dementia include Alzheimer's disease (AD), and vascular or multi-infarct dementia (VD).

Although the loss of cognitive functions is debilitating in itself, more than 80% to 90% patients with dementia experience some form of behavioral symptoms such as anxiety, agitation, depression, and apathy during, the course of the disease.[2-4] These symptoms and mood disorders are among the most difficult aspects of dementia and are a major cause of additional disabilities, patient distress, caregiver burden, and institutionalization.[5,6] Current treatment strategies consist of a series of therapeutic interventions, both pharmacologic and nonpharmacologic with the goals of delaying the progression of the disease and its associated functional decline, improving the quality of life and dignity of patients and their caregivers, controlling symptoms, and providing comfort during all the stages of dementia.

For controlling the neuropsychiatric symptoms of dementia such as agitation, aggression, and delusions, nonpharmacological and pharmacological symptomatic therapies are available.[7]

Cholinesterase inhibitors can be effective in maintaining cognitive functions in mild to moderate AD, but they are less effective for very mild or severe forms of the disease and are only 40% to 50% effective.[8] No drugs have been approved for VD; however, these drugs are used off label. Most of the

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research has focused on how best to treat individuals that already have the disorder in order to improve their quality of life. One approach that has shown great potential involves the use of quantitative electroencephalography (qEEG)–guided neurofeedback (NF) training. Other conditions that show an increase in theta activity, such as attention deficit hyperactivity disorder (ADHD) have been shown to respond positively to theta downtraining and beta uptraining using NF. Dementia, which also shows an increase in slow activities and a decrease in higher frequency activities may also benefit from the same type of NF treatment. Recent work has shown that default mode network (DMN) abnormalities have been found in ADHD[9] and Alzheimer's disease.[10] This network may serve as a regulatory function in a healthy brain.

Studies that use qEEG in dementia patients are in agreement with conventional EEG findings and report increased delta or theta power,[11-26] a decreased mean frequency,[23,27-29] decreased beta power,[24,30] and decreased occipital dominant frequency.[15,20] The amount of theta activity shows the best correlation with cognitive deterioration[25,31-35] and clinical outcome in longitudinal follow-up.[21,24,25,36,37] Increased delta seems to be a correlate of severe advanced dementia that occurs subsequent to increased theta.[25,37,38]

Multiple studies report accurate discrimination of patients with AD from depressed patients and normal controls using qEEG measures of slow activity. Several qEEG studies of dementia patients report high correlations between the severity of cognitive impairment and amount of EEG slowing. These features are absent in depression and are localized in multi-infarct dementia, which enables these disorders to be differentiated from Alzheimer's type dementia.[11,27,39,40]

EEG Biofeedback

Neurofeedback is an operant conditioning paradigm aimed at training individuals to better regulate the biological functioning of their own brain by the self-regulation of EEG rhythmic activity, and is traditionally referred to as EEG biofeedback, NF, or neurotherapy.

In NF training, the EEG is acquired and analyzed and the resultant frequency activity parameters are fed back to the subject in the form of a graphical display and/or auditory tones. The desired activities can be either enhanced or inhibited. The changing of desired activities is controlled by setting thresholds and these thresholds determine whether the display moves or stops, and/or the tones play or stop. As the sessions are repeated, the thresholds are gradually modified inhibiting the undesired activities and reinforcing the desired activities thereby conditioning to endure these activities.[41] Since the 1960s studies have shown that through neurotherapy patients can be taught to promote normal functioning in the brain by normalizing dysfunctional brainwave patterns characterized by excessive slow wave activity. A standard practice in neurofeedback is to analyze a baseline qEEG during an initial assessment, and build custom NF protocols designed to reward the normalization of each client's individual abnormalities.[42,43]

Ros et al[44] were able to show that at around 30 minutes after training, NF induced a statistically significant upregulation of functional connectivity within the dorsal anterior cingulate/mid-cingulate cortex (dACC/MCC) of the salience network in the experimental but not in the sham group. Hence utilizing functional magnetic resonance imaging (fMRI) and a placebo-control group they were able to extend the findings of Ros et al[44] demonstrating that the adult cortex is sufficiently plastic that a mere half hour of targeted volitional activity (ie, NF) is capable of intrinsically reconfiguring the brain's functional activity to last above and beyond—and at least as long as—the time period of training itself. Therefore, they concluded that accumulating data suggest that maintaining the cortex in a persistent oscillatory pattern via NF effectively "conditions" the neuronal circuits to produce the same pattern with a higher probability in the future.

A recent study by Ghaziri et al[45] showed that a NF protocol designed to improve sustained attention showed increased fractional anisotropy in white matter pathways implicated in sustained attention, and gray matter increases were detected in cerebral structures involved in this type of attention using structural MRI. When beta1 activity was increased by using NF training, a significant enhanced visual and auditory sustained attention performance was observed as measured by the integrated visual auditory (IVA) continuous performance test.

Thus, both these studies show that NF training is not only capable of inducing changes in brain structure that is associated with the functions being trained but also that these changes last even after the training has ceased, suggesting a promising basis for its use to treat cognitive disorders under physiological conditions.

A summary of the latest NF studies investigating the effect on cognitive functions are given in Table 1. Some of these results indicate that an elderly individual can be trained to modify the amplitude of certain wave ranges and to regulate brain EEG activity more efficiently.

Because of the above listed effects of NF, the current study was conducted to investigate the following:

- By using qEEG neurometric analysis as a biomarker, is it possible to differentiate other axis I diagnoses (eg, depression) from dementia, and if it is possible to differentiate between AD and VD.
- If this group could benefit from qEEG-guided and individualized NF treatment in a clinical setting, without any other treatment.
- Can the changes in the subject's core dementia symptoms, induced by NF training, be measured objectively using validated measures (MMSE, Clinical Global Impression [CGI], Test of Variables of Attention [TOVA], and qEEG)?

Methods

The study included 20 subjects (mean age 68.9 ± 10.6 years) of whom 9 (mean age 62.9 ± 12.3 years) were male and 11 were female (mean age 68.4 ± 9.6 years). Of the 20 subjects, 4

Table 1. Summary of Studies of Cognitive Effects of Neurofeedback (NF).

