THE RELATIONSHIP BETWEEN EEG DATA, COGNITIVE FUNCTIONING AND NEUROPSYCHIATRIC SYMPTOMS IN ELDERLY PATIENTS WITH ALZHEIMER'S DISEASE

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Abstract

Background: Alzheimer's disease is a growing problem in our society. Current treatment options are limited, so it might be worthwhile to consider neurofeedback training as a new treatment option. That is, if it can be confirmed that there are significant relations between cognitive functioning and EEG data. The current study examines if there are significant relationships between cognitive functioning, neuropsychiatric symptoms and brain activity. **Methods**: a neuropsychological screening and qEEG were administered pre-treatment. Twelve patients were included in the analyses. **Results:** ten of the variables comprehending cognitive functioning, depression, quality of life and behaviour correlated significantly with components reflecting the delta, theta, alpha and beta frequency bands. **Conclusions:** relations between cognitive functioning and activity in certain brain areas are diverse and cannot be defined within one location in the brain. However, there are significant correlations between subscales measuring specific aspects of cognitive functioning and some brain areas. For depression a significant correlation was found between cognitive complaints and central activity. Concerning quality of life and behaviour a higher quality of life and less behavioural problems were found to be related to more activity in the anterior as well as posterior areas of the brain.

Samenvatting

Achtergrond: de ziekte van Alzheimer is een groeiend probleem in onze samenleving. De huidige behandelmogelijkheden zijn beperkt, dus wellicht is het zinvol om neurofeedback training te overwegen als nieuwe behandeloptie. Echter, dan moet eerst worden bevestigd dat er significante relaties zijn tussen cognitief functioneren en EEG data. Deze studie onderzoekt of er significante relaties bestaan tussen cognitief functioneren, neuropsychiatrische symptomen en hersenactiviteit. **Methoden**: een neuropsychologische screening en een qEEG werden afgenomen voordat de neurofeedback training plaatsvond. Twaalf proefpersonen werden geïncludeerd in de analyses. **Resultaten**: tien van de variabelen die cognitief functioneren, depressie, kwaliteit van leven en gedrag omvatten correleerden significant met de componenten die de delta, theta, alfa en beta band weerspiegelen. **Conclusies**: relaties tussen cognitief functioneren en activiteit in de hersenkwabben zijn divers en kunnen niet worden benoemd onder één hersengebied. Er worden wel significante correlaties gevonden tussen specifieke aspecten van cognitief functioneren en schedellocaties. Betreffende depressie werd een significante correlatie gevonden tussen cognitieve klachten en centrale activiteit. Voor kwaliteit van leven en gedrag werd gevonden dat een hogere kwaliteit van leven en minder gedragsproblemen gerelateerd zijn aan meer activiteit in de anterieure en posterieure hersengebieden.

Keywords: neurofeedback, qEEG, Alzheimer's disease, cognitive functioning, depression, quality of life, behaviour, frequency band, scalp location.

1. Introduction

Alzheimer's disease (AD) and dementia are a growing problem in our aging society and a rapidly increasing subject of concern for healthcare. Worldwide, nearly 35.6 million people are diagnosed with dementia. It is expected that this number will double by 2030 and triple by 2050. Dementia affects people in all countries and currently costs the world more than US$604 billion per year (1). AD is responsible for 60 – 80% of all dementia cases (2,3). It is characterized by cognitive decline, behavioural and psychological symptoms, and reductions in functioning and independence (2). In our aging society, a growing number of patients are diagnosed with dementia while they are still in the early stages of the disease. Most of them function relatively well in their daily activities when the suspicion for dementia is first raised (4). As the disease progresses it becomes increasingly difficult to manage the disease and guard the patients' (and their caregivers') independence and well-being. The management of dementia may be further complicated by the presence of neuropsychiatric symptoms as depression and behavioural problems. Estimated rates of psychological and behavioural problems range from 60 – 80%. These psychological and behavioural problems, rather than the cognitive problems or functional impairments, have been found to impose the biggest burden on caregivers (5). To relieve both patients and caregivers, who play a significant role in guarding the independence of patients with AD, it is important to find effective methods for managing behavioural and psychological symptoms of dementia.

There is increasing recognition of the complexity of AD, the likelihood that multiple treatments will be needed at different stages of the disease and that treatment will require more than drugs (6). Momentarily, there are no cures for AD. The treatments available are limited and mostly pharmacological. Two groups of drugs have become licensed for treatment: acetylcholinesterase inhibitors (Donepezil, Rivastagmine, Galantamine) and glutamate receptor antagonists (Memantine). The most these drugs can achieve is to modify the manifestations of AD. In addition, they might have side effects which may limit the ability of patients to take the drugs (7). Pharmacological treatments for behavioural and psychological symptoms of dementia also have limited efficacy and possible adverse effects (8,9). With regard to non-pharmacological treatments there is general agreement that the outcomes vary. High quality studies are scarce and there is lack of evidence on the effectiveness of some well-established approaches as multisensory stimulation, music therapy, bright light therapy and behaviour management (10).

Considering the limited efficacy of both the pharmacological and non-pharmacological treatment options for AD, it might be time to review the possibility of treatment from a broader perspective. One therapy which is being investigated as a possible treatment for patients with AD is neurofeedback (NFB); also known as electroencephalography (EEG) biofeedback. NFB is a conditioning procedure in which individuals learn to self-regulate (i.e. actively

control and change) their brain activity. Both classical and operant conditioning concepts are used for conditioning the patients' EEG. The EEG is produced by synchronous postsynaptic potentials from thousands to millions of neurons and is usually recorded at the scalp. When the data are amplified, digitized and plotted a raw EEG signal appears as a composite oscillatory pattern. This signal can then be filtered to isolate narrow frequency bands, which are defined in Hz. Those frequency bands reflect specific brain sources and functions (11). NFB training aims to change the amplitude of one or more of those frequency bands in the brain (delta: 0 – 4 Hz; theta: 4 – 7 Hz; lower and upper alpha: 7 – 12 Hz; sensorimotor rhythms: 12 – 15 Hz; beta: 15 – 20 Hz and gamma 30 – 80 Hz). During NFB training desirable brain activity is rewarded and undesirable brain activity is inhibited (12). The encouragements and discouragements are given through visual and/or auditory representations of converted EEG signals from specific cortical areas (13). The training of the brain through NFB is enabled by plasticity: the ability of the brain to change neural structures and functions in response to experiences and environmental influences. During aging plasticity remains: the connections in the brain are not fixed, but retain the capacity to change with learning (11,14). The normal aging process involves a decrease of overall EEG activity and a decrease of the power of the alpha band, combined with increased delta and/or theta activity (15). AD accelerates the normal aging process. Patients with AD show even more theta activity, compared to healthy aging individuals. More delta activity and a reduction in alpha and beta activity were also observed (16). Therefore, NFB training in patients with AD should aim to reduce activity in the low frequency bands (i.e. delta and theta activity) and increase activity in the high frequency bands (i.e. alpha and beta activity). NFB training is sometimes used to try to normalize the EEG and thereby improve several cognitive functions (17). There are several studies which have reported enhanced cognitive performance in patients with neurological diseases following non-invasive brain stimulation (11,14),17). Becerra et al. (17) suggested that NFB training may be useful for the treatment of elderly people with electroencephalographic risk of cognitive impairment. They found that in normal elderly subjects, high theta EEG activity is the best predictor of cognitive impairment. Furthermore, relationships between brain regions and specific cognitive functions have been found. While the occipital lobes perform mainly basic functions (like visual perception), the frontal lobes perform higher cognitive functions (like planning and reasoning) (19).

