The Effectiveness of Neurofeedback on Cognitive Functioning in Patients with Alzheimer's Disease

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Abstract

Alzheimer's Disease (AD) is the most common form of dementia. In a qEEG, patients with AD present a greater amount of theta activity compared to normal aging individuals. An excess of delta and a decrement of alpha and beta is also observed. Little is known about the effect of neurofeedback in patients with dementia. However, it has been successfully applied in the treatment of different disorders.

The objective of this study was to examine if neurofeedback has a positive effect on the cognitive performance in patients with AD. Ten patients whose qEEG met the typical pattern for patients with AD received neurofeedback training. These patients were compared with 123 AD patients who received treatment as usual (TAU). Participants were between the age of 61 and 90. All patients received a test designed to assess cognitive functioning pre- and post-treatment.

The test-retest reliability of the TAU group for the total CAMCOG score was 0.84 and varied between the subscales from 0.56 to 0.78. Individual results, analyzed with a reliable change index (RCI), indicated that patients who received neurofeedback treatment had stable cognitive functions. When the groups were compared; patients with neurofeedback treatment showed an improvement in learning memory, other cognitive functions were stable. In comparison, patients with TAU had an overall decrement in cognitive functioning, with the exception of orientation in time.

In sum, neurofeedback has a positive effect on the cognitive performance of patients with AD. Patients who received neurofeedback treatment had stable cognitive functions and an increase in the recognition and recall of information, whereas TAU patients showed a decrement in these functions.

1. Introduction

Dementia is a syndrome characterized by progressive deterioration of cognitive function, most commonly of memory, but other domains such as language, praxis, visual perception and most notably executive function are also often affected. As cognitive function worsens, there is increasing interference with the patients' daily activities leading to loss of independence and eventually for some the need for nursing home care [1]. Dementia has an increasing incidence as people age.

Dementia is a symptom of several clinical syndromes, in which Alzheimer's Disease (AD) is the most common form. Seventy percent of all patients with dementia have AD. Vascular dementia (VD) is observed in approximately 15 percent of all dementia patients. In addition to AD and VD, other forms of dementia are frontotemporal dementia (FTD), dementia with Lewy bodies (DLB) and dementia due to Parkinson's disease (PD). FTD usually has an early onset (around the age of 40, 50) compared to AD and VD. The discussion of the various types of dementia goes beyond the scope of this paper and will not be mentioned here. For further reading Jonkers, Slaets and Verhey (2009) [2] is recommended.

Until the age of 85 the age-specific incidence of dementia for men and woman are almost equal. In older patients, the incidence is higher in women than in men. This difference could probably be largely explained by the difference in mortality between men and women [2].

The diagnoses ‘probable’ or ‘possible’ AD is made by clinical criteria established by the National Institute of Neurologic and Communicative Disorders and Stroke – Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) [3]. Patients should have dysfunction of at least two or more areas of cognition (orientation to place and time, memory, language, praxis, attention, visual perception and problem solving skills), with progressive worsening of memory and other cognitive functions, no disturbance of consciousness and onset between ages 40 and 90, most often after the age of 65. Scales and inventories designed to screen for dementia contain orientation items as these test functions that are sensitive to the most common dementing processes, such as both recent and remote memory, mental clarity, and some aspects of attention. Other areas of common interest are fund of knowledge and language skills [4].

AD is associated with functional and structural alterations in a distributed network of brain regions supporting memory and other cognitive domains. Hippocampal atrophy and ventricular enlargement have been associated with AD but also with MCI and normal aging. Patients with AD have the highest levels of hippocampal atrophy and ventricular enlargement. Patients with MCI have intermediate levels and these levels are the lowest for people who age ‘normally’ [5]. Microscopically, the neuropathological changes are characterized by extracellularly located senile plaques and intracellularly located neurofibrillary tangles. Current therapies to treat AD are minimally effective and do not alter the disease process [6]. They may ease symptoms by providing temporary improvement and reducing the rate of cognitive decline [7]. Although the available (non)pharmacologic therapies for dementia can help with the management of symptoms, there is a need to develop more effective interventions [8].

Neurofeedback refers to a form of operant conditioning in which desirable brain activity is rewarded and undesirable brain activity is inhibited. It is a comprehensive training system that promotes growth and change at the cellular level of the brain [9]. Neurofeedback training works directly with the brain. Each participant trains at his or her own pace. Neurofeedback can facilitate changes in brain wave patterns. These brain wave patterns, or electrical activity, are registered with an electroencephalograph (EEG). The classis names of the EEG bands are delta, theta, alpha and beta. These consist of several frequencies. Each brain wave frequency can be measured in terms of hertz and microvolts. Slow frequencies are less than 10 Hz, fast

frequencies are faster than 13 Hz. Microvolts measure the amplitude. Slower frequencies tend to have higher amplitudes than faster frequencies. When slow frequencies dominate, the brain is moving slowly. When fast frequencies dominate, the brain is moving along from one task to another. Neurofeedback training is aimed at changing the amplitude of a selected frequency. See table 1 for a list of the common frequency bandwidths and their general characteristics. Neurofeedback training has been successfully applied in the treatment of different disorders in adults and children. It has shown positive effect in the treatment of anxiety [10-12], Attention Deficit Hyperactivity Disorder (ADHD) [13-15], autism [16, 17], depression [12, 18] and epilepsy [19, 20].