Study	Study Type	Neurofeedback	Improvement in
Vernon et al (2003)[46]	Healthy control group	Only 8 sessions of NF	Memory recall
Angelakis et al (2007)[47]	Double-blind controlled in a small sample of normal *elderly* adults	Rewarding the dominant alpha frequency	Cognitive processing speed and executive function
Hoedlmoser (2008)[48]	Randomized parallel group design healthy subjects	Only 10 sessions of NF	Sleep onset latency and subsequent declarative learning
Festa et al (2009)[49]	A controlled study with 26 elderly subjects with *early-stage Alzheimer's disease*	Trained to normalize brain waves outside norms in 4 brain areas (C3, C4, P3, P4)	Selective improvement in the efficiency of processing within the posterior sensory cortical network
Berman and Frederick (2009)[50]	27 subjects with *dementia* compared with a waiting list control	NF	Memory and some aspects of executive function
Keizer et al (2010)[51]	17 healthy subjects (15 completed 8 sessions and 2 completed 7 sessions)	Uptraining of gamma and beta	Gamma-targeted training improved recollection, whereas beta-targeted training improved familiarity memory
Escolano et al (2011)[52]	16 healthy subjects NF vs control group	Enhancing the upper alpha	Working memory
Zoefel et al (2011)[53]	14 healthy subjects NF vs control group	Five sessions within 1 week by means of feedback dependent on the current upper alpha amplitude	Enhancement of cognitive performance larger for the NF group than for a control group
Becerra et al (2012)[54]	14 healthy *elderly* subjects randomized controlled trial	Theta absolute power was reduced	Experimental group showed greater improvement in EEG and behavioral
Nan et al (2012)[55]	Randomized control 16 healthy subjects	Uptraining of alpha activity	Improvement of short-term memory was positively correlated with the increase of the relative amplitude in the individual upper alpha band during training
Guetz et al (2014)[56]	30 healthy subjects randomized, sham controlled, double blind	Uptraining of upper alpha, sensory-motor rhythm (SMR)	While the SMR protocol resulted in improving automatic, item-specific and familiarity-based processes in memory, the upper alpha protocol resulted in improved strategic and controlled recollection
Koberda (2014)[57]	250 patients uncontrolled	LORETA *Z*-score	71% of static cognitive dysfunction patients showed objective improvement. Most of the patients showed subjective improvement and reduction of qEEG abnormalities

completed university (20%), 2 graduated from high school (10%), 1 graduated from middle school (5%), and 13 had an elementary school education (65%). The average length of illness was 3.3 ± 1.8 years. An informed consent was obtained from all subjects, and from the subjects who could not provide and informed consent, one was obtained from a family member.

Inclusion Criteria

All patients met the *DSM-IV* guidelines for dementia and had to have total MMSE score of 26 or less. Finally, the baseline Food and Drug Administration (FDA)–approved NxLink database classification needed to show similarity with the primary degenerative dementia (AD) or primary degenerative dementia of vascular origin (VD) discriminants at the $P < .1$ level or better and be confirmed by the interviewing physician. Additionally, the subjects should not have a major physical illness and the baseline laboratory tests (hemogram, vitamin B_{12}, vitamin B_6, folic acid, thyroid-stimulating hormone) had to be normal.

Exclusion Criteria

Exclusion criteria were

- Electrophysiological changes classified by the NxLink database as being similar to those seen in depression at the $P < 0.1$ level or better.

- Any clear evidence of delirium or a history of any other psychiatric disorder (eg, schizophrenia, anxiety disorder, primary insomnia, head trauma, etc), suicide risk, abnormal blood test results, and any other physical or neurological condition that would preclude them from inclusion.

The demographic and medical information for the subjects is given in Table 2.

Each subject was administered an MMSE at screening and after every 10 hours of NF treatment to monitor the course of the treatment. In addition, the visual subtest of the TOVA test was administered to all subjects at baseline and every 10 hours of NF treatment. The evaluations performed every 10 hours were used to monitor the treatment and adjust the protocol. For the purposes of this study, only the pretreatment and very last evaluations were included. A pretreatment medication-free qEEG was recorded for each of the 20 subjects. In order to ensure that the baseline EEG was not contaminated by any medication, all subjects were washed out for up to 7 half-lives of the medications they were taking (eg, if they were on donezepil, the its 7 half-lives is 21 days, so qEEG was recorded on the 22nd day). All qEEGs were recorded with an FDA-approved Lexicor Neurosearch-24 qEEG system (software version 3.10). The electrodes were applied using an Electrocap by ElectroCap International. Nineteen channels were recorded eyes closed with the subject reclining in a resting position. Ten minutes were recorded and during the recording artifact and vigilance control was performed by a trained electrophysiologist medical doctor who was blinded as to the diagnosis and the treatment protocol selected for the subjects. EEG signals were sampled at 128 samples per second per channel. After the recording an artifact-free 1-minute sample was selected from the 10-minute recording to be submitted to the normative comparison software. The selection was done by the first author who is a board-certified qEEG expert. The selected 1 minute samples were analyzed with a normative neurometric approach using the Nx-Link database software (version 2.40). The FDA-approved NxLink database software is based on the work of E. Roy John.[39] In neurometric QEEG analysis, the raw digital EEG is analyzed and a set of predetermined multivariate features are extracted from each of the recorded brain areas. Measures include the absolute and relative power of the standard delta, theta, alpha, and beta bands for each of the recorded brain areas along with measures of symmetry and coherence. These multivariate features are then compared against an age-stratified normative database called the NxLink database, which has validated normal values for each of the multivariate features across all age groups. The comparison yields the deviation from normal in the form of standard deviation units (z-scores). In this way, any significant deviation from normal (z-scores above and below 1.96) can be easily ascertained. The rationale of qEEG-guided NF is that by normalizing (bringing the z-scores to be between ±1.96 or better) in areas that show deviation will also improve the symptoms controlled by the brain areas that show deviation. A second comparison that is done is comparing the subjects multivariate features extracted for the raw digital EEG to a database of multivariate features of different diagnostic groups (unipolar depression, bipolar disorder, schizophrenia, postconcussive syndrome, dementia, ADHD, and learning disabilities), which can also be used as a biomarker for the disorder.[58]

Neurofeedback Treatment

All the NF training was performed using FDA-registered Thought Technology Infinity (version 6). Each session was of 60-minute duration with a 5-minute break after 30 minutes of training. Sessions were administered daily.

Electrodes were placed according to the international 10-20 system. Between 10 and 96 hours, NF training sessions were completed, depending on the case. Treatment termination was based on the changes (a decrease) of symptoms in comparison to the pretreatment complaints. The mean number of sessions was 45.0 ± 27.3 hours. Electrode sites for training were selected based on the qEEG analysis (using the Nx-Link database). The location of the deviant z-scores is most important no matter what the EEG measure. A general rule is to link the patient's symptoms to deviant z-scores located in regions of the scalp related to functional specialization in the brain and the patient's symptoms.[59-61]

The most commonly trained brain areas were

Monopolar (linked to ipsilateral ear): FP1, FP2, F3, F4, C3, C4, O1, O2.

Although the normative comparisons were done using a linked ear reference the training system did not include the ability to use a linked ear reference and therefore the ipsilateral ear was used the rationale being that this change in reference would not affect the training since the difference would be negligible for these purposes

Bipolar: FP1-F3, Cz-C4, P3-T5, FP1-F7, P4-T6.

The most commonly used protocols were

Inhibit Delta, inhibit Theta, inhibit Beta (21-32Hz)
Inhibit Delta, inhibit Theta
Inhibit Alpha Coherence, inhibit Alpha, inhibit Delta

The list given below is a general summary of training protocols used for the study.