It is thought that NFB training might also have a positive effect on behaviour and psychological aspects, such as depression and quality of life. There is much support for theories which relate EEG frontal cortical asymmetry (increased frontal alpha and increased frontal beta asymmetry) to depression (20). Also, an increased resting beta power was found in depressive males (21). Dias & van Deusen (22) wrote a review on NFB and depression. They found only six studies which presented original clinical data and all those studies had

methodological limitations. However, the results were encouraging: an effectiveness of 92% (23) and long-lasting effects were found (24). The permanent elimination of the alpha asymmetry which Beahr et al. (24) found is especially remarkable, because several studies have found that after drug treatment for depression the asymmetry remained, indicating a continued vulnerability for future depressive episodes (25,26). Hammond (27) found significant improvements after NFB training in 77.8% of the depressed patients included in his study.

According to the world health organization, quality of life (QoL) is defined as individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns (28). QoL is a very important consideration in medical care and refers to the patients' ability to enjoy normal activities and everyday life. Little research is done on relationships between quality of life and EEG data and on the effects of NFB on QoL. However, up until now results are promising. Larson, Ryan and Baerentzen (29) report the on-going effectiveness of NFB training on improving health conditions through symptom reduction and enhancing QoL. NFB training has improved the perceptions of QoL in patients with diabetes mellitus type 1 (30). Case studies have found improvements of QoL after NFB training in patients with chronic fatigue symptoms (31) and movement disorders (32).

According to Vernon et al (33) NFB training is a potentially successful technique to influence behaviour, because of the associations between changes in alpha activity and alterations in mood and/or cognition. Unfortunately, little research is done on the association between behavioural changes, EEG activity and NFB training (in general as well as in patients with dementia). However, there are several studies which describe that NFB training targeting cognitive impairment also results in improvements in behaviour (11,17).

To find out how to administer NFB training in a manner that might positively influence cognitive functioning and decrease neuropsychiatric symptoms it must be examined whether cognitive functioning and neuropsychiatric symptoms are related to activity in different areas of the brain in elderly patients with AD.

1.1 The Present Study

The objective of this study is to examine if there are significant relations between frequency bands and certain brain areas. Furthermore, this study aims to assess whether activity in the brain correlates significantly with variables comprehending cognitive functioning, depression, quality of life and behaviour in elderly patients with Alzheimer's disease. It is relevant to determine this, because most neurofeedback therapists who use qEEG's say that they think they perform better trainings based on qEEG abnormalities specific for the patient's disease or complaints (34). Thus, before it can be assessed whether

NFB training is potentially efficacious in improving cognitive functioning and reducing neuropsychiatric symptoms it has to be examined which qEEG abnormalities are related to cognitive functioning and neuropsychiatric symptoms in elderly patients with Alzheimer's disease. Based on the existing literature it is expected that there are clear links between cognitive functioning and qEEG abnormalities (11,17,35,36). Literature describes positive relations between cognitive functioning and the alpha rhythm (37) and also positive correlations between cognitive impairment and theta activity (Beccera et al., 2011). However, alpha frequency is inversely correlated with age after the twentieth year of life (38) and is known to be lower in patients with Alzheimer's disease (39). So, it is expected that there are negative correlations between cognitive functioning and the alpha and theta rhythms in elderly patients with Alzheimer's disease. Concerning the neuropsychiatric symptoms the existing literature suggests that depression correlates with increased frontal alpha and beta asymmetry and an increased beta power (20,21). The existing literature does not provide enough information to form explicit expectations concerning the relation between quality of life, behaviour and qEEG abnormalities. Yet, some studies describe that NFB training targeting cognitive impairment also results in improvements in behavioural measures (11,17). Furthermore, it is expected that a higher age will correlate with less alpha and beta activity and more delta and theta activity (15,16).

2. Methods

2.1 Participants

Participants for the current study were recruited through the outpatient memory clinic from the Catharina Hospital in Eindhoven. Patients who got the diagnosis 'probable Alzheimer's disease' were contacted if they met the inclusion criteria. Patients received the diagnosis 'probable Alzheimer's disease' after visiting the memory clinic. Diagnosis was based on the findings of a geriatrician (physical examination, blood tests), a psychologist (neuropsychological screening), a nurse (heteroanamnesis) and a neurologist (MRI scan). To meet the inclusion criteria, patients should have a total score of 60 points or higher on the Cambridge Cognitive examination (CAMCOG) (40): a cognitive screening instrument for dementia. This cut off score is seen as an indication that the patient is at an early stage of Alzheimer's disease. Additionally, patients had to be older than sixty years and should be living independently (or possibly assisted). The patients should be able to visit the hospital twice a week for a period of fifteen weeks in a row. Because of the neuropsychological screening, a sufficient understanding of the Dutch language was required. Furthermore, patients had to get a positive advice for participation in the study by the multidisciplinary team of the memory clinic. This team consisted of the above mentioned geriatricians, neurologists, psychologists and nurses. Patients with a medical history of psychiatric or neurological disorders, such as epilepsy, stroke or a brain/spinal tumor were excluded. A total of twelve patients with AD participated in this study. Unfortunately, two patients did not complete the study. One patient quit the study because of hip surgery. The other patient quit because of anxiety. Participants were offered a travel allowance.

Table 1 shows the group means and standard deviations of gender, age and education for the total group of participants. More males than females were included in the study. The participants were aged between 61.10 and 83.0 years. Deviation IQ scores, calculated from total scores on the Nederlandse Leestest voor Volwassenen (41) according to the norms of Mulder et al. (42), differed between 67 and 145 (M = 106.17, SD = 25.56). The educational level was on average around four according to Verhage's education scale. This is equal to secondary professional education.

Table 1.

Descriptive Statistics for the Pre-Treatment Measurement

	Pre-treatment (N=12)					
Variable	*Gender*		*Age*		*Education*	
	Male (N)	Female (N)	M	SD	M	SD
	8	4	72.23	6.89	4.25	1.71

2.2 Apparatus

2.2.1 qEEG

The quantative EEG (qEEG) was made with the DeyMed TruScan, using TruScan software. Subsequently, the EEG data were processed to a qEEG using Neuroguide software. This software processes data with both 'linked-ear' and 'laplacian' montages. Through a Fast Fourier Transformation (FFT) the following frequencies were analysed: delta (1 – 4 Hz); theta (4 – 8 Hz); lower alpha (8 – 10 Hz); upper alpha (10 – 12 Hz); lower beta (12 – 15 Hz); midrange beta (15 – 18 Hz); upper beta (18 – 25 Hz); high beta (25 – 30 Hz); lower gamma (30 – 35 Hz); upper gamma (35 – 40 Hz) and high gamma (40 – 50 Hz).

2.2.2 Questionnaires

2.2.2.1.Nederlandse Leestest voor Volwassenen

The Nederlandse Leestest voor Volwassenen (NLV) is the Dutch version of the National Adult Reading Test. Both tests consist of a set of words that have an irregular pronunciation. Participants read the words aloud. The total score is the number of correctly pronounced words. The NLV provides a good estimation of premorbid intelligence levels in patients with brain diseases and/or damage, and also for patients with dementia. The internal consistency and inter-rater reliability of the NLV are respectively 0.89 – 0.95 and 0.95 – 0.96 (41).