Table 1. Common Frequency Bandwidths [21]

Common bandwidth name	Frequency range (in Hz)	General description or characteristics
Delta	0.5-3.5	Slowest and highest amplitude of brainwaves. What we experience when we are asleep
Theta	4-8	Daydream like state of mind which is associated with mental inefficiency
Alpha	8-12	Associated with a state of relaxation and represents the brain shifting into a idling gear, relaxed and a bit disengaged, waiting to respond when needed
Beta	> 13	Associated with a state of mental, intellectual activity and outwardly focused concentration

In the normal aging process, the EEG changes in the pattern of brain electrical activity concern a decrease in frequency and amplitude (increased delta and/or theta) [22-25]. Patients with AD present a greater amount of theta activity compared to normal aging individuals. An excess of delta and a decrement of alpha and beta is also observed [24, 26, 27]. In patients with AD, the amount of delta and theta activity needs to be decreased and the amount of alpha and beta activity needs to be increased. As previously stated, the aim of neurofeedback is to change the amplitude of a selected frequency. Therefore, it is expected that neurofeedback would have a positive effect on the treatment of AD, especially on the cognitive performance of patients with AD.

The present study is part of a large clinical randomized trial in which the results of this study will play a (small) part. In the clinical trial a crossover design is used; the participants in the clinical trial will be assigned, by chance, either to the treatment or the control condition. In the treatment condition, the participant starts with the neurofeedback treatment and then he or she receives TAU. In the control condition, the participant starts with TAU after which he or she will receive the neurofeedback treatment. In the present study and in the large clinical trial, all participants are treated with cholinesterase inhibitors.

The aim of the present study is to answer the question whether neurofeedback has a positive effect on the decline of cognitive functioning in patients with AD. It is hypothesized that the cognitive performance of patients with AD will stay stable, or preferably improve, after neurofeedback treatment. In order to explore the research question, patients with AD which have had neurofeedback treatment are compared with patients with AD who received TAU.

2. Methods

2.1 Participants

Participants for the neurofeedback study were recruited through the outpatient memory clinic from the Catharina hospital in Eindhoven. Patients who were diagnosed with 'probable' AD were contacted if they met the inclusion criteria. The inclusion criteria comprised a positive advice for participation by the multidisciplinary team of the memory clinic. This team consisted of a geriatrician, neurologist, psychiatrist, psychologist and a nurse. Furthermore, patients should have had a score of 60 points or higher on a screening instrument for dementia, the Cambridge Cognitive examination (CAMCOG) [28]. This cut-off score was used as an indication that the patient was in an early stage of the disease. Patients should have been older than 60 years of age and living independently (or possibly assisted living). Additionally, they should have been able to visit the hospital twice a week for a period of fifteen weeks. With respect to the neuropsychological screening, a sufficient understanding of the Dutch language was required. Finally, their qEEG had to meet the typical pattern for people with AD. Patients with a medical history of neurological (epilepsy, stroke, tumor) or psychiatric disorders were excluded. A total of ten patients with AD participated in the neurofeedback group. They were aged between 61.9 and 82.8 years (mean age = 71.5 years).

The TAU group consisted of one hundred twenty-three patients from the memory clinic of the Catharina hospital in Eindhoven. The group solely consisted of patients with the diagnosis 'probable' dementia. These patients have had two screening measurements for dementia. The first screening was administered in order to diagnose the patients. After the diagnosis, patients were treated with cholinesterase inhibitors. After approximately half a year a follow up

screening was administered. Patients of the TAU group were aged between 63.7 and 89.4 years (mean age = 78.5 years).

2.2 Materials

2.2.1 Cambridge Cognitive Examination (CAMCOG)

The Cambridge Cognitive Examination (CAMCOG), a neuropsychological screening, is the objective test portion of an instrument developed for the early diagnoses and monitoring of dementia in the elderly, the Cambridge Mental Disorders of the Elderly Examination-Revised (CAMDEX) [4]. It is mainly developed to contribute to the early diagnosis of dementia in people older than 65 years [28]. This study used the Dutch translation [29].