The monopolar sites given below were selected according to subjects' qEEG. The criteria to shift from one site to another were based on the z-score findings of the QEEGs[59] repeated every 20 sessions. Since only 2 channels were used for training, each 2 sites were trained for approximately 10 sessions and then the training was performed on the next 2 sites. In this way, the head was covered. The bipolar sites were selected based on the scientific literature and are as follows:

Table 2. Demographic Information of Subjects.

Subject No.	Sex	Education	Age (Years)	Length of Illness	Previous Dx	Current Dx	Treatment Rx	MRI Findings
1	M	PS	60	4	DEP	VD		Cortical atrophy, lateral ventricual asymmetry, nonspecific findings in deep bifrontal areas
2	F	PS	63	5	AD	VD	Donezapil, memantine, citalopram, quetiapine	Advanced cortical atrophy, which may be indicative of Alzheimer's disease
3	F	PS	71	3	DEP	AD	Citalopram	Noticeable cerebral-cortical central atrophy
4	M	UN	73	3	AD	AD		Cerebral-cortical central atrophy
5	F	PS	54	3	ND	VD	Olanzepine	Semiovale and periventricular microangiopatic ischemic gliosis in the deep white matter of the bilateral frontoparietal areas
6	F	PS	67	2	DEP/DE	AD	Donezapil, mitrazepine, citalopram, piracetam, memantine, vanlafaxine, rivastigmine, reboxatine	Central cerebral cortical atrophy, and diffuse white matter signals relating high-grade microvascular ischemia
7	M	PS	68	4	AD	VD	Donezapil, ginkgo biloba	Lacuner infarcts in bilateral thalamus and pons. Some binding of ischemic-gliotic lesions observed in the bilateral forceps major and minor, corona radiate, insular cortex and in subcortical white matter. Noticeable cerebral atrophy
8	M	UN	87	9	DEM	AD	Donezapil, memantine, citalopram	Marked cerebral atrophy indicative of a neurodegenerative process. Pontin ischemia and signals indicative of a high-grade microvascular ischemia observed in both cerebral hemispheres
9	F	PS	82	2	AD	AD	Donezapil, quetiapine	
10	M	HS	58	3	AD	VD	Donazepil	An asymmetric expansion of the hemispheric sulci, more prominent in the left parietal area and an expansion of the lateral ventricles (related to cortical cerebral atrophy)
11	F	PS	79	1	AD	VD		Expansion of the cortical sulci related to an atrophy of the sylvian fissure. Evidence of chronic ischemic-gliotic changes in the periventricular areas, the centrum semiovale and in deep subcortical white matter structures
12	M	PS	59	6	DEP	AD	Pimozide, citalopram alprazolam, trazedone, paroxetine, maprotiline, amitriptyline, lamotrigine, clomipramine, valnafaxine, sertraline, mianserin, quetiapine, olanzepine, thioridazine, mitrazepine	Cerebral cortical atrophy. Pathologic signals related to microvascular ischemic glioses in the white matter bordering the lateral ventricles

(continued)

Table 2. (continued)

Subject No.	Sex	Education	Age (Years)	Length of Illness	Previous Dx	Current Dx	Treatment Rx	MRI Findings
13	M	PS	86	2	DEP	AD	Mitrazepine, alprazolam, imipramine, paroxetine, velnaflaxine	Cerebral atrophy. Diffuse chronic gliotic ischemic foci observed in the bilateral centrum semiovale corona radiate, in the periventricular white mater and at the basal ganglion level
14	M	PS	58	2	DEP	VD	Rivastigmine, memantine, ecitalopram, piracetam	Prominence of the cortical sulci especially in the bifrontoparietal areas. Nonspecific signals (ischemic-gliotic?) in the left frontal lobe and the periventricular deep white matter
15	F	HS	85	3	DEP	VD	Donezepil, memantine, galantamine, ginkgo biloba	Advanced cerebral cortical atrophy with signals related to a low-grade microischemia in the white matter
16	F	MS	72	1	AD	AD	Cinnarizine	Advanced cerebral cortical atrophy
17	F	UN	69	3	AD	VD		Cerebral cortical atrophy with signals related to a low grade microischemia in the white matter
18	M	UN	55	3	VD	VD	Escitalopram, rivastigmine	
19	F	PS	52	3	DEP	AD	Psychotherapy	Expansion of the hemispheric sulci and lateral ventricles
20	F	PS	68	4	VD	VD	Oxcarbazepine	Noticeable advanced asymmetric cerebral atrophy on the right side

Abbreviations: DX, diagnosis; Rx, prescription; M, male; F, female; UN, university; HS, high school; MS, middle school; PS, primary school; AD, Alzheimer's disease; VD, vascular dementia.

FP1-FP2, Fp1-F3, F3-Fz, F7-F8: Theta or alpha inhibit, delta inhibit, beta (21-32 Hz) inhibit to improve attention, short-term memory, and word finding.
F3-C3, Cz-C3: reward beta (15-18Hz), inhibit theta (4-8Hz) bipolar montage to improve mood.

Left frontal, central-temporal-parietal-occipital area electrode sites were selected for procedural memory and brain area 24, the anterior cingulate for being the hub of the affective limbic system. Brain area 40 representing cognitive reasoning and imagination was also used.

F3, Fz, F4: Theta or alpha inhibit, delta inhibit, beta (21-32 Hz) inhibit bipolar montage
F7-T5: Theta or alpha inhibit, delta inhibit, beta (21-32 Hz) inhibit bipolar montage
F7-T5: Beta (14-18 Hz) reward, Theta or alpha inhibit, delta inhibit bipolar montage
Cz-C4 SMR reward, Theta or Alpha inhibit, Delta inhibit, bipolar montage
P3-T5: Beta(14-18 Hz) reward, Theta or Alpha inhibit, Delta inhibit bipolar montage
P3-T5: Theta or Alpha inhibit, delta inhibit, Beta (21-32 Hz) inhibit bipolar montage
Pz-O1, Pz-O2, Pz-P4, P4-T6, T3-T5, T4-T6: Theta or Alpha inhibit, Delta inhibit, beta (21-32 Hz) inhibit bipolar montage[59]

The sensory area was selected for sleep regulation. BA 24 anterior cingulate: hub of affective limbic system.

Cz-C4: Reward SMR, Delta-inhibit, Theta-inhibit, bipolar montage[62]

Coherence training was performed according to *z*-scores. Hypercoherence (increased coherence in comparison to norms) can be considered as a lack of differentiation of brain functions or as a decrease in "flexibility" of functioning[59]:

FP1-FP2, F3-F4, P3-P4, O1-O2: coherence-inhibit, Alpha-inhibit, Beta(21-32)-inhibit, or Beta(13-32)-inhibit, bipolar montage

Results

The baseline NxLink database classification showed similarity with primary degenerative dementia (AD) in 9 cases; primary degenerative dementia vascular origin (multi-infarct dementia) in 11 cases.

The diagnoses given to the subjects before coming to our center and the symptoms recorded are given in Table 3.

The most common diagnosis after AD (40%) was a primary diagnosis of depression (40%). When the subjects were evaluated in our center, a dementia diagnosis was confirmed (Table 3, panel A). Most patients suffered from sleep disturbances and anhedonia (75% and 65%, respectively) followed by anxiety and nervousness (40% and 30%, respectively; Table 3, panel B).