2.2.2.2. Cambridge Cognitive Examination

The Cambridge Cognitive Examination (CAMCOG) is a concise neuropsychological screening instrument to determine cognitive decline in the elderly. It was developed for the early diagnosis and monitoring of dementia in the elderly. The screening compromises a large number of cognitive functions. The 67 items of the CAMCOG are grouped into eight subscales, namely: orientation (time and place); language (comprehension and expression); memory (past, recent and learning); attention; praxis (construction and ideomotor); calculations; abstract reasoning and perception. For the CAMCOG the educational attainment is divided in three levels: low, average and high. There are different cut off scores for the different educational levels. Also, different cut off scores are used for the various age groups (40). The internal consistency is 0.82 for the first administration and 0.89 for the second (43). The inter-rater reliability ranged from 0.83 – 1.00 (44,45).

When a CAMCOG score is mentioned in the present study, this score is not the raw CAMCOG score, but a proportion of that score: the score obtained on a (sub)scale divided by the maximum score of the same (sub)scale.

2.2.2.3 Mini Mental Status Examination

The Mini Mental Status Examination (MMSE) is a short screening instrument for cognitive impairment in older adults. It covers a variety of cognitive domains. All eleven items of the MMSE are included in the CAMCOG screening, so administration of the CAMCOG also yields an MMSE score.

2.2.2.4 Beck Depression Inventory-II-NL

This self-report questionnaire is used to measure the overall severity of depression. It was developed to assess symptoms in accordance with the DSM-IV criteria. The questionnaire contains 21 rows with statements of complaints from which the patient is supposed to choose the statement that best describes his/her feelings for the last two weeks, including today. The total score is a measure of the overall severity of depression. It can indicate a minimal, light, moderate or severe depression. The total score can be divided into three subscales, namely the affective, somatic and cognitive dimension. For certain circumstances, such as research into the effects of a given treatment, usage of the three subscales can add relevant extra information. The internal consistency ranges from $\alpha=0.92 – 0.93$. The test-retest reliability was $r=0.93$ ($\alpha= <0.001$) (46).

2.2.2.5 Cornell Scale for Depression in Dementia

The Cornell Scale for Depression in Dementia (CSDD-D) is a rating scale for depression in moderate to severe dementia. The scales are rated by a clinician based on information obtained through an interview with the patient and a caregiver (nurse/partner/relative). The interview focuses on signs and symptoms occurring during the week preceding the interview. Adding all item scores will result in a total score which indicates either the absence of significant depressive symptoms, or a probable or definite major depression. The total score can be divided into five domains, namely: mood related characteristics, behavioural disturbances, physical characteristics, cyclic functions and disturbances in thought contents. The coefficient alpha was 0.84, suggesting that the CSDD-D is internally consistent (47). In the current study only four subscales were administered, namely: mood related characteristics, behavioural disturbances, physical characteristics and cyclic functions.

2.2.2.6 Neuropsychiatric Inventory Questionnaire

This questionnaire was designed as a measuring instrument to get an impression of possible psychopathological symptoms in patients with Alzheimer's disease or other dementias. It includes twelve behavioural aspects, namely: delusions; hallucinations; agitation/aggression; depression/dysphoria; fear; euphoria/elation; apathy/indifference;

disinhibited behaviour; irritability/lability; aimless repetitive behaviours; nocturnal restlessness/sleeping disorders and changes in appetite/eating behaviour. The Neuropsychiatric Inventory Questionnaire (NPI-q) is based on an interview with a caregiver of the patient, who should be well informed with regard to any problems. The NPI-q is specifically suitable for assessing behavioural changes in a specific time period, for example to record changes which occur as a result of treatment (48). The test-retest reliability between the total symptom and distress scores on the NPI-q were 0.80 and 0.94 respectively ($\alpha < 0.001$) (49).

2.2.2.7 The World Health Organization Quality of Life questionnaire

This questionnaire should be self-administered and was developed to provide a short quality of life assessment. The World Health Organization Quality of Life questionnaire (WHOQOL-BREF) allows the gathering of quality of life data on four domains, namely: physical health, psychological health, social relationships and the environment. In addition the WHOQOL-BREF provides a rating on a scale of one to five for the patients' overall perception of quality of life and the patients' overall perception of health. This way the questionnaire can facilitate the understanding of diseases and the development of treatment methods (28). The reliability of the WHOQOL-BREF is α=0.89. All reliability values are above 0.70, which demonstrates adequate internal consistency (50).

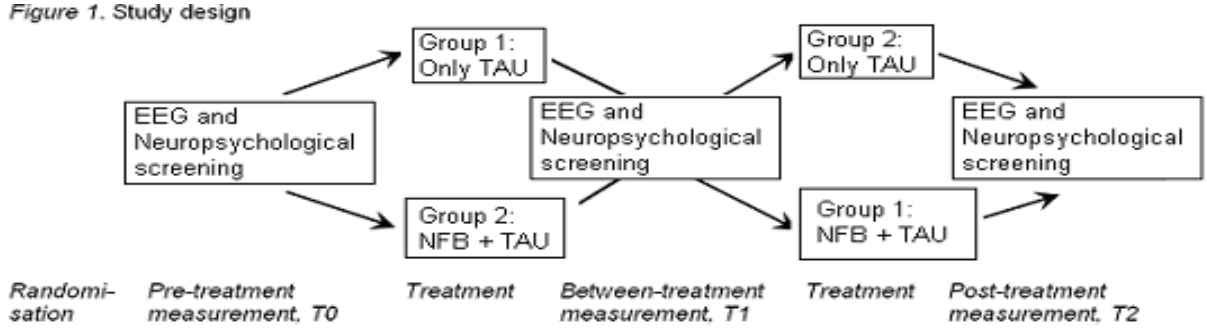
2.3 Procedure

2.3.1 Selection

When a patient received a positive advice for participation in the present study from the multidisciplinary team of the memory clinic, the patient was given an information package and attended an informative meeting. If the patient decided to participate in the study, he/she was asked to sign an informed consent form. Then, he/she was randomly assigned to the group which started with only treatment as usual (TAU condition) or the group which started with TAU and neurofeedback training (NFB condition). Seven patients were assigned to the NFB condition and five patients were assigned to the TAU condition. The present study is part of a large clinical randomized trial with a crossover design. The TAU group first received fifteen weeks of treatment as usual, followed by biweekly neurofeedback sessions for a time period of fifteen weeks. The NFB group first received neurofeedback sessions twice a week for fifteen weeks in a row, followed by fifteen weeks treatment as usual. So, during the course of the participation in the study all participants were allowed to follow standard treatment procedures. The crossover design will control for any effects of these procedures. However, the current study takes only the pre-treatment scores into account; allowing to use a single group of twelve participants instead of two groups of five participants each. Figure 1

shows the design of the study. An EEG scan was scheduled at the Neurofeedback Institute Nederland (NIN) and the patient received an invitation for the scheduled scan and a schedule with regard to the NFB training. In the same week as the scheduled EEG scan, a neuropsychological screening took place (pre-treatment measurement, T0). After fifteen weeks of TAU/NFB a second EEG scan was scheduled at the NIN. A neuropsychological screening took place in the same week as the EEG scan (between-treatment measurement, T1). After the entire thirty weeks a third EEG scan was scheduled at the NIN, combined with a neuropsychological screening (post-treatment measurement, T2). When the last EEG scan and neuropsychological screening were completed, a final meeting was planned to discuss the study with the patient and to give the patient the opportunity to ask questions.

