ARTICLE

Coherence of brain electrical activity: a quality of life indicator in Alzheimer's disease?

Coerência da atividade elétrica cerebral: indicador da qualidade de vida na doença de Alzheimer?

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ABSTRACT

Objective: To investigate the relationships between quality of life (QOL) and clinical and electroencephalogram (EEG) aspects in patients with Alzheimer's disease (AD). **Method:** Twenty-eight patients with mild or moderate AD, 31 with Parkinson's disease (PD), and 27 normal controls (NC) were submitted to: CERAD neuropsychological battery, Hamilton Depression and Anxiety Rating Scales, Functional Activities Questionnaire, QOL scale for patients with AD, and quantitative EEG measures. **Results:** AD and PD patients had similar QOL (31.0 ± 5.8; 31.7 ± 4.8, respectively), worse than that of NC (37.5 ± 6.3). AD patients had lower global interhemispheric theta coherence (0.49 ± 0.04; 0.52 ± 0.05; 0.52 ± 0.05; respectively) than PD and NC. Multiple linear regression for QOL of AD patients revealed that global interhemispheric theta coherence, and Hamilton depression scores were significant factors (coefficients; 58.2 and -0.27, respectively; R^2, 0.377). **Conclusion:** Interhemispheric coherence correlates with QOL regardless of cognitive and functional variables and seems to be a neurophysiological indicator of QOL in AD patients.

Keywords: Alzheimer's disease, EEG, quality of life, Parkinson's disease.

RESUMO

Objetivo: Investigar relações entre qualidade de vida (QV) e aspectos clínico-eletrencefalográficos (EEG) em pacientes com doença de Alzheimer (DA). **Método:** Vinte e oito pacientes com DA, 31 com doença de Parkinson (DP) e 27 controles normais (CN) foram submetidos a avaliações neurocognitivas, escala de depressão de Hamilton e de qualidade de vida para pacientes com DA, questionário de atividades funcionais e medidas do EEG. **Resultados:** A QV foi similar nos grupos DA e DP (31,0 ± 5,8; 31,7 ± 4,8, respectivamente), mas inferior ao CN (37,5 ± 6,3). No grupo DA houve menor coerência inter-hemisférica global teta (CIGT) do que em DP e CN (p < 0,05). Regressão múltipla linear para QV no grupo DA revelou a CIGT e a escala de Hamilton como fatores significativos (coeficientes; 58,2; -0,27, respectivamente; R^2, 0,377). **Conclusão:** A CIGT correlaciona-se com a QV independentemente de variáveis cognitivas e funcionais e parece ser um indicador neurofisológico da QV em pacientes com DA.

Palavras-chave: doença de Alzheimer, EEG, qualidade de vida, doença de Parkinson.

Alzheimer's disease (AD), a chronic and progressive disease, is the most common neurodegenerative illness in older people, and its prevalence is increasing because of higher life expectancy. AD causes cognitive and behavioral decline, compromising the ability of an individual to carry out activities of daily living and to work, and thereby has major psychosocial and quality of life (QOL) repercussions.

The clinical manifestations of Parkinson's disease (PD) are essentially motor, but cognitive and behavioral disturbances also occur, characterizing dementia in approximately 30% of the cases[1,2].

Today the most common and well-known definition of QOL is that of the World Health Organization (WHO), which defines it as an individual's perception of his position in life in the context of the culture and value systems in which he lives and in relation to his goals, expectations, standards, and concerns[3].

In people with dementia, QOL is not an isolated concept among many measurements but the main objective of professional care[4].

Logsdon et al.[5] used the Quality of Life-Alzheimer's disease (QOL-AD) psychometric analysis in a large sample of AD patients and their caregivers and found that is possible for patients with a Mini-Mental State Examination (MMSE) score greater than 10 to reliably and validly rate their own QOL. QOL assessment has been used by studies on the care and treatment of AD patients[6,7].

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By assessing electrical brain activity, electroencephalograms (EEG) have many clinical applications, are inexpensive and risk-free, and many quantitative (qEEG) analyses became possible after the development of digital EEG. Some of these analyses include analysis of absolute power in different frequency bands of brain rhythms and analysis of coherence.

Analysis of absolute power reveals the increases in theta and delta activities and decreases in alpha and beta powers that occur in AD patients[8], and analysis of coherence shows the temporal relationships between different regions, that is, it measures functional connectivity between regions[9]. In patients with mild cognitive impairment or AD/PD dementia, absolute power and coherence measurements correlate significantly with performance in neuropsychological tests[10,11].

Resting state with eyes closed qEEG may show the degenerative changes caused by AD and is considered a noninvasive method for diagnosing and assessing dementia[6].