When the psychotropic medications the subjects had taken over their lifetime, and the treatment they were on when they came to our center was tabulated it was observed that most of the subjects (55%) were given more than one treatment medication (Table 4a).

Table 3. Previous Diagnoses and Symptoms Summary.

Diagnosis/Symptoms	n	%
A: Diagnosis		
Alzheimer's disease	8	40
Depression	8	40
Vascular dementia	2	10
Depression and dementia	1	5
Dementia	1	5
B: Symptoms		
Sleep disturbance	15	75
Anhedonia	13	65
Anxiety	8	40
Nervousness	6	30
Problems urinating	3	15
Ringing in ears	2	10
Paranoia	2	10
Dizziness/loss of balance	1	5
Obsessions	2	10

Table 4. Summary of Treatment Drugs.

A: No. of Treatment Drugs Used

No. of Drugs Used	Drugs Over Lifetime		Drugs at Admission		Drugs After Treatment	
Mean	2.9		1.6		0.00	
SD	3.8		1.4		0.00	
No. of Different Drugs	n	%	n	%	n	%
0	4	20	7	35	23	100
1	5	25	4	20	0	0
2	3	15	2	10	0	0
3	2	10	6	30	0	0
4	3	15	1	5	0	2
≥5	3	15	0	0	0	0

B: Types of Treatment Drugs Used

Drug Type	Over Lifetime, %	At Admission, %
Antidementia	45	40
Antipsychotic	15	30
Antidepressant	30	30
Cognitive activator	15	5
Antiepileptic	10	5
Anxiolitic	10	10

Table 5. NxLink Diagnosis.

Discriminant	n	%
Alzheimer's disease	9	45
Vascular dementia	11	55

The most common treatment was an antidementia drug, followed by antidepressants and antipsychotics (Table 4, panel B). The diagnoses obtained when the baseline qEEGs of this population were compared against the NxLink database are presented in Table 5.

The evaluating physician confirmed these diagnoses.

MMSE: The Mini Mental State Examination Results

The most widely used test for globally assessing cognitive functioning is the MMSE, which assesses orientation, registration, attention, calculation, memory, language, and visuospatial abilities.[63] The MMSE was evaluated by a neuropsychiatrist who was blinded as to the electropysiological evaluations and the treatment protocol of the subjects.

The results are given in Table 6 and Figure 1.

The pre-post changes were analyzed using a 1-way analysis of variance (ANOVA) with correction for intra- and intersubject variability. According to the results, an average 6-point increase in the MMSE scores were observed and these changes were seen regardless of the dementia type. In this particular group, 3 patients had come to us with MMSE results conducted previously. For illustrative purposes, the previous MMSE results were plotted along with the results obtained in this study, and are given in Figure 2.

Although these 3 subjects were being treated, a decline in their MMSE scores was observed. After NF treatment not only was this decline arrested, but the scores increased passed their previous MMSE score. Because of the small sample size, these data are being presented for illustrative purposes only.

Despite being treated for their disorder, all these patients declined as evident from their MMSE scores. After NF treatment all 3 show a dramatic increase in their MMSE scores.

When the changes in the MMSE subscores were analyzed (Table 7, Figure 3), a general increase was observed in all the scores. The increase in the Orientation and Recall subscales were found to be significant (using a *t* test for unequal variances).

Since education levels of the subjects varied, the effect of education was analyzed using a 2-factor ANOVA. The results showed a significant main effect for treatment, $F(1, 19) = 8.07$ ($P < 0.01$, $\eta^2 = 0.19$). Education alone and the interaction of treatment and education were not significant. There was no relation between the number of sessions and the magnitude of the changes.

TOVA: Test of Variables of Attention Results

The TOVA is a continuous performance test designed to objectively measure attention, impulsivity and adaptability in a clinical setting with norms for ages from 4 to 80+ years. It provides objective measurement in the diagnosis and treatment monitoring of attention problems in disorders that cause disturbances in attention. It is a 21.6-minute task that records the speed, accuracy and consistency of responses to a visual or an auditory stimulus presented in 2-second intervals. These measurements (accurate to ±1 ms) are then compared against a normative group. The results of the TOVA test are reported as standard scores (average standard = 100, SD = 15). Standard scores above 85 are considered to be in the normal range, scores between 80 and 85 are considered borderline, and scores less than 80 are outside normal limits. Scores less than 70 are considered significantly below normal ranges.[64,65] The visual portion of TOVA was conducted at baseline and after treatment. As the results given in Table 8 and Figure 4 show, there is an increase (normalization) in the TOVA scores after treatment where the subjects show significantly less commission errors. There is an improvement in the other variables; however, they were not significant, which may be related to the high variance (divergent levels of performance) in the group.[66]

CGI: Clinical Global Impressions Results

The CGI rating scale is a commonly used scale that measures symptom severity, treatment response and the efficacy of treatments in studies of patients with mental disorders.[67] In this study, changes in the severity scale, pre- and posttreatment were assessed by the same neuropsychiatrist who performed the MMSE evaluations. The results are given in Figure 5.

The average CGI Severity score for the group was 3.9 (±1.2) at the beginning of the study, and at the end of treatment the average CGI Severity score was 2.3 (±1.3). This change was found to be significant.

Quantitative EEG Results

After completing treatment, a follow-up qEEG was recorded from all patients, and the NxLink database comparison was rerun. The results showed that 5 (1 AD and 4 VD) patients did not classify as being similar to the dementia cohort of the database anymore, and another 5 patients (4 AD and 1 VD) decreased their probability, of classifying as similar to the dementia database (4 from $P = .025$ to $P = .05$, and 1 from $P = .05$ to $P = .1$).

After treatment, an overall decrease in theta activity was observed, $F(1, 19) = 7.44$, $\eta^2 = 0.29$, $P < .01$ (based on repeated-measures ANOVA correcting for intersubject variability). An increase in alpha and beta activities were also observed but these were not statistically significant.

A significant decrease, $F(1, 19) = 56.71$, $\eta^2 = 0.75$, $P < .01$ (based on repeated-measures ANOVA correcting for intersubject variability), in interhemispheric coherence was also seen after treatment.

Discussion

This study shows that NF treatment was effective in this group of subjects regardless of the type of dementia they had. This is

Table 6. Summary of Mini Mental State Examination (MMSE) Scores.