Figure 1. Study design



In the current study only the pre-treatment measurement (T0) was taken into account

2.3.2. Neuropsychological screening

There were three evaluations: pre-, between- and post-treatment. During the pre-treatment evaluation the Nederlandse Leestest voor Volwassenen (41), the CAMCOG (40), D-KEFS Trailmaking Test (51), the WHOQOL-BREF (28), the CSDD-D (47), the NPIq (48) and the BDI-II-NL (46) were administered. During the between- and post-treatment evaluations the CAMCOG, D-KEFS Trailmaking Test, the WHOQOL-BREF, the CSDD-D, the NPIq and the BDI were administered. In case the last CAMCOG administration had taken place less than three months before the evaluation (e.g. at the memory clinic), the CAMCOG was not administered, but the data from the last CAMCOG administration at the memory clinic were used. The administration of the neuropsychological screenings took place at the Catharina hospital by students of the master Medical Psychology.

2.3.3 qEEG

Pre-, between-, and post-treatment an EEG scan was made at the NIN. The EEGs were recorded in two conditions: eyes open (EO) for ten minutes and eyes closed (EC) for ten minutes. Then, the EEG data were transformed into a qEEG report.

2.3.4. Ethics

The current research was approved by the medical ethics committee from the Catharina Hospital in Eindhoven. The research was conducted in accordance with the declaration of Helsinki and the regulations from the WMO. The span of the research is quite long and the biweekly visits can be intense for elderly patients. Patients were told about the duration and intensity in advance of the research and were encouraged not to start, or to quit, the study if they felt it was too much for them.

2.3.5. Analyses

Analyses were performed using SPSS 19.0 for Windows. For the present study the crossover design was not taken into account. Analyses were performed using only the pre-treatment scores; allowing to use a single group of twelve participants instead of two groups of five participants each. For all statistical tests alpha levels of .05 were used.

Correlations between all the scores and subscores comprehending cognitive functioning, depression, quality of life and behaviour were computed by means of Pearson's correlation coefficient. Variables included in analyses were total scores on the CAMCOG, the D-KEFS Trail Making Test, WHOQOL-BREF, BDI-II-NL, CSDD-D and NPI-q and scores on the various subscales (see table 2). Based on those correlation coefficients a number of low correlating variables were selected onto which further analyses were carried out. For an overview on which variables were retained, see table 2.

To reduce the amount of data resulting from the pre-treatment qEEG, principal components analysis (PCA) was performed. The extraction of components by a PCA involves determining the smallest number of components that can be used to best represent the relations among a set of variables. It can reduce a complex data set to reveal simplified dynamics that often underlie the data. So, a component is effectively a new virtual variable summarizing the more complex data. PCA was computed per frequency band for the delta, theta, alpha and beta band. The gamma frequency band was not included in the analyses, because literature shows that the gamma band does not seem to have clear links with cognitive functioning, depression, quality of life and behaviour. The eyes open and eyes closed condition were taken into account at once.

In order to assess if the components representing the frequency bands correlated with the variables comprehending cognitive functioning, mood, behaviour and quality of life Pearson product-moment correlations were computed for the pre-measurement moment.

Table 2.

Various Tests with Corresponding Subscales and the Low Inter-Correlating Variables Retained for Analysis After Computing Pearson Product-Moment Correlation Coefficients

Test	Subscales	Variables retained
CAMCOG	Total score	Total score
	Orientation – total / time / place	Orientation – total / time
	Language – total /comprehension / expression	Language – comprehension
	Memory – past / recent / learning	
	Attention	Attention
	Praxis – total / construction / ideomotor	Praxis – total
	Calculations	
	Abstract reasoning	
	Perception	Perception
	Memory section / Non-memory section	Memory section / Non-memory section
	MMSE	
D-KEFS Trail Making Test	Total score	Total score
WHOQOL-BREF	Total score	Total score
	Overall perception of QoL/ health	Overall perception of health
	Physical health	
	Psychological	
	Social relationships	
	Environment	
BDI-II-NL	Total score	Total score
	Cognitive / somatic / affective domain	Cognitive domain
CSDD-D	Total score	Total score
	Mood related characteristics	
	Behavioural disturbances	
	Physical characteristics	
	Cyclic functions	Cyclic functions
NPI-q	Total score (# Yes)	Total score (# Yes)
	Severity / Emotional strain on:	
	Delusions	
	Hallucinations	
	Agitation/aggression	
	Depression/dysphoria	Depression/dysphoria
	Fear	
	Euphoria/elasion	Euphoria/elasion
	Apathy/indifference	
	Disinhibited behaviour	
	Irritability/lability	
	Aimless repetitive behaviour	
	Nocturnal restlessness/ sleep disorder	Nocturnal restlessness/ sleep disorder
	Appetite/changes in eating behaviour	

3. Results

3.1 Principal components analysis

The qEEG values of the pre-treatment EEG scans were, per frequency band, subjected to principal components analysis (PCA). In every PCA analysis there were nineteen variables and twenty-four cases included for twelve participants. For all PCA's the number of cases was double the amount of participants, because the eyes open and eyes closed condition were taken into account at once. The small sample size might have negatively affected the factorability of the data. The strength of the intercorrelations among the items were mostly strong enough; the correlation matrices showed that most coefficients were above .3. Due to the small amount of subjects Bartett's test of sphericity and the Kaiser-Meyer-Olkin measure of sampling adequacy could not be computed. So, the factorability of the data could not be assessed and assumptions might be violated. Analyses were still performed, but results should be interpreted carefully. The decisions with regard to the amount of components that was retained for further research was based on Catell's scree test. In addition, the total amount of components retained should account for approximately 90% of the variance and preferably eigenvalues should exceed one. To aid in the interpretation of all components, Varimax rotation was performed.

3.1.1 Delta

Principal components analysis revealed the presence of two components with eigenvalues exceeding 1, explaining 80.5% and 9.7% of the variance respectively. An inspection of the screeplot revealed a clear break after the second component. Using Catell's scree test is was decided to retain two components for further analysis. The two-component solution explained a total of 90.3% of the variance. The components were named 'anterior delta' and 'posterior delta'.

3.1.2 Theta

Principal components analysis revealed the presence of two components with eigenvalues exceeding 1, explaining 85.1% and 9.2% of the variance respectively. An inspection of the screeplot revealed a clear break after the second component. Using Catell's scree test is was decided to retain two components for further analysis. The two-component solution explained a total of 94.2% of the variance. Components were named 'anterior theta' and 'posterior theta'.

3.1.3 Alpha

Principal components analysis revealed the presence of one component with an eigenvalue exceeding 1, explaining 91.8% of the variance. An inspection of the screeplot

revealed a clear break after the first component. Using Catell's scree test is was decided to retain one component for further analysis. The one-component solution explained a total of 91.8% of the variance. The component was named 'alpha'.

3.1.4 Beta

Principal components analysis revealed the presence of two components with eigenvalues exceeding 1, explaining 74.3% and 9.9% of the variance respectively. An inspection of the screeplot revealed a clear break after the second component. Using Catell's scree test is was decided to retain two components for further analysis. The two-component solution explained a total of 84.2% of the variance. The two components were named 'central beta' and 'posterior beta'.