The CAMCOG's 67 items are grouped into eight subscales. *Orientation* (ten items dealing with time and place); *Language* (seven comprehension items, six naming items, category fluency, and four word definitions); *Memory* (recall and recognition of six pictured objects, name and address recall and ten 'information type' items); *Attention* (counting from 20 to 1 and serial sevens [five subtractions of seven]); *Praxis* (copying geometric figures and following commands); *Calculations*; *Abstract thinking* (similarities between pairs of items); and *Perception* (e.g. recognition of objects depicted from unusual angles and stereognosis). Impairments on the scales *Total CAMCOG*, *Orientation* and *Memory* are indicative for AD [4, 30]. Therefore, this study measured cognitive impairment using these three scales and their subscales. Seven items do not contribute to the total score but are included to permit calculation of an MMSE total score (five items) or to acquire additional qualitative information (two items). The scores range from 0 (severe cognitive impairment) to 105 (no cognitive impairment). In the present study, when a CAMCOG score is mentioned, this score is not the 'real' CAMCOG score, but a proportion of that score: the obtained score on a (sub)scale divided by the maximum score of the same (sub)scale.

The CAMCOG divides the educational level in three classes: low, average and high. People with a low educational level are able to score lower on the CAMCOG than people with an average or high level of education before their scores are interpreted as impaired. People with a low level of education usually have a lower IQ, hence it is more difficult for them to answer the questions and perform the tasks than more educated people. In the present study, the level of education has not been included. However, in the large randomized clinical trial, the educational level will be taken into account.

2.2.2 qEEG

The qEEG was registered with the DeyMed True Scan, using True Scan software. The EEG data was processed to a qEEG with Neuroguide software. This software processes data with both 'linked-ear' and 'Laplacian' montages. The EEG signal was processed with a Fast Fourier Transformation (FFT) to the following frequencies: delta (1 - 4 Hz), theta (4 - 8 Hz), lower alpha (8 - 10 Hz), upper alpha (10 - 12 Hz), SMR (12 - 15 Hz), beta (15 - 18 Hz), high beta (18 - 25 Hz), gamma (30 - 35 Hz) and high gamma (35 - 40 Hz). For all these frequencies, z-scores of the absolute and relative power were estimated for all 19 scalp locations.

2.2.3 Neurofeedback

For the neurofeedback training, Brainmaster Atlantis software was used. A 17-inch monitor and a speaker set was used for the visual and auditory feedback. Furthermore, three gold plated electrodes were used. To place the electrodes, an abrasive conductive gel (eg. NuPrep Gel) and a gel that's conducts electricity (eg. Ten20 conductive paste) were used. An impedance meter (checktrode) was used to check the contact between the electrode and the skin.

2.3 Procedure

2.3.1 Selection

The patients of the memory clinic of the Catharina hospital in Eindhoven, who met the in- and exclusion criteria were contacted. If they were interested in participating, an information package was sent and the patient and his/her partner were invited for a meeting in which information about the study was provided. If the patient and his/her partner decided to participate, they were asked to sign an informed consent.

2.3.2 Neuropsychological screening

There were two measurement moments: pre- and post-treatment. In the two measurement moments the CAMCOG screening was administered in order to determine the cognitive functioning of the participants. The administering took place at the Catharine hospital by students of the Master Medical Psychology. When the participants were screened for dementia at the memory clinic, a screening with the CAMCOG already took place. In case the test has been taken longer than three months before, the CAMCOG was administered again.

2.3.3 qEEG

Pre-treatment, an EEG was made at the 'Neurofeedback Instituut Nederland' (NIN). The EEG was recorded in two conditions; eyes open (EO, for ten minutes) and eyes closed (EC, for ten minutes). The EEG data was then transformed to a qEEG report. The qEEG data of the participant was compared to a normative database of Neuroguide [31]. Based on this qEEG an individualized training protocol was determined (see table 2). Post-treatment, an EEG registration also took place.

Table 2. Various training locations and the individual training protocols for each participant

ID	Training protocol		Training location
1	5 - 8 Hz down	12 - 15 HZ up	Cz / A1 (reference), A2 (ground)
2	5 - 8 Hz down	20 - 30 HZ down	Fz / A1 (reference), A2 (ground)
3	5 - 8 Hz down	20 - 30 HZ down	P4 / A1 (reference), A2 (ground)
4	6 - 9 Hz down		Fz / A1 (reference), A2 (ground)
5	5 - 8 Hz down		Cz / A1 (reference), A2 (ground)
6	20 - 30 Hz down	9 - 12 HZ up	Fz / A1 (reference), A2 (ground)
7	4 - 7 Hz down		Fz / A1 (reference), A2 (ground)
8	5 - 7 Hz down	9 - 12 HZ up	Pz / A1 (reference), A2 (ground)
9	8 - 10 Hz up		Pz / A1 (reference), A2 (ground)
10	14 - 18 Hz down	8 - 11 HZ up	Pz / A1 (reference), A2 (ground)

2.3.4 Neurofeedback

Within two weeks after the pre-treatment measurement, the neurofeedback treatment started. The sessions took place twice a week for fifteen weeks. That amounts to a total of thirty sessions. Data was acquired by placing electrodes on the scalp of the participant according to the International 10-20 system [32]. Recording with a single channel EEG required the placement of three separate leads on the head [9]. The active electrode was placed on the individual training location, depending on the training protocol (see table 2). The reference electrode was placed on the earlobe contra lateral to the location of the active electrode and the ground electrode was placed on the other earlobe. The scalp and earlobe locations were cleaned with an abrasive conductive gel (NuPrep Gel™) before the electrodes were placed. Each electrode cup was filled with special gel that conducts electricity (Ten20 conductive paste™). An impedance meter was used to determine if there was good contact between the electrode and the skin. Impedances were kept below 5 KΩ which is a standard for assessment [33].