A: Changes in the MMSE Scores	All Patients	Alzheimer's Disease	Vascular Dementia
n	20	9	11
Pre Mean	18.80	19.22	18.45
Post Mean	24.50	25.22	23.91
Pre SD	6.40	7.63	5.56
Post SD	5.78	6.50	6.34
Change	5.70	6.00	5.45
$F(1, 19), (1, 8), (1, 10)$	101.03	117.82	33.15
$\eta^2(1, 19), (1, 8), (1, 10)$	0.84	0.94	0.77
Significance	$P < .01$	$P < .01$	$P < .01$

B: Changes in the MMSE Scores of Subjects Who Had Previous MMSE Scores

Subject No.	Previous MMSE	Pre MMSE	Post MMSE	Years Between Previous and Pre
1	15	14	28	4
2	26	23	27	4
3	25	17	23	3

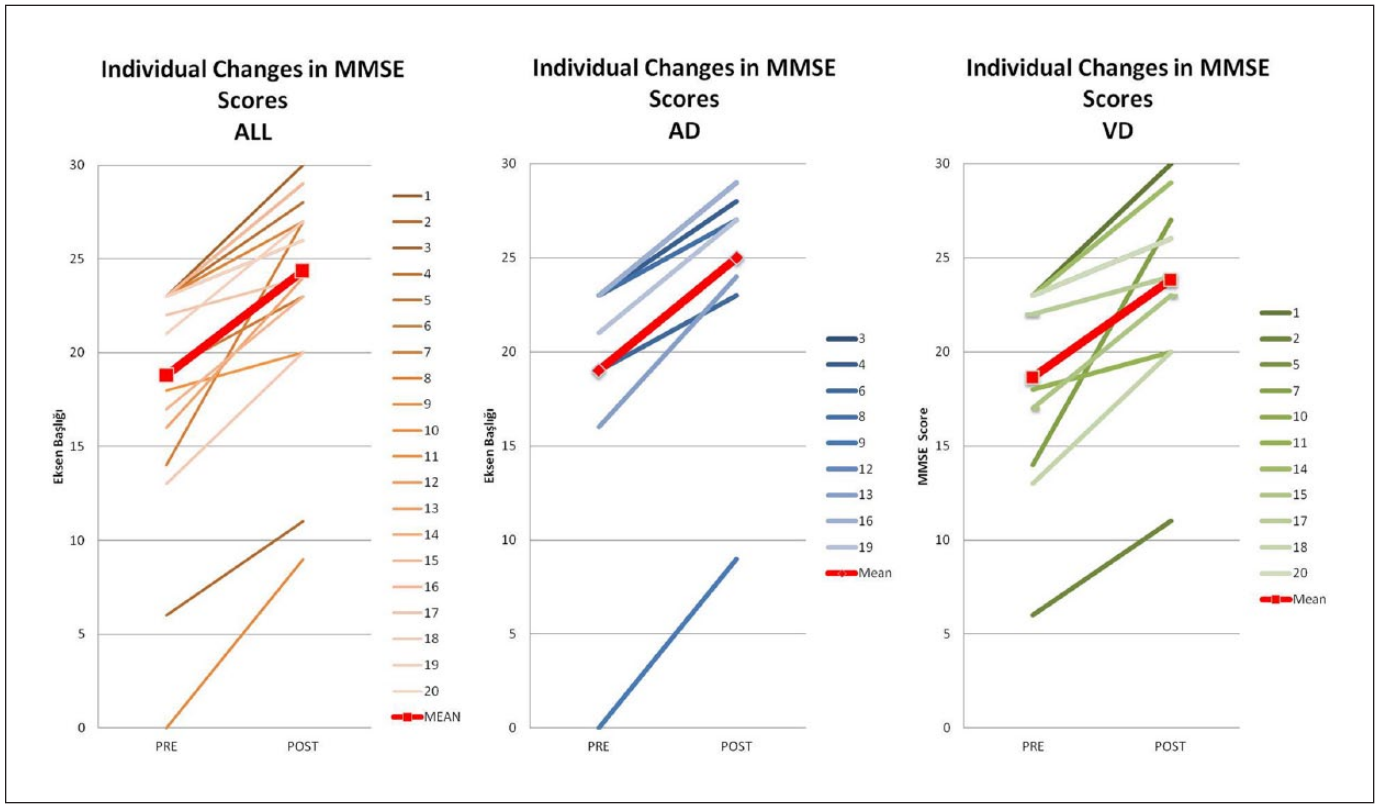

Figure 1. The pre and post Mini Mental State Examination (MMSE) values are shown here for all patients (ALL), and the 2 diagnostic groups separately (AD = Alzheimer's disease, VD = vascular dementia). After neurofeedback (NF) training, the MMSE scores show an increase, and these changes were found to be significant at a $P < .001$ level, based on an analysis of variance with correction for inter- and intrasubject variability.

especially important since drugs for dementia are only effective in 50% of patients and in some patients, they can have serious side effects.

Bellelli et al[68] showed that at 9 months of acetylcholinesterase inhibitor (ACHEI) treatment only naive patients improved, whereas nonnaive patients decreased their MMSE score.