3.2 Components versus scalp locations

Table 3 (see the appendix) shows which of the nineteen scalp locations load strongly on the eight components retained from the previously mentioned PCA analyses. The bottom row of the table displays the labelling of the locations for the eight components. For example, for component 'anterior delta' strong loadings consist of mainly anterior locations, but also central locations. In figure 1, 2, 3 and 4 (see the appendix) the strong loading scalp locations for every component are shown graphically per frequency band. The orange circles stand for the strongest loadings; the yellow circles for the slightly weaker loadings.

3.3 Pearson product-moment correlation

For the pre-treatment measurement moment the relationships between the eight components reflecting the qEEG values and the variables comprehending cognitive functioning, mood, behaviour and quality of life were investigated using Pearson product-moment correlation coefficients. All Pearson correlation coefficients, associated p-values and coefficients of determination between the variables and the components are shown in table 4 in the appendix.

3.4 Components versus cognitive functioning and neuropsychiatric symptoms

As can be seen in table 4 there are various significant correlations between the variables and the components reflecting the different frequency bands. In table 5 the significant correlations are highlighted and interpreted.

Table 5.
Significant Correlations Between Variables and Components, Related to Scalp Locations

Variable	Correlates significant with - Component	Is related to – Locations
Gender	Posterior delta	Posterior and central
Age	Posterior theta	Posterior and central
	Alpha	All locations
Orientation in place	Anterior theta	Anterior
	Posterior beta	Posterior
Concept of language	Posterior delta	Posterior and central
	Central beta	
Perception	Posterior delta	Posterior and central
D-KEFS Trail Making Test total score	Central beta	Central
BDI cognitive	Central beta	Central
WHOQOL total score	Anterior theta	Anterior and posterior
	Posterior beta	
Overall perception of health	Anterior theta	Anterior
Euphoria Y/N	Anterior theta	Anterior

Gender is significantly correlated with the posterior delta component; indicating that being a female is related to more activity in the posterior and central locations in the brain. Age is significantly correlated with components posterior theta and alpha. The correlations are positive, meaning that a higher age seems to correlate with more activity on all scalp locations. For orientation in place a significant correlation with the anterior theta and posterior beta components can be seen. These are negative correlations, indicating that a lower score on the subscale orientation in place is related to more activity in the anterior as well as posterior locations in the brain. The subscore concept of language is significantly correlated with the posterior delta and central beta components. The correlations are positive, meaning that a better understanding of language seems to be related to more activity in the central and posterior locations in the brain. For perception a significant negative correlation with the posterior delta component can be seen, indicating that a lower score on the subscale perception is also related to more activity in the central and posterior locations of the brain. The total score on the D-KEFS Trail Making Test is significantly correlated to component central beta. This correlation is positive, meaning that a higher score on the test is related to more central activity. For the subscore cognitive complaints from the BDI-II-NI a significant

positive correlation can be seen with the central beta component. This indicates that experiencing more cognitive complaints is related to more central activity. The WHOQOL-total score and the overall perception of health subscore are significantly related to the anterior theta and posterior beta components. The correlations are positive, indicating that a better perception of quality of life and health is related to more activity in the anterior as well as posterior locations in the brain. Euphoria, a subscale from the NPI-q, is significantly negatively correlated with the anterior theta component, indicating that a lower score on this subscale is related to more activity in the anterior locations in the brain.

In summary, no obvious relationship between cognitive functioning in general and activity in the various scalp locations was found. However, there are significant correlations between subscales measuring specific aspects of cognitive functioning and the scalp locations. For depression a significant correlation was found between cognitive complaints concerning depression and central activity. Concerning quality of life and behaviour it was found that a higher quality of life and less behavioural problems are related to more activity in the anterior as well as posterior areas of the brain.

4. Discussion

The objective of this study was to examine if there are significant relationships between the delta, alpha, theta and beta frequency bands and the brain areas used for qEEG's in this research. Furthermore, this study aimed to assess whether activity in the brain correlates significantly with variables comprehending cognitive functioning, depression, quality of life and behaviour in elderly patients with Alzheimer's disease.

Based on the existing literature it was expected that there are clear links between cognitive functioning and qEEG abnormalities (11,17,35,36). More explicitly, it was expected that there are negative correlations between cognitive functioning and the alpha and theta rhythms in elderly patients with Alzheimer's disease. Concerning the neuropsychiatric symptoms the existing literature suggested that depression correlates with increased frontal alpha and beta asymmetry and an increased beta power (20,21). The existing literature did not provide enough information to form explicit expectations concerning the relation between quality of life, behaviour and qEEG abnormalities. Furthermore, it was expected that a higher age correlates with less alpha and beta activity and more delta and theta activity (15,16).

Results of the current research showed a significant relation between older age and activity in the posterior theta and alpha frequency band. Thus, the hypothesis that higher age correlates with less alpha and beta activity and more delta and theta activity was partly confirmed. With regard to the location of the activity a higher age correlated with more activity on all scalp locations. No obvious relationship between cognitive functioning in general and activity in the various scalp locations was found. However, there were significant correlations between subscales measuring specific aspects of cognitive functioning and the scalp locations. For depression a significant correlation was found between cognitive complaints concerning depression and activity in the central beta frequency band. So, the hypothesis that depression would correlate with increased frontal alpha and beta asymmetry and increased beta power was also partly confirmed: more beta power was seen, but the asymmetry was not found. Concerning quality of life and behaviour it was found that a higher quality of life and less behavioural problems are related to activity in the anterior theta and posterior beta frequency band. A higher quality of life and less behavioral problems are related to more activity in the anterior and posterior locations in the brain.

Results are promising. It seems that cognitive functioning, depression, quality of life and behaviour are indeed related to activity in certain brain locations. This suggests that NFB might indeed be used to normalize the EEG and thereby improve cognitive functions and reduce neuropsychiatric symptoms. Thus, it is useful to examine whether neurofeedback training is potentially efficacious in improving cognitive functioning and reduce neuropsychiatric symptoms in elderly patients with AD. However, as a consequence of the relatively small amount of subjects and some missing values in the various questionnaires

and qEEG data, results have to be interpreted with caution and care. Moreover, results cannot be generalized to the entire elderly population as more men than women were included in the study. The current study is part of a large randomized clinical trial, so the relationships which were found will be re-examined when data on more participants have been gathered. Another limitation is that all patients were seen by different interns. This might have influenced the results as a consequence of different personalities, social capabilities and methods of treatment.

The limitations mentioned above provide perspectives for future research. During the continuation of the larger study, in which the current research played a part, a control group will be added. This will minimize the chance of alternative explanations of the results when the cross-over design is taken into account. Furthermore, two interns will see each patient alternately, which limits the influence of individual capabilities of the experimenter. When more participants (and controls) have been gathered the effect of NFB training on cognitive functioning, depression, quality of life and behaviour in elderly patients with Alzheimer's disease can be assessed. Then, if there positive effects are found, the long-term effects of NFB training should be examined. To do this, all participants can be invited for a follow-up measurement one, two and three years after the post-treatment measurement moment. Also, it might be interesting to set up a double-blind study including a sham neurofeedback control group to control for unspecific effects. In addition, NFB training seems to have few-side effects at the moment, but future research should focus on those side-effects to be sure there are few.

All in all there seem to be relations between cognitive functioning, depression, quality of life and behaviour and activity in certain brain areas. The relations between cognitive functioning and activity in the various lobes of the brain are diverse and cannot be defined within one specific location in the brain. However, there are significant correlations between subscales measuring specific aspects of cognitive functioning and brain areas. For depression a significant correlation was found between cognitive complaints and central activity. Concerning quality of life and behaviour it was found that a higher quality of life and less behavioural problems are related to more activity in the anterior as well as posterior areas of the brain.