The neurofeedback treatment started with a single channel EEG record of one minute with 'eyes open'. Subsequently, a twenty minute training session was conducted with three breaks after five minutes. During the training sessions, the participant sat in front of a computer screen and watched a movie. He or she received visual and auditory feedback. If the training

went according to the protocol, the movie was shown in a higher contrast and the participant heard a beep. The thresholds were adjusted manually to maintain a reward frequency around 70 percent and an inhibited threshold around 10 percent. After ending the four training sessions, a final EEG registration of one minute with 'eyes open' was administered.

2.4 Analyses

Analyses were performed using SPSS 19.0 for Windows. p values of < 0.05 were taken as significant. All following analyses treated the *Neurofeedback* group as reference and compared the *TAU* group against it.

The test-retest reliability was computed using the TAU group of one hundred twenty-three patients. A T-test (SPSS paired samples T-test) with *Measurement* (pre-treatment, post-treatment) as independent variable and the eight CAMCOG scores as dependent variable (*Total CAMCOG Score, Total Orientation Score, Orientation in Time, Orientation in Place, Total Memory Score, Past Memory, Recent Memory and Learning Memory*) was conducted.

Individual performance on the CAMCOG was analysed with a reliable change index (**RCI**). The RCI for the CAMCOG and the various (sub)scales were computed according to the formula of Jacobson and Truax [34]:

$$RCI = (X_2 - X_1)/S_{diff}$$

$$S_{diff} = \sqrt{2}*(S_E)^2$$

$$S_E = s_1 * \sqrt{1 - r_{xy}}$$

The outcomes of the previous mentioned analysis were used to calculate the RCI's of the (sub)scales.

Table 3. Data from the first neurofeedback participant (Total CAMCOG Score)

Symbol	Definition	Values
X_1	Score on the pre-treatment measurement	0.69
X_2	Score on the post-treatment measurement	0.83
S_1	Standard deviation pre-treatment	0.124
r_{xy}	Test-retest reliability	0.844
SE	Standard error of measurement	0.049
S_{diff}	Standard error of difference between the two test scores	0.069

The group performance on the **CAMCOG** and the subscales of the CAMCOG were analysed with a Mixed Linear Model analysis, using the procedure *lme* in the R statistical Software [35] with *Cognitive Function* as dependent variable, *Measurement* (pre-treatment, post-treatment) as fixed factor and *participant ID* as random factor. *Age* is included as a

covariate. The simple effects were analysed with a paired-samples t-tests in order to investigate changes in scores (decrease, increase or stabilization) for each group separately.

3. Results

3.1 Participants

Table 4 shows the group means and SD of 'age at inclusion', 'sex of the participants, 'total days' between the administrations and 'the total CAMCOG score' for de different groups. The participants in the neurofeedback group were younger than the participants in the TAU group. Furthermore, the total days between the pre- and post-treatment measurements and the pre-treatment measurement of the total CAMCOG score differed for both groups.

Table 4. Study sample characteristics

	Neurofeedback (N = 10)		**TAU (N = 123)**		**NFB-TAU**	
Measure	**M**	**(SD)**	**M**	**(SD)**	**t(131)**	**p**
Age at inclusion	71.5	6.74	78.5	5.12	-6.92	.000
Sex						
Female	3		82			
Male	7		41			
Total days	153.40	52.59	388.07	227.98	-8.88	.000
Total CAMCOG score	0.80	0.10	0.68	0.12	0.12	.004

3.2 Test-retest reliability

When looked at the manual of the CAMDEX-R [29] the test-retest reliability (r_{xy}) after one year for the total score was 0.97 (n = 387) and varied between the (sub)scales from 0.49 to 0.87. In the TAU group the r_{xy} for the total CAMCOG score was 0.84 and the scores from the various (sub)scales varied from 0.56 to 0.78 (table 5).

Table 5. Mean scores, SD and r_{xy} for the pre- and post-treatment measurements of all the (sub)scales

	Mean		SD		
(sub)scale	pre	post	pre	post	r_{xy}
Total CAMCOG Score	.68	.64	.12	.16	.84
Total Orientation Score	.70	.64	.22	.23	.68
Orientation in Time	.60	.58	.29	.30	.57
Orientation in Place	.80	.71	.22	.23	.56
Total Memory Score	.51	.45	.17	.20	.78
Past Memory	.54	.49	.23	.25	.70
Recent Memory	.62	.50	.29	.30	.63
Learning Memory	.47	.43	.19	.22	.70

3.3 Individual Performance (RCI)

RCI's for each neurofeedback participant are computed. The RCI for the Total CAMCOG score of the first participant (see table 3 for the values) is:

$RCI = (X_2-X_1)/S_{diff}$ $\quad$ $RCI = (.83-.69) / .0693 = 2.020$

$S_{diff} = \sqrt{2*(S_E)^2}$ $\quad$ $S_{dif} = \sqrt{2} * .049^2 = .0693$

$S_E = s_1 * \sqrt{1- r_{xy}}$ $\quad$ $S_E = .12408 * \sqrt{1-0.844} = .049$

The RCI's for the other (sub)scales and participants are calculated similarly. Positive values indicate an increase in score, negative values a decrease. A zero score means no change. Scores above 1.96 or below 1.96 indicate a reliable change ($p < .05$). In other words; it is unlikely that the change is due to a measurement error.