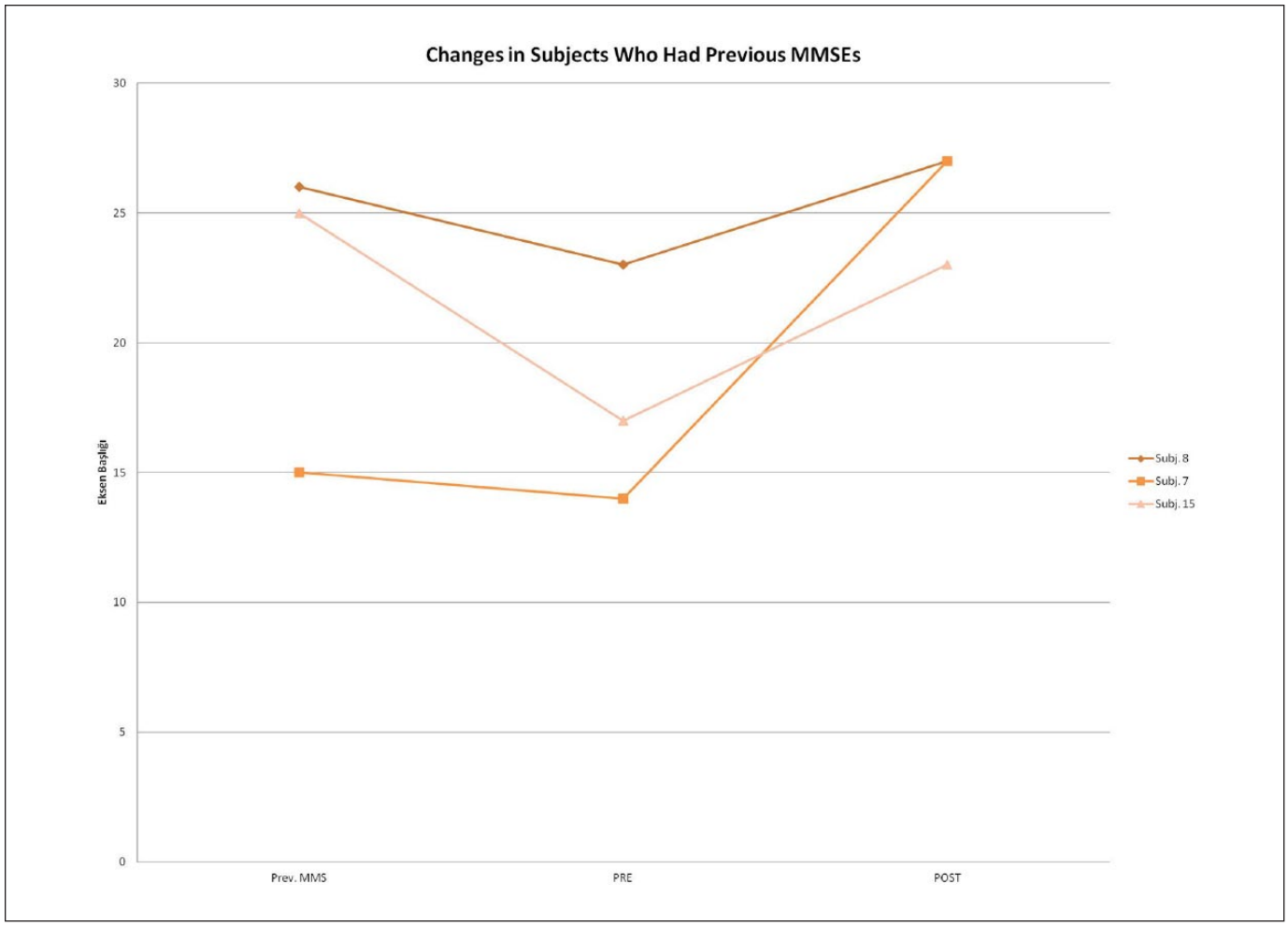

Figure 2. In this figure, the changes in Mini Mental State Examination (MMSE) scores of 3 subjects who had MMSE results previous to coming to our center are shown. Although they were under treatment, the MMSE scores declined when they were evaluated at our center. Neurofeedback (NF) treatment was not only able to recover the decline but increase the MMSE scores.

Table 7. Changes in the Mini Mental State Examination (MMSE) Subscales.

	Orientation	Registration	Attention	Recall	Language	Copying
Pre	5.7	2.5	3.6	0.4	5.6	0.7
Post	7.9	2.9	4.4	1.4	6.8	1.2
Pre CI	4.52-6.88	2.02-2.98	2.68-4.52	0.05-0.75	4.59-6.61	0.09-1.31
Post CI	6.72-9.08	2.81-2.99	3.70-5.10	0.83-1.97	5.97-7.63	0.41-1.99
Change	2.21	0.47	0.74	1.00	1.16	0.42
Significance	$P < .01$	NS	NS	$P < .01$	NS	NS

Abbreviations: CI, confidence interval; NS, nonsignificant.

Raschetti et al[69] showed that at 9 months, improvement was restricted to those patients who were good responders at 3 months. The study by Calabria et al[70] shows the efficacy of ACHEI treatment in population of mild-to-moderate AD patients enrolled in a "real-world" observational study, with a 21-month follow-up. The results show that the naive patients gained 1.6 MMSE points after 3 months of treatment, remain stable until 15 months, and declined by 1.2 points at month 21. Nonnaive patients show a minor improvement at month 3 (0.7 MMSE points) and decline faster, dropping by about 4 points at month 21.

Birks and Harvey[71] reviewed 16 randomized controlled trials showing that donepezil improved the cognitive functions in both 5 and 10 mg/d after 24 weeks, about 1.5 points on the MMSE versus placebo groups, and in 10 mg/d after 52 weeks (about 2 points on MMSE). Galantamine- and rivastigmine-

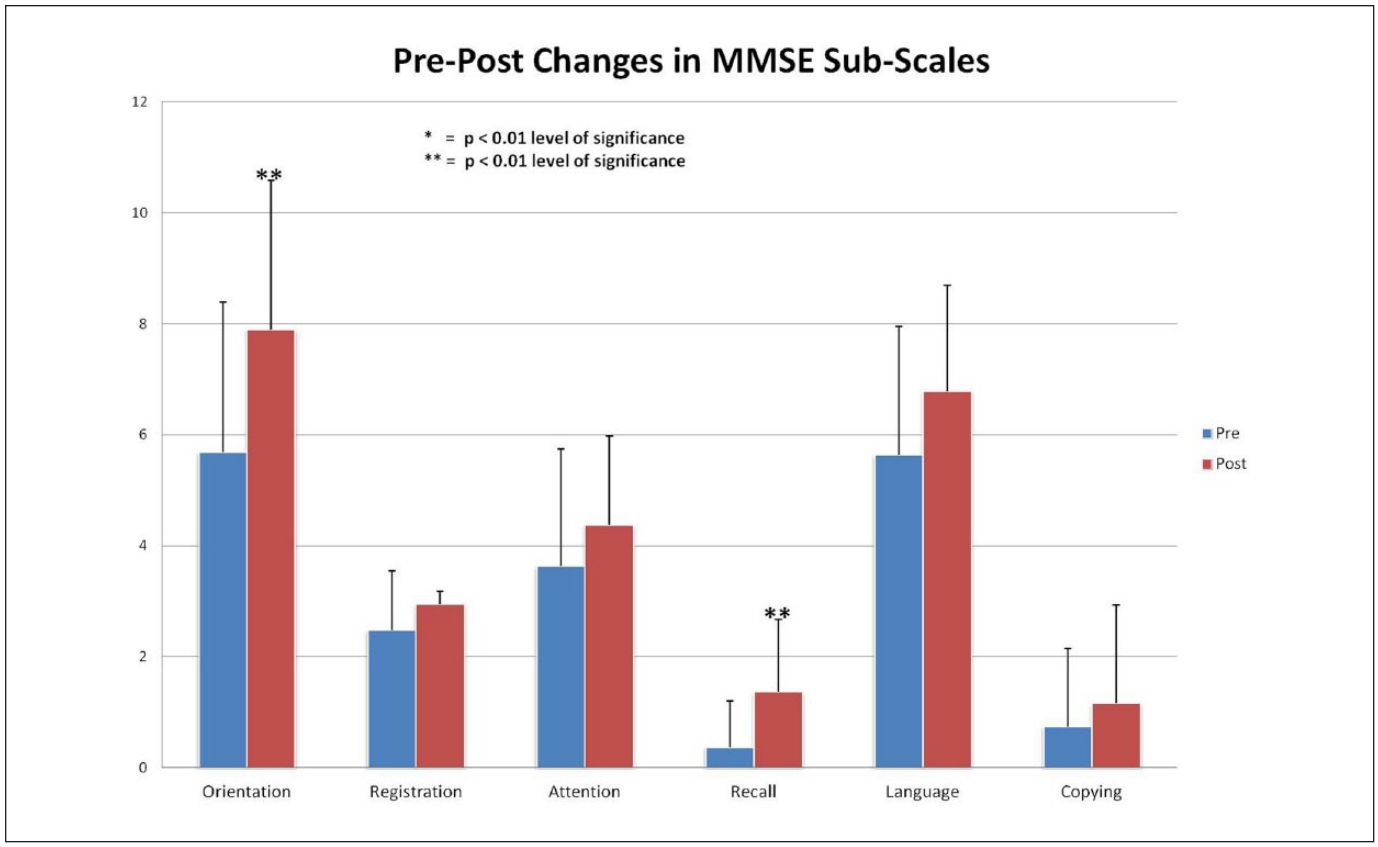

Figure 3. When the Mini Mental State Examination (MMSE) subscales were analyzed, a statistically significant increase ($P < .01$) in the Orientation subscale scores and a statistically significant increase ($P < .01$) in the Recall subscale scores were seen.