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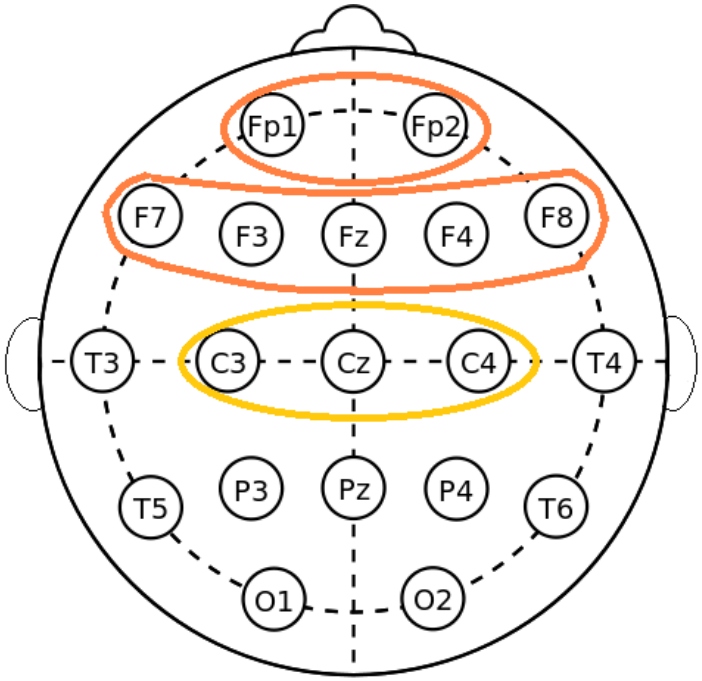
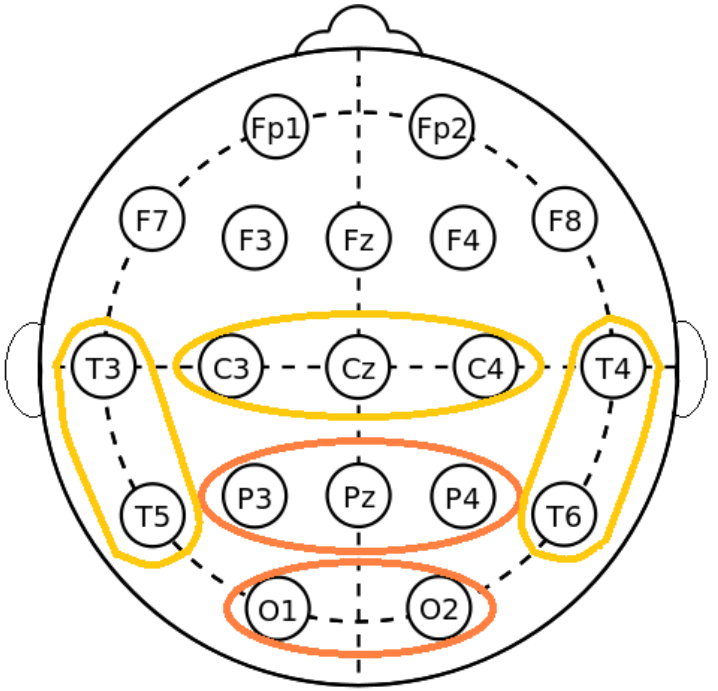
6. Appendix

Table 3.
Loadings of the Different Scalp Locations on the Components

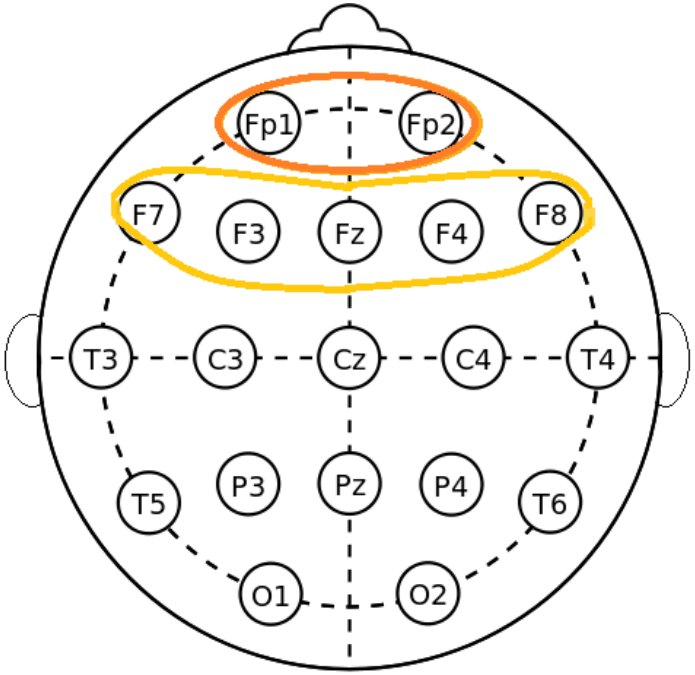
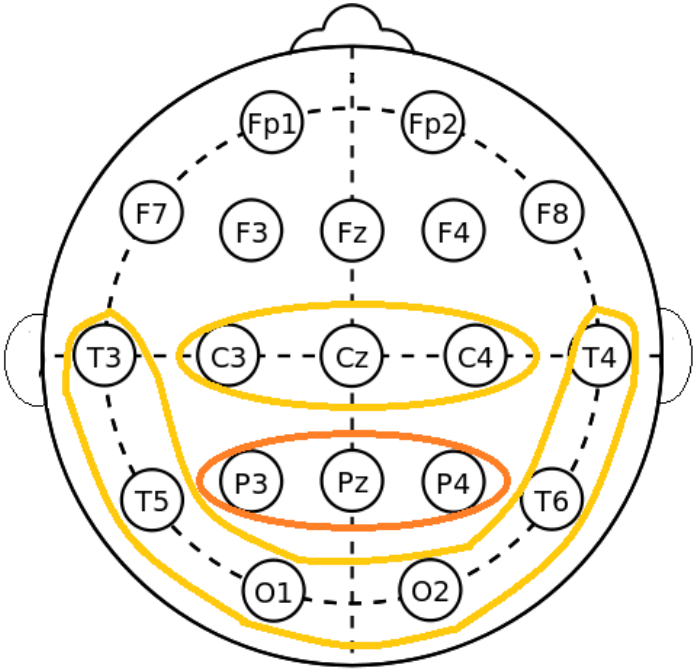
Component / *Location*	Anterior delta	Posterior delta	Anterior theta	Posterior theta	Alpha	Central beta	Posterior beta
Cz	.675	.665	,491	,845	,992	,868	,450
C3	.738	.622	,539	,827	,882	,794	,538
C4	.626	.678	,370	,874	,982	,790	,482
Fz	.917	.339	,676	,683	,947	,730	,601
F3	.918	.378	,734	,661	,971	,474	,847
F4	.812	.403	,659	,690	,964	,560	,767
F7	.851	.441	,801	,571	,968	,536	,675
F8	.849	.450	,752	,650	,969	,644	,502
FP1	.949	.272	,952	,274	,911	,327	,904
FP2	.965	.234	,963	,249	,890	,260	,828
O1	.215	.846	,339	,808	,945	,115	,370
O2	.390	.796	,401	,835	,927	,184	,348
Pz	.353	.849	,364	,915	,955	,789	,394
P3	.257	.872	,335	,932	,947	,764	,454
P4	.500	.797	,319	,911	,955	,706	,419
T3	.629	.577	,545	,812	,980	,777	
T4	.583	.685	,465	,856	,960	,343	
T5	.274	.895	,371	,895	,967	,479	,298
T6	.508	.764	,372	,896	,986	,509	,414
	Anterior, also central	Posterior, also central	Anterior, also central	Posterior	All brain areas	Central	Posterior