Table 6 shows an overview of the various pre- and post-treatment measurements for each participant and (sub)scale. Table 7 displays the various RCI's for each participant. One participant had a significant increase in the (sub)scales *Total CAMCOG Score* and *Learning Memory*. Another had a significant increase in the subscales *Orientation in Place* and *Past Memory*, and a decrement in subscale the *Recent Memory*. A third participant also had a decrement in the subscale *Recent Memory*. Overall the neurofeedback participants did not show an increase in scores. However, they also did not show a decrement. Simply put; the participants which had neurofeedback treatment had stables scores on the various (sub)scales.

Table 6. Pre- and post-treatment measurement scores for each participant and (sub)scale

ID	Total CAMCOG Score		Total Orientation Score		Orientation in Time		Orientation in Place		Total Memory Score		Past Memory		Recent Memory		Learning Memory	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	.69	.83	.90	.90	.80	.80	1	1	.59	.81	.67	.83	1	1	.47	.76
2	.69	.74	.60	.80	.80	.80	.40	.80	.63	.59	.33	.67	.75	.25	.71	.65
3	.69	.65	.60	.50	.40	.40	.80	.60	.56	.63	.50	.67	.75	.75	.53	.59
4	.93	.96	.90	1	.80	1	1	1	.78	.89	1	1	1	1	.65	.82
5	.79	.80	.60	.60	.20	.20	1	1	.44	.52	.50	.67	1	.50	.29	.47
6	.84	.90	.80	.90	.60	.80	1	1	.85	.93	1	1	1	1	.76	.88
7	.69	.71	.80	1	.80	1	.80	1	.41	.37	.50	.17	.75	.75	.29	.35
8	.92	.91	1	1	1	1	1	1	.93	.85	.83	.83	1	1	.94	.82
9	.83	.80	.80	.80	.60	.60	1	1	.63	.74	.50	.67	1	.75	.59	.76
10	.88	.87	.80	.60	.80	.60	.80	.60	.70	.81	.83	.83	.50	.75	.71	.82

Table 7. RCI scores for 10 neurofeedback participants

ID	Total CAMCOG Score	Total Orientation Score	Orientation in Time	Orientation in Place	Total Memory Score	Past Memory	Recent Memory	Learning Memory
1	2.020	0	0	0	1.933	.924	0	1.960
2	.721	1.144	0	1.988	-.351	1.963	-2.026	-.405
3	-.577	-.572	0	-.994	.615	.982	0	.405
4	.433	.572	.738	0	.966	0	0	1.149
5	.144	0	0	0	.703	.982	-2.026	1.216
6	.866	.572	.738	0	.703	0	0	.811
7	.289	1.144	.738	.994	-.351	-1.906	0	.405
8	-.144	0	0	0	-.703	0	0	-.811
9	-.433	0	0	0	.966	.982	-1.013	1.149
10	-.144	-1.144	-.738	-.994	.966	0	1.0132	.743

x = RCI ≤ or ≥ than 1.96
0 = no change between pre- and post-treatment measurements
Positive values = increase in score between pre- and post-treatment measurements
Negative values = decrease in score between pre- and post-treatment measurements

3.4 Group Performance (LME)

The neurofeedback participants and the TAU group are viewed as groups and are compared with each other. See table 9 for an overview of the effects. Compared to the *TAU* group, patients in the *Neurofeedback* group had higher scores on the following (sub)scales: *Total CAMCOG* [F(1,131) = 11.857; p = .001], *Orientation in Place* [F(1,131) = 4.300; p = .040], *Total Memory* [F(1,131) = 12.689; p = .001], *Past Memory* [F(1,131) = 6.479; p = .012], *Recent Memory* [F(1,131) = 9.693; p = .002] and *Learning Memory* [F(1,131) = 10.032; p = .002]. However, no difference between the groups was found for the subscales *Total Orientation* (p = .068) and *Orientation in Time* (p = .193). Table 8 displays an overview of the mean scores for both groups.