Table 8. Changes in the Visual TOVA Test.

	Omission Errors	Commission Errors	Reaction Time	Reaction Time Variability
Pre	69.2	79.8	98.2	65.2
Post	78.4	108.1	104.4	83.2
Pre CI	54.56-83.84	67.35-92.25	84.53-111.87	55.08-75.32
Post CI	63.59-93.21	102.31-113.89	93.40-115.40	66.90-99.50
Change	9.15	28.23	6.23	18.00
Significance	NS	$P < .01$	NS	$P < .05$

Abbreviations: TOVA, Test of Variables of Attention; CI, confidence interval; NS, nonsignificant.

based treatment[72] showed similar results. Recently, Wallin et al[73] published the outcomes of a 3-year long donepezil-based treatment in a routine clinical setting showing a mean change from baseline of 3.8 for MMSE. According to our results, an average 6-point increase in the MMSE scores were observed and these changes were seen regardless of the dementia type during a treatment period from 1 to 6 months. A longer follow-up of NF treatment matching the 3-year period of Wallin et al[73] would be useful in assessing whether this observed increase would be sustained.

One possible mechanism for how NF works is the theory that different conditions, including dementia, arise due to dysfunctions in networks instead of specific areas of the brain. Specifically, dementia may be related to dysfunction in the core networks that comprise the triple network model. These core networks are the default mode network, which involves portions of the medial prefrontal cortex, medial temporal lobe, posterior cingulate cortex, precuneus, and the medial, lateral, and inferior parietal cortex, and activates during intrinsic activity without external stimulus; the salience network, which involves the anterior insula (AI), anterior cingulate cortex (ACC), as well as the subcortical areas of the amygdale and substantia nigra/ventra tegmental area, and is a system involved in integrating and regulating somatic, autonomic, and emotional information; and the third network is the central executive network, which is based in the dorsolateral prefrontal

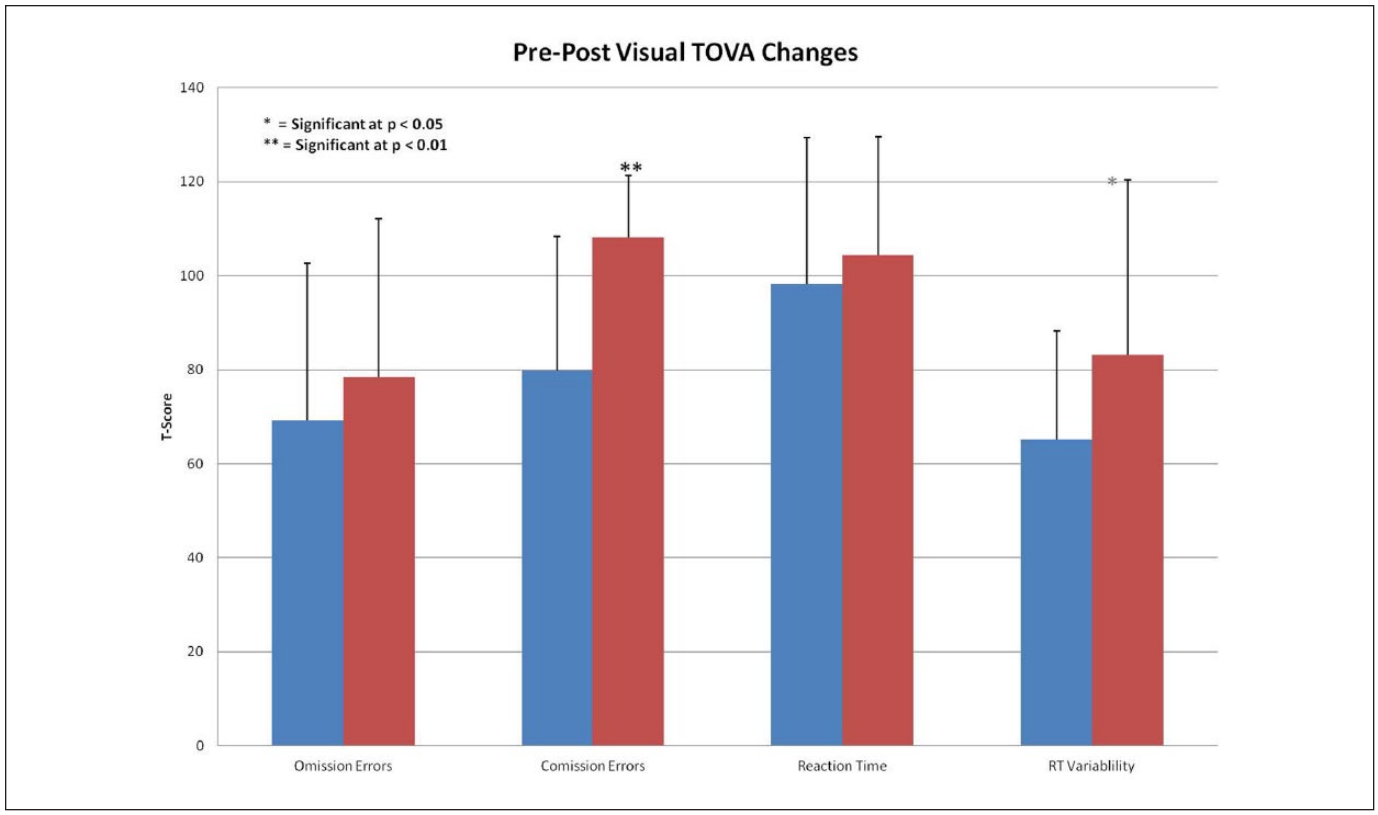

Figure 4. The Test of Variables of Attention (TOVA) shows a significant decrease of commission errors ($P < .01$) and to a lesser degree reaction time (RT) variability *$P < .5$) after neurofeedback (NF) treatment. The remaining scores show an improvement; however, they were not statistically significant.