Figure 1.
Scalp Locations Loading Strongly on the Delta Components

Anterior delta	Posterior delta
	

Orange are the strongest loadings
Yellow are the slightly weaker loadings

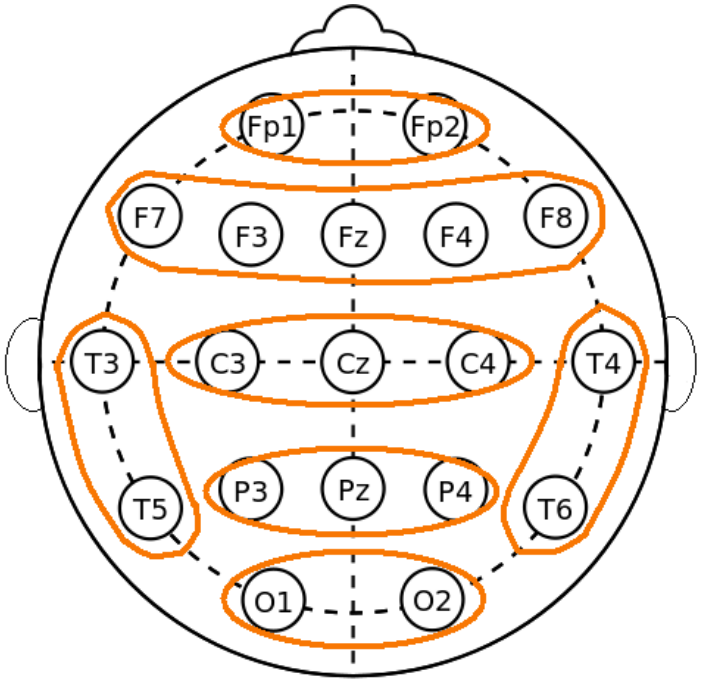
Figure 2.
Scalp Locations Loading Strongly on the Theta Components

Anterior theta	Posterior theta
	

Orange are the strongest loadings
Yellow are the slightly weaker loadings

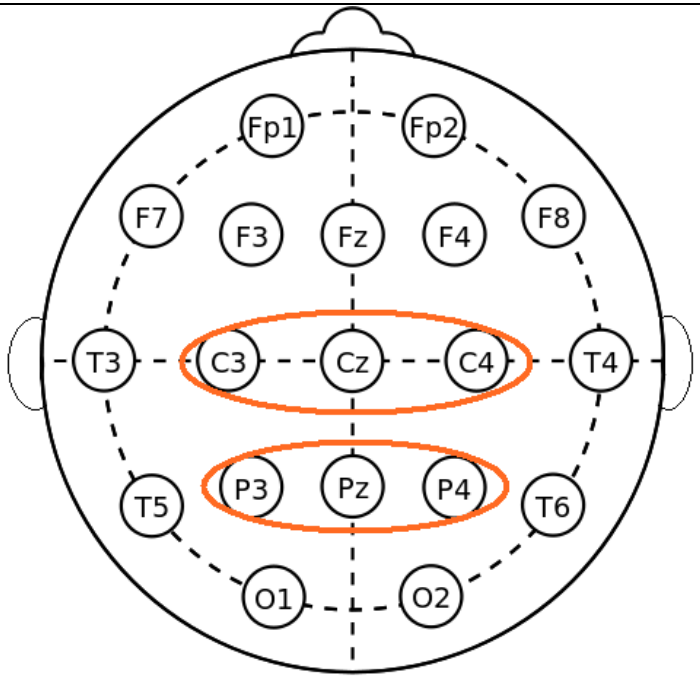
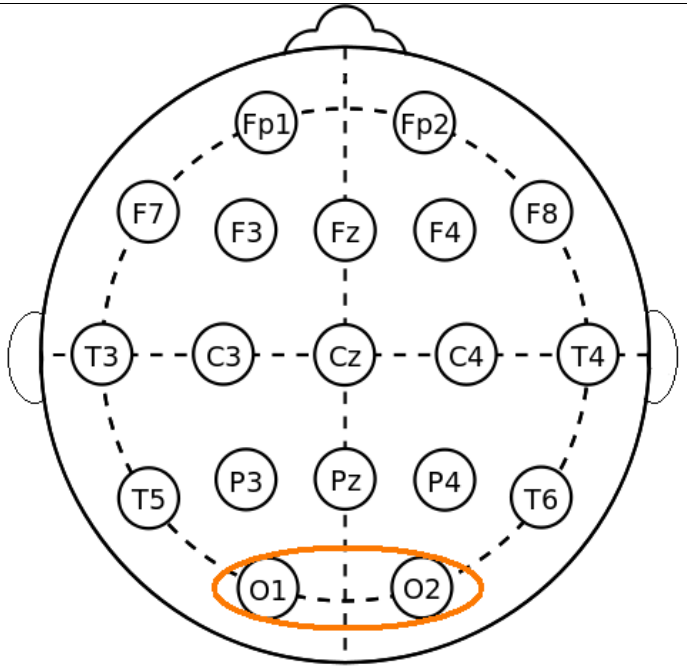
Figure 3.
Scalp Locations Loading Strongly on the Alpha Component

Alpha



Orange are the strongest loadings
Yellow are the slightly weaker loadings

Figure 4.
Scalp Locations Loading Strongly on the Beta Components

Central beta	Posterior beta
	

Orange are the strongest loadings
Yellow are the slightly weaker loadings

Table 4.
Pearson Product-Moment Correlation Coefficients for the Ten Components Reflecting the qEEG Values and Cognitive Functioning, Depression, Quality of Life and Behaviour – Pre-Treatment Measurement Moment

Variables	Anterior delta	Posterior delta	Anterior theta	Posterior theta	Alpha	Beta A	Beta B
Gender							
Pearson correlation	.387	.598*	.391	.421	.298	.538	.449
Sig. (2-tailed)	.214	.040	.209	.173	.347	.071	.143
Coefficient of determination	15.0%	35.8%	15.3%	17.7%	8.9%	28.9%	20.2%
N	12	12	12	12	12	12	12
Education							
Pearson correlation	.159	.182	.202	-.076	.039	.190	-.004
Sig. (2-tailed)	.621	.571	.530	.815	.904	.555	.990
Coefficient of determination	2.5%	3.3%	4.1%	0.6%	0.2%	3.6%	0.0%
N	12	12	12	12	12	12	12
Date							
Pearson correlation	-.383	.004	-.232	.266	.328	.148	-.210
Sig. (2-tailed)	.220	.990	.468	.403	.298	.646	.513
Coefficient of determination	14.7%	0.0%	5.4%	7.1%	10.8%	2.2%	4.4%
N	12	12	12	12	12	12	12
Age							
Pearson correlation	.090	.544	.319	.734**	.723*	.487	.340
Sig. (2-tailed)	.781	.067	.312	.007	.008	.108	.280
Coefficient of determination	0.8%	29.6%	10.2%	53.9%	52.3%	23.7%	11.6%
N	12	12	12	12	12	12	12
NLV score							
Pearson correlation	.270	.402	.294	.011	.170	.452	.114
Sig. (2-tailed)	.395	.195	.354	.972	.596	.140	.724
Coefficient of determination	7.3%	16.2%	8.6%	0.0%	2.9%	20.4%	1.3%
N	12	12	12	12	12	12	12
CAMCOG total							
Pearson correlation	-.172	.048	-.083	-.215	-.093	.080	-.165
Sig. (2-tailed)	.593	.883	.798	.502	.774	.804	.608
Coefficient of determination	3.0%	0.2%	0.7%	4.6%	0.9%	0.6%	2.7%
N	12	12	12	12	12	12	12