For the following (sub)scales, scores on the pre-treatment measurement were significantly higher than scores on the post-treatment measurement: *Total CAMCOG* [F(1,131) = 24.648; p = .000], *Total Orientation* [F(1,131) = 10.187; p = .002], *Orientation in Place* [F(1,131) = 17.926; p = .000], *Total Memory* [F(1,131) = 19.243; p = .000], *Past Memory* [F(1,131) = 4.083; p = .045], *Recent Memory* [F(1,131) = 28.035; p = .000] and *Learning Memory* [F(1,131) = 7.258; p = .008]. No difference between the measurements was found for the subscale *Orientation in Time* (p = .363). Table 8 displays an overview of the mean scores of the pre- and post-treatment measurements for each participant.

Table 8. Mean scores and SD for both groups and for the pre- and post-treatment measurement

	Group		Measurement	
Measure	**NFB (SD)**	**TAU (SD)**	**Pre (SD)**	**Post (SD)**
Total CAMCOG	.81 (.09)	.66 (.13)	.69 (.13)	.65 (.16)
Total Orientation	.80 (.15)	.67 (.21)	.71 (.21)	.66 (.23)
Orientation in Time	.70 (.24)	.59 (.26)	.61 (.29)	.59 (.30)
Orientation in Place	.89 (.16)	.76 (.20)	.80 (.21)	.73 (.24)
Total Memory Score	.68 (.17)	.48 (.17)	.52 (.17)	.47 (.21)
Past Memory	.70 (.22)	.51 (.22)	.55 (.23)	.51 (.26)
Recent Memory	.83 (.18)	.56 (.27)	.64 (.29)	.52 (.31)
Learning Memory	.64 (.18)	.45 (.19)	.48 (.19)	.45 (.22)

Table 9. Overview of the effects of the various CAMCOG (sub)scales

	Difference between Groups		**Difference between Measurements**		**Group*Measurement Interaction**	
df: 1,131	F	p	F	p	F	p
Total CAMCOG	11.857	.001***	24.648	.000***	5.312	.023*
Total Orientation	3.385	.068	10.187	.002**	2.157	.114
Orientation in Time	1.711	.193	.834	.363	.570	.452
Orientation in Place	4.300	.040*	17.926	.000***	2.317	.130
Total Memory Score	12.689	.001***	19.243	.000***	8.437	.004**
Past Memory	6.479	.012*	4.083	.045*	3.080	.082
Recent Memory	9.693	.002**	28.035	.000***	.046	.831
Learning Memory	10.032	.002**	7.258	.008**	8.184	.005**

* = p < .05, ** = p < .01, *** p < .001

An interaction effect of *Group*Measurement* was found for the *Total CAMCOG* [F(1,131) = 5.312; p = .023], the *Total Orientation* [F(1,131) = 2.157; p = .016], the *Total Memory* [F(1,131) = 8.437; p = .004] and *Learning Memory* [F(1,131) = 8.184; p = .005]. This indicated that the mean score of the two groups was different for the two measurements for each of the previous mentioned (sub)scales. No differences were found for the (sub)scales *Total Orientation* (p = .114), *Orientation in Time* (p = .452), *Orientation in Place* (p = .130), *Past Memory* (p = .082) and *Recent Memory* (p = .831).