Depression and changes in the MMSE and Instrumental Activities of Daily Living are important factors associated with QOL in AD patients[7,12]. However, knowledge about QOL factors in AD is limited. Linear regression analysis assessing these factors has shown that the self-rating QOL model explains less than 50% of the variance[4,7].

This study hypothesizes that qEEG variables can contribute to the neurophysiological basics of AD and better characterize QOL-related factors. There are no such studies in the literature.

The objective of this study was to investigate possible relationships between QOL and qEEG analyses of absolute power and coherence in AD patients and compare them with those of PD patients and normal controls.

METHOD

Subjects

This study included a group of AD patients and two control groups, one with Parkinson's disease patients and another with individuals without neurological or psychiatric changes:

(1) Group with AD included 28 patients that meet the DSM IV (American Psychiatric Association, 1994)[13] criteria for dementia and the NINCDS/ADRDA criteria for probable AD[14]. The exclusion criteria were scoring less than eleven in the MMSE, indicative of severe dementia, taking antipsychotics, and having comorbidities that reduce life expectancy significantly. Twelve patients were on acetylcholinesterase inhibitors and four were on antidepressants. They were all living at home;

(2) Group with PD included 31 patients with clinical diagnosis of probable PD according to the criteria provided by Calne et al.[15]. All patients were on L-dopa and were evaluated in the on phase;

(3) Normal control (NC) group included 27 individuals without any history of cognitive decline or previous neurological or psychiatric disorder, matched with the AD group for gender distribution, age, and education level.

All study participants were recruited at the outpatient clinics of the *Hospital e Maternidade Celso Pierro* of PUC-Campinas and had a closely related informant available.

Procedures

The patients and controls were submitted to the following procedures: clinical-neurological assessment; CERAD neuropsychological battery (Consortium to establish a registry for Alzheimer's Disease); Pfeffer functional activities questionnaire; Neuropsychiatric Inventory; Hamilton Depression Rating Scale (HDRS)[16]; Clinical Dementia Rating – CDR; executive function tests, Quality of life scale in Alzheimer's disease (QOL-AD), and qEEG.

The Neuropsychiatric Inventory assesses 10 behavioral disturbances present in patients with dementia: delusions, hallucinations, dysphoria, anxiety, agitation/aggression, euphoria, disinhibition, irritability/lability, apathy, and aberrant motor activity. The score of each item is given by multiplying the frequency (range 1-4) by the severity (range 1-3), and the total score is given by adding the individual item scores.

The Pfeffer functional activities questionnaire investigates the patients' ability to carry out activities of daily living. The score reflects the severity of disability in each activity. Scores higher than five indicate functional impairment. The instrument has been validated for the Brazilian population[17].

QOL was assessed by the patient's version of the QOL scale for Alzheimer's disease developed by Logsdon et al.[5], adapted and validated for the Brazilian population[18]. The scale, structured with simple language and straightforward answers, was designed to minimize the effects of the cognitive decline in AD. The patients answered the questions during an interview, answering thirteen 4-point Likert-type questions (1 = poor and 4 = excellent). The total score ranges from 13 to 52. Although QOL-AD may also be administered to caregivers, this study administered the instrument only to patients (QOL self-ratings) to investigate their perception and related it directly to the qEEG.

Brain computed tomography or magnetic resonance imaging and laboratory testing were also carried out on the patients to rule out other causes of dementia and symptomatic Parkinsonism.

Electroencephalogram

The EEG procedures were the same as those used previously in another study[19] that addressed other questions, had distinct purposes, and made other original scientific contributions.

The EEG was recorded with a resolution of 12 bits, 0.5-35 Hz filters and 200 samples per second, using the Braintech 3.0 equipment (EMSA), with impedance maintained below 10 kΩ. The exam was carried out with the patients lying on their backs, in a silent environment with low intensity lighting. The electrodes were placed according to the International 10-20 System, with the use of an additional

two electrodes placed 1 cm below (left side) and above (right side) the external angle of the eyelid, with the objective of evaluating eye movements. The data referring to the electrodes Fp1, Fp2, F8, and F7 were not computed due to frequent contamination by artifacts related to eye movements. The inter-connected ear lobe electrodes served as the reference. The data were recorded during approximately 12 minutes, alternating resting periods with eyes closed with alert periods when the eyes were open, each period lasting 2 minutes. The individual was stimulated to remain awake when symptoms of somnolence appeared. Stretches of somnolence or sleep were excluded from the quantitative analysis.

About 25 epochs were selected for the quantitative EEG while alert and resting (eyes closed), each lasting 2.56 s. Epochs with more than 100 μV on the electro-oculogram were excluded from the means. After applying the Fast Fourier Transform, the absolute powers (microvolts^2/Hz) of 17 electrodes were studied (Fp2, Fp1 and Oz were not included) in the following frequency bands: delta (0.8 to 3.9 Hz), theta (4.29 to 7.8 Hz), alpha (8.2 to 12.5 Hz) and beta (12.9 till 36.3 Hz). To obtain a normal distribution, the values for absolute power were substituted by their logarithms.