Variables	Anterior delta	Posterior delta	Anterior theta	Posterior theta	Alpha	Beta A	Beta B
Orientation total							
Pearson correlation	-.301	.074	.001	-.099	-.037	-.186	.069
Sig. (2-tailed)	.341	.819	.999	.759	.909	.564	.832
Coefficient of determination	9.1%	0.5%	0.0%	1.0%	0.1%	3.5%	0.5%
N	12	12	12	12	12	12	12
Orientation in place							
Pearson correlation	-.478	-.306	-.645*	-.112	-.363	-.149	-.754**
Sig. (2-tailed)	.116	.333	.024	.728	.247	.644	.005
Coefficient of determination	22.8%	9.4%	41.6%	1.3%	13.2%	2.2%	56.9%
N	12	12	12	12	12	12	12
Concept of language							
Pearson correlation	-.213	.761**	.141	.376	.445	.576*	.241
Sig. (2-tailed)	.506	.004	.662	.228	.147	.050	.450
Coefficient of determination	4.5%	61.0%	2.0%	14.1%	19.8%	33.2%	5.8%
N	12	12	12	12	12	12	12
Attention							
Pearson correlation	-.440	-.250	-.477	-.163	-.294	.006	-.569
Sig. (2-tailed)	.152	.434	.117	.613	.354	.984	.053
Coefficient of determination	19.4%	6.3%	22.8%	2.7%	8.6%	0.0%	32.4%
N	12	12	12	12	12	12	12
Praxis							
Pearson correlation	-.087	-.357	-.268	-.208	-.210	-.152	-.349
Sig. (2-tailed)	.787	.255	.399	.516	.513	.637	.266
Coefficient of determination	0.8%	12.7%	7.2%	4.3%	4.4%	2.3%	12.2%
N	12	12	12	12	12	12	12
Perception							
Pearson correlation	-.411	-.622*	-.512	-.585*	-.568	-.378	-.411
Sig. (2-tailed)	.184	.031	.089	.046	.054	.225	.185
Coefficient of determination	16.9%	38.7%	26.2%	34.2%	32.3%	14.3%	16.9%
N	12	12	12	12	12	12	12
Memory section							
Pearson correlation	.075	.333	.238	-.138	-.024	.043	.190
Sig. (2-tailed)	.816	.290	.457	.670	.941	.895	.555
Coefficient of determination	0.6%	11.1%	5.7%	1.9%	0.1%	0.2%	3.6%
N	12	12	12	12	12	12	12

Variables	Anterior delta	Posterior delta	Anterior theta	Posterior theta	Alpha	Beta A	Beta B
\Non-memory section							
Pearson correlation	.319	-.192	-.314	-.216	-.121	.087	-.400
Sig. (2-tailed)	.312	.550	.321	.501	.707	.788	.198
Coefficient of determination	10.2%	3.7%	9.9%	4.7%	1.5%	0.8%	1.6%
N	12	12	12	12	12	12	12
D-KEFS TMT							
Pearson correlation	-.525	.247	-.210	.242	.230	.578*	-.255
Sig. (2-tailed)	.080	.439	.512	.449	.473	.049	.423
Coefficient of determination	27.6%	6.1%	4.4%	5.9%	5.3%	33.4%	6.5%
N	12	12	12	12	12	12	12
BDI total							
Pearson correlation	-.123	-.112	.232	.159	.430	.105	-.037
Sig. (2-tailed)	.753	.774	.549	.683	.248	.787	.925
Coefficient of determination	1.5%	1.3%	5.4%	2.5%	18.5%	1.1%	0.1%
N	9	9	9	9	9	9	9
BDI cognitive							
Pearson correlation	.498	-.150	.159	-.288	.035	.312	-.419
Sig. (2-tailed)	.209	.722	.707	.489	.934	.452	.300
Coefficient of determination	24.8%	2.3%	2.5%	8.3%	0.1%	9.7%	17.6%
N	8	8	8	8	8	8	8
CSDD-D total							
Pearson correlation	.160	.148	.165	-.082	-.218	-.168	.155
Sig. (2-tailed)	.681	.705	.672	.835	.573	.665	.690
Coefficient of determination	2.6%	2.2%	2.7%	0.7%	4.8%	2.8%	2.4%
N	9	9	9	9	9	9	9
CSDD-D cyclic functions							
Pearson correlation	.452	.450	.596	-.317	-.030	-.027	.642
Sig. (2-tailed)	.221	.224	.090	.406	.939	.945	.062
Coefficient of determination	20.4%	20.3%	35.5%	10.0%	0.1%	0.1%	41.2%
N	9	9	9	9	9	9	9
WHOQOL total							
Pearson correlation	.499	.438	.641*	.235	.446	.221	.609*
Sig. (2-tailed)	.098	.154	.025	.462	.146	.490	.035
Coefficient of determination	24.9%	19.2%	41.1%	5.5%	19.9%	4.9%	37.1%
N	12	12	12	12	12	12	12

Variables	Anterior delta	Posterior delta	Anterior theta	Posterior theta	Alpha	Beta A	Beta B
Overall perception of health							
Pearson correlation	.459	.181	.606*	.202	.384	-.268	.479
Sig. (2-tailed)	.133	.574	.037	.528	.218	.399	.115
Coefficient of determination	21.1%	3.3%	36.7%	4.1%	14.7%	7.2%	22.9%
N	12	12	12	12	12	12	12
Depression Y/N							
Pearson correlation	.258	-.462	.136	-.193	-.018	-.461	-.402
Sig. (2-tailed)	.537	.249	.748	.647	.966	.250	.323
Coefficient of determination	6.7%	21.3%	1.8%	3.7%	0.0%	21.3%	16.2%
N	8	8	8	8	8	8	8
Euphoria Y/N							
Pearson correlation	-.647	-.047	-.759*	.330	.060	-.130	-.592
Sig. (2-tailed)	.083	.912	.029	.424	.888	.758	.122
Coefficient of determination	41.9%	0.2%	57.6%	10.9%	0.4%	1.7%	35.0%
N	8	8	8	8	8	8	8
Sleep Y/N							
Pearson correlation	-.477	.312	-.671	-.083	-.459	.153	-.179
Sig. (2-tailed)	.232	.452	.068	.845	.252	.717	.671
Coefficient of determination	22.8%	9.7%	45.0%	0.7%	21.1%	2.3%	3.2%
N	8	8	8	8	8	8	8
# Yes NPI-q							
Pearson correlation	-.128	.499	-.150	.387	.362	.605	-.132
Sig. (2-tailed)	.702	.208	.724	.343	.378	.112	.755
Coefficient of determination	49.3%	24.9%	2.3%	15.0%	13.1%	36.6%	1.7%
N	8	8	8	8	8	8	8

* Correlation is significant at the .05 level (2-tailed)
** Correlation is significant at the .01 level (2-tailed)
cd = coefficient of determination (r^2 . 100%)