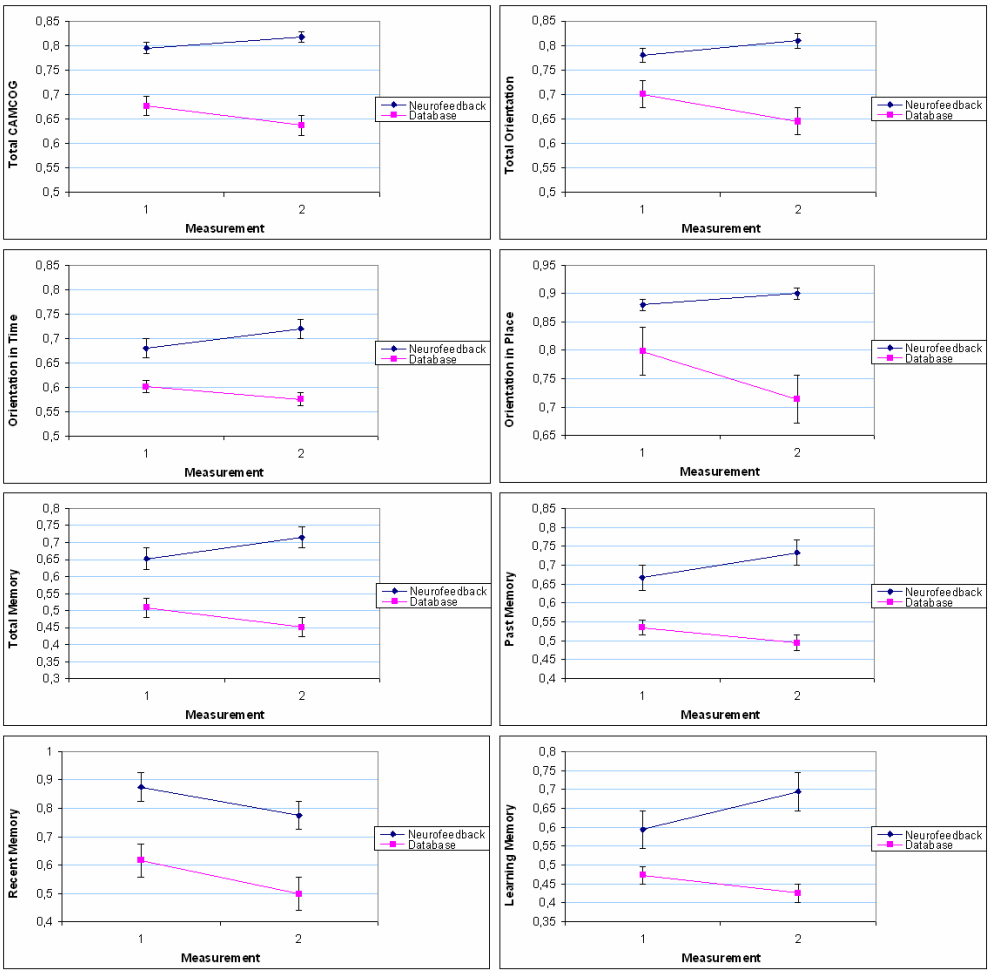

Figure 1. The interactions between the two groups (Neurofeedback and TAU) and the two measurements for all eight (sub)scales.

To analyze the effect of the total days between the pre- and post-treatment measurement, the factor *Total days* was included as continuous factor in stead of the fixed factor *Measurement*. The *Group* [F(1,131) = 7.786; p = .006], *Measurement* [F(1,131) = 27.933; p = .000] and *Interaction* effects [F(1,131) = 4.983; p = .027] of the total CAMOG score remained. *Age* (when included as covariate) did not have an effect or interaction effect on the total CAMCOG score (see table 10). In sum, *Total days* and *Age* did not have an impact on the effects that were found.

Table 10. Overview of the Effects with *Age* as covariate

df: 1;131	F	p
Group	11.686	.001***
Measurement	24.816	.000***
Age	2.452	.120
Group*Measurement	4.977	.027*
Group*Age	.082	.775
Measurement*Age	.258	.621
Group*Measurement*Age	.584	.446

* = p < .05, ** = p < .01, *** p < .001

Paired-samples t-tests were conducted in order to investigate changes in scores (decrease, increase or stabilization) for each group separately. When focused on the *Neurofeedback* group, this group had a higher mean score on *Memory Learning* after the treatment [t(9) = -2.613; p = .028]. There was no improvement on the other (sub)scales, but also no decline (resp, p = .207, .468. .343, .726, .052, .269 and .223). Participants in the *TAU* group had a decline in mean score between the pre- and post-treatment measurement for *Total CAMCOG* [t(122) = 5.290; p = .000], *Total Orientation* [t(122) = 3.410; p = .001], *Orientation in Place* [t(122) = 4.441; p = .000], *Total Memory*; [t(122) = 4.926; p = .000], *Past Memory* [t(122) = 2.418; p = .017], *Recent Memory* [t(122) = 5.133; p = .000] and *Learning Memory* [t(122) = 3.326; p = .001]. The subscale *Orientation in Time* did not differ between the pre- and post-treatment measurement (p = .293). See table 11 for an overview of the previous mentioned outcomes.

Table 11. Mean scores and SD for the pre- and post-treatment measurements for both groups

	Neurofeedback (N = 10)				TAU (N = 123)			
Measure	**Pre (SD)**	**Post (SD)**	**t(9)**	**p**	**Pre (SD)**	**Post (SD)**	**t(122)**	**p**
Total CAMCOG	.80 (.10)	.82 (.10)	-1.358	.207	.68 (.12)	.64 (.16)	5.290	.000
Total Orientation	.78 (.14)	.81 (.19)	-.758	.468	.70 (.22)	.64 (.23)	3.410	.001
Orientation in Time	.68 (.23)	.72 (.27)	-1.000	.343	.60 (.29)	.58 (.30)	1.055	.293
Orientation in Place	.88 (.19)	.90 (.17)	-.361	.726	.80 (.22)	.71 (.23)	4.441	.000
Total Memory Score	.65 (.17)	.71 (.18)	-2.234	.052	.51 (.17)	.45 (.20)	4.926	.000
Past Memory	.67 (.24)	.73 (.24)	-1.177	.269	.54 (.23)	.49 (.25)	2.418	.017
Recent Memory	.88 (.18)	.78 (.25)	1.309	.233	.62 (.29)	.50 (.30)	5.133	.000
Learning Memory	.59 (.20)	.69 (.17)	-2.613	.028	.47 (.19)	.43 (.22)	3.326	.001

6. Discussion

This study explored the cognitive functioning of AD patients with and without neurofeedback treatment. The aim was to explore whether neurofeedback is a potential intervention in decreasing the cognitive decline in patients with AD. Based on the previously discussed literature [22-27] it is hypothesized that the cognitive performance of patients with AD will stay stable, or preferably improve, after neurofeedback treatment.