The absolute power averages were calculated for all the electrodes together (global averages).

To analyze for coherence, this was defined as:

$$\text{Coh}_{xy}(f) = [R_{xy}(f)]^2 = \frac{[G_{xy}(f)]^2}{G_{xx}(f)\, G_{yy}(f)}$$

Where $G_{xy}(f)$ denotes the spectral density of the cross-power and $G_{xx}(f)$ and $G_{yy}(f)$ are the respective spectral densities of the power. The interhemispheric coherences between the following pairs of homologue electrodes were calculated: frontal left-right (F3-F4); mid temporal left-right (T3-T4) and occipital left-right (O1-O2). The global averages for interhemispheric coherence were also calculated. The frontal-occipital (F4-O2, F3-O1) average coherence was measure for the intrahemispheric delta, theta, alpha and beta band coherences.

Individuals in the NC group underwent anamnesis, neurological examination, neurocognitive and behavioral assessments, and qEEG.

Data analysis

The continuous variables were expressed as mean and standard deviation (SD), and the categorical variables were expressed as frequencies (%). The student's t-test, analysis of variance (ANOVA), and Pearson Chi-squared test were used to compare the continuous variables and categorical variables.

Multiple regression were used to determine the relationship between predictor variables and continuous outcome variables (dependent variables) using variables with p < 0.10 in the respective prior correlation analyses (independent variables). The data were treated by the software Statistical Package for the Social Sciences (SPSS), version 22. The significance level was set at 5%.

The software IBM SPSS 20.0 determined how QOL-AD scores associated with the study cognitive and behavioral variables, and analyzed qEEG absolute power and coherence in the Groups AD, PD, and NC at a significance level of 5% (p < 0.05).

The effect size was measured by calculating Cohen's f^2 within a multiple regression model[20].

Approval by the Research Ethics Committee

The project was approved by PUC-Campinas' Research Ethics Committee under protocol number no. 0433/11. Appropriate ethical safeguards and protocols have been followed including agreement of patients or their relatives.

RESULTS

Sociodemographic and clinical aspects

Table 1 shows the sociodemographic data and results of the Mini-Mental State Examination, semantic verbal fluency, Neuropsychiatric Inventory, Pfeffer functional activities questionnaire, and QOL-AD of the AD, PD, and NC groups.

Table 1. Age, gender, education level, Mini-Mental State Examination, verbal fluency, Pfeffer functional activities questionnaire, Neuropsychiatric Inventory, Hamilton Depression Scale and Quality of Life – Alzheimer's Disease Patient's Version (QOL-AD) for the Alzheimer's disease (AD), Parkinson's disease (PD), and normal control (NC) groups.

Subjects	AD (N = 28)	PD (N = 31)	NC (N = 27)	Comparison (AD x NC)	p-value (AD x PD)
Age (years)	77.1 (5.6)	68.8 (10.4)	74.0 (6.5)	0.063	0.000*
Male/Female	9/19	21/10	10/17	0.635	0.004**
Education level (years)	3.2 (2.4)	4.2 (3.2)	6.5 (4.5)	0.001*	0.214
Mini-Mental State Examination	15.8 (3.9)	24.0 (4.7)	26.8 (2.0)	0.000*	0.000*
Verbal fluency	5.8 (3.4)	10.7 (4.6)	14.4 (3.9)	0.000*	0.000*
Pfeffer questionnaire	18.4 (9.5)	4.6 (7.2)	0.5 (1.5)	0.000*	0.000*
Neuropsychiatric Inventory	19.0 (15.6)	14.2 (13.6)	2.9 (5.7)	0.000*	0.839
Hamilton Depression Scale	12.8 (7.3)	10.1 (7.9)	4.6 (4.3)	0.000*	0.171
QOL-AD	31.0 (5.8)	31.7 (4.8)	37.5 (6.3)	0.000*	0.673

The standard deviations for the means are in parentheses. *t-test, p < 0.05; **Chi-square, p < 0.05.

The ages and gender distribution of the AD and NC groups did not differ significantly. However, the education level of the AD group was significantly lower than that of the NC (t-test, p < 0.05).

The AD group performed worse in the MMSE and verbal fluency test than the PD and NC groups (t-test, p < 0.05).

The AD group scored higher in the functional activities questionnaire than the PD and NC groups. However, the AD and PD groups scored similarly in the Hamilton Depression Scale and Neuropsychiatric Inventory; their scores were higher than those of the NC group (t-test, p < 0.05).

The NC group had higher QOL-AD scores than the AD and PD groups. The scores of the latter two were similar (t-test, p < 0.05).