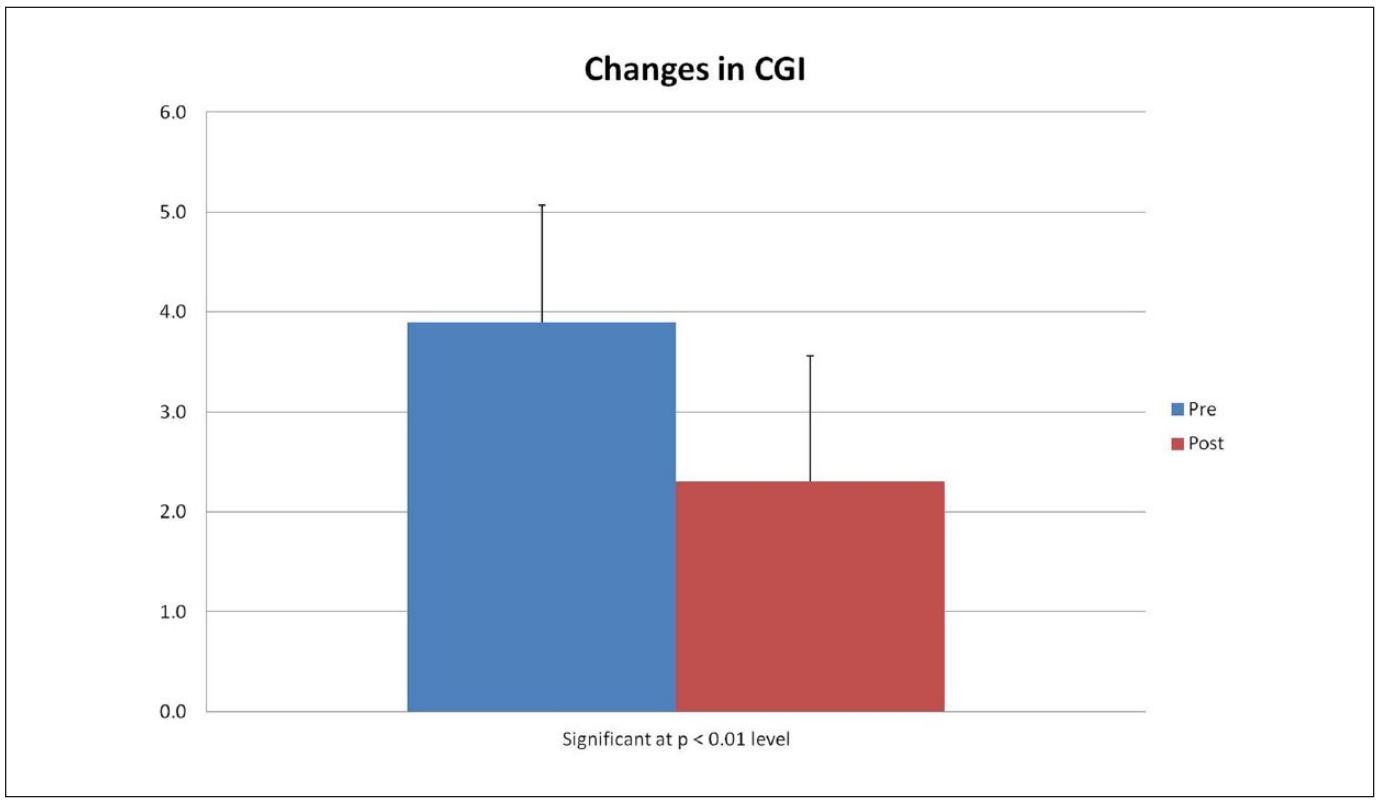

Figure 5. The pre-post Clinical Global Impressions (CGI) changes showed a statistically significant decrease.

cortex and the lateral posterior parietal cortex and is involved in maintaining and applying memories to cognitive tasks, and other executive functions. It is proposed that NF, by regulating the connectivity between these networks, is able to relieve the symptoms of a variety of disorders, including dementia.[74]

One problem seen in this study, which mirrors the real world, is the use of multiple medications to address the different symptoms the patient might have. Therefore, for the cognitive decline, an antidementia drug is prescribed, for agitation, an antipsychotic, and to stabilize the mood, an antidepressant is prescribed. Because this is a geriatric population it is very likely that they also take other medications to address comorbid physiological problems (eg, cardiovascular, hypertension, metabolic, etc). Therefore, all these medications increase the risk of side effects and may put undue stress on an already fragile physiology.

In this study, we were able to remove all patients from all medication. Only 1 patient was given medication for a short time to manage her agitation. At the end of the study, none of the patients needed any medication, and all observed improvements were still evident in follow-up visits. The patient's families noticed an improvement in the patients' mood, anxiety, sleep problems, and agitation. According to the families, the patients became more engaged and more productive in their daily lives. These findings were confirmed by us in follow-up interviews.

EEG biofeedback is not a one-size-fits-all type of treatment. Each treatment protocol must be personalized to each patient, and regularly monitored and adjusted for optimum treatment effect. That is, it is tailored to the individual and therefore focuses on the specific problems a person may have, thus making it more effective than a one-size-fits-all method. With the growing importance of personalized medicine, these types of treatments may become more common in the future. This issue has recently been addressed by the Report of the National Advisory Mental Health Council's Workgroup in its August 2010 report. According to the report, definition of personalized is as follows:

> Personalized means that there is something known about the individual that differentially predicts how he or she will respond to a given treatment. Evidence-based treatment algorithms are helpful, but too general, with little tailoring based on individual differences (e.g., genomic variations), and supported by very little actual evidence beyond acute treatment.[75]

The goal of this study was to explore the utility of NF in the treatment of dementia. The results show that NF may be effective in this patient population. These findings are preliminary at best, and need to be followed up by carefully designed controlled studies. However, with all the problems that exist with current treatment modalities this treatment seems to be effective without having any untoward effects may be useful in this patient population. A major limitation of this study is that it did not have a control group, and it was not blinded. However, recent comparisons between randomized control studies and randomized observational studies have shown that there is no great difference in treatment effects between the 2, and that observational studies do provide relevant treatment information.[76-79] There is a lack of placebo-controlled studies in dementia using NF. This may be partly because of the fact that according to the Helsinki accords, sham- or placebo-controlled studies are ethically acceptable for those disorders for which no effective treatment is available; therefore, an active treatment control (treatment equivalence) design is most appropriate for those clinical studies examining disorders for which there is a known, effective treatment.[80] This being the case, successful blinded placebo-controlled studies are being conducted using NF where efficacy is being demonstrated.[56,81] In dementia treatment, it follows that according to Helsinki criteria the appropriate studies would be comparing NF with FDA-approved dementia drugs. Unfortunately, for VD, an approved treatment medication still does not exist.

One major limitation of this study is that other noncontributing factors, such as the prolonged patient therapist interaction (because of the high number of sessions) could not be assessed and ruled out. Another limitation of this study is that 2 different patient populations were included (Alzheimer's type dementia, vascular type dementia, with moderate and severe patients in each group). The sample size of the study was not large enough to evaluate these confounding factors.

Author Contributions

T. Surmeli contributed to conception; contributed to acquisition and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. E. Eralp contributed to conception; contributed to analysis and interpretation; drafted manuscript; critically revised manuscript; agrees to be accountable for all aspects of work ensuring integrity and accuracy. I. Mustafazade contributed to interpretation. H. Koss contributed to acquisition. G.E. Özer contributed to acquisition and analysis. O.H. Surmeli contributed to analysis.

Authors' Note

Signed written consent, where all the procedures were explained to the subjects, was obtained from each of the participants. For those subjects who could not sign the consent form, consent was obtained from the subject's immediate family.

Declaration of Conflicting Interests

The author(s) declared no conflicts of interest with respect to the research, authorship, and/or publication of this article.

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