On an individual level, neurofeedback treatment stabilized cognitive performance in patients with AD. When the groups were compared; participants with neurofeedback treatment showed an improvement in learning memory. The other cognitive functions were stable. In comparison, participants with TAU had an overall decrement in cognitive functioning, with the exception of orientation in time. In sum, as hypothesized, neurofeedback

treatment has a positive effect on the cognitive performance of patients with AD. Participants who received neurofeedback treatment had stable cognitive functions and an increase in the recognition and recall of information, whereas participants in the TAU group showed a decrement in these functions.

To the authors' knowledge, only two studies applied neurofeedback to the elderly with the aim of improving cognitive activity. Becerra et al. [24] assessed the effectiveness of neurofeedback in healthy elderly people with abnormally high theta activity. Positive changes were observed in cognition including attention, executive functions and memory. However, the improvement of memory was also observed in the control group. The control group in the previous mentioned study was treated with a sham neurofeedback treatment. Becerra et al. [24] stated that the improvement in memory processes observed in both groups may be due to a placebo effect. Angelakis et al. [36] reinforced alpha power, which correlated positively with cognitive performance. Their results suggest that neurofeedback improves memory. In sum, Becerra et al. [24] found an improvement in memory for the treatment as well as the control group. Angelakis et al. [36] found an improvement in memory processes. The present study found stable cognitive functions and an increase in learning memory for the neurofeedback group, whereas an overall decline was found for the TAU group. The results of the present study are not in agreement with the previously discussed studies. This could be due to the fact that both Becerra et al. [24] and Angelakis et al. [36] included normally elderly with only subjective complaints of memory loss but no objective evidence of memory dysfunction. This study, as well as other studies [37, 38], suggests that a certain level of neuronal plasticity persists, even in AD.

It should be noted that there is a methodological issue that could, besides the operant training, explain the stabilized cognitive performance and the differences between the two groups. The neurofeedback group differed from the TAU group. Patients in the neurofeedback group were obligated to visit the hospital twice a week. This stimulates the patient to undertake more activities. In comparison, the TAU group did not have this obligation and were presumably less active than the neurofeedback group. Patients with AD frequently show an increase in apathy, which is a recurring symptom of AD [39]. It is possible that increased activity results in improved cognitive functions since apathy and cognitive performance are related [40]. Further research could address this issue by implementing a device that monitors the physical activity of a patient (e.g. pedometer). That way, insight can be obtained in the physical activity of participants in both groups.

This study is part of a large randomized clinical trial which uses a cross-over design. This design ensures that the groups do not differ in age and total days between the pre- and post-treatment measurements. However, this design does not address the differences in activation and attention the participants receive between the neurofeedback and TAU group. In order to take this into account the TAU group, as well as the neurofeedback group, has to be obligated to visit the hospital twice a week. However, this is not feasible due to the amount of effort the elderly patients have to invest. This is a considerable limitation of the study. Another limitation of this study is the low number of participants which participated. However, the clinical trial will re-examine the effect of neurofeedback in decreasing the cognitive decline in patients with AD when a reasonable amount of participants has been reached. Another issue is the level of education which has not been taken into account. People with higher IQ, education or occupational attainment have lower risks of developing dementia, AD or VD. They have greater cognitive reserves. The cognitive reserve hypothesis postulates that among those who have greater initial cognitive reserves (in contrast to those with fewer reserves) greater brain pathology occurs before the clinical symptoms of disease become manifest [41, 42]. Thus, if there are differences in educational level, the group with the highest educational level will show a faster decline in cognition and function after diagnoses.

A strong point of this study is that both the neurofeedback group and the TAU group used cholinesterase inhibitors. There is a significant difference between the groups. This implicates that neurofeedback in combination with cholinesterase inhibitors has a positive effect on the cognitive performance of patients with AD, especially on the recognition and recall of information. However, the previous mentioned differences between the groups, the attention the patients receive from the practitioner and the level of activation, could reinforce this effect. In order to explore the mere effect of neurofeedback, the treatment both groups receive need to be the same and the patients have to stop taking their medication. As long as neurofeedback is not acknowledged as a treatment for AD, the termination of the medication cannot be ethically justified. Another strength of this study is that the training protocol is individualized. This is important, since research has shown that there is considerable heterogeneity in the EEG patterns that are associated with diagnostic categories and symptoms, like AD. The use of one standard protocol may increase the risk on an ineffective or adverse treatment [43].

The results of this study indicate that neurofeedback, in combination with treatment with cholinesterase inhibitors, may be a potential treatment by which the progressive deterioration in patients with AD can be stabilized. There are still some limitations that need to be

addressed. However, it is hypothesized that the forthcoming clinical trial will be able to address these issues and assess the potential of neurofeedback as a treatment for AD. Future research can investigate if neurofeedback leads to changes in the behavior and qEEG of patients with AD. Does the stabilization of the deterioration lead to changes in the behavior of patients with AD (e.g. decrease in apathy) and are these changes visible in their qEEG?

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