Qualitative electroencephalogram

Comparative analysis of global absolute powers (delta, theta, alpha, and beta) showed that the theta band of the AD group was higher than that of the NC but the difference was not significant (t-test, p = 0.079). The AD and PD theta bands did not differ (data not shown).

The delta, theta, alpha, and beta frontal-occipital (F4-O2, F3-O1) means of the AD, PD, and NC groups did not differ.

Table 2 shows that the mean global interhemispheric theta, alpha, and beta coherences of the AD group were smaller than those of the PD and NC groups (t-test, p < 0.05).

Correlations between quality of life and qEEG

Pearson's correlation coefficients between the QOL-AD scale scores and the main cognitive, behavioral, and functional variables were calculated, as well as between the qEEG variables of the three groups (Table 3).

In the AD group, QOL-AD correlated positively with semantic fluency (CC = 0.472, p = 0.011). A significant negative correlation between The QOL-AD of the three groups correlated negatively with their Hamilton scale scores (CC = 458, p < 0.014). The QOL-AD of the PD and NC groups also correlated negatively with their Neuropsychiatric Inventory scores. QOL-AD did not correlate significantly with the age, educational level, Mini-Mental State Examination, Pfeffer Questionnaire, and Neuropsychiatric Inventory of the three groups.

The QOL-AD of the AD group correlated positively with their interhemispheric theta coherence (CC = 0.517, p = 0.005).

The qEEG and QOL-AD scores of the PD and NC groups did not show correlation.

The multiple regression equation for the AD group showed that the significant factors for QOL-AD were interhemispheric theta global coherence and Hamilton depression Scale score (p = 0.003) (Table 4). Age, education level, verbal fluency, Pfeffer Questionnaire score, and other qEEG measurements were excluded from the equation because they were not significant. The Cohen's f^2 index of 0.605 is considered of large effect.

Table 2. Interhemispheric global delta, theta, alpha, and beta coherences of the Alzheimer's disease (AD), Parkinson's disease (PD), and normal control (NC) groups.

Coherences	AD (N = 28)	PD (N = 31)	NC (N = 27)	Comparison (AD x NC)	p-value (AD x PD)
Delta	0.546 (0.050)	0.576 (0.064)	0.575 (0.064)	0.081	0.061
Theta	0.492 (0.043)	0.525 (0.055)	0.521 (0.053)	0.044*	0.021*
Alpha	0.474 (0.057)	0.505 (0.041)	0.526 (0.046)	0.000*	0.017*
Beta	0.414 (0.050)	0.449 (0.068)	0.443 (0.054)	0.046*	0.026*

The standard deviations for the means are in parentheses. *t-test, p < 0.05.

Table 3. Pearson's correlation coefficients (CC) between the total Quality of Life – Alzheimer's disease (QOL-AD) scores and the clinical variables and qEEG of patients with Alzheimer's disease (AD), Parkinson's dsease (PD), and normal controls (NC) groups.

Clinical-EEG variables	Bivariate QOL-AD relationships					
	AD (N = 28)		PD (N = 31)		NC (N = 27)	
	CC	p	CC	p	CC	p
Age	0.229	0.241	-0.172	0.354	0.497	0.008*
Education Level	0.075	0.706	-0.193	0.307	0.338	0.085
Mini-Mental State Examination	0.092	0.643	0.097	0.469	-0.252	0.214
Verbal fluency	0.471	0.011*	-0.043	0.744	-0.030	0.884
Pfeffer Questionnaire	-0.251	0.197	-0.069	0.618	-0.263	0.185
Neuropsychiatric Inventory	-0.096	0.627	-0.541	0.002*	-0.382	0.049*
Hamilton Depression Scale	-0.458	0.014*	-0.457	0.001*	-0.610	0.001*
Interhemispheric coherence						
Delta	0.195	0.321	0.007	0.959	0.060	0.766
Theta	0.517	0.005*	0.068	0.597	-0.126	0.531
Alpha	-0.019	0.923	0.219	0.091	-0.228	0.252
Beta	0.075	0.703	0.174	0.177	-0.024	0.905

*Pearson's correlation coefficient, 2-tailed, p < 0.05.

Table 4. Multiple regression and Cohen's f^2 index for the total Quality of Life – Alzheimer's Disease (QOL-AD) scores: predictor variable with significant effects for the 28 patients with Alzheimer's disease.

Significant predictor	R²	Coefficient	Standardized coefficient	95%CI for coefficient	p-value	Cohen's f^2
	0.377					0.605
Interhemispheric theta coherence		58.229	0.425	11.962 104.496	0.016	
Hamilton Depression Scale		-0.274	-0.345	-0.541 -0.006	0.046	

According to multiple regression, the the Hamilton Depression Scale score is the only significant factor for QOL-AD in the Groups PD and NC (p = 0.000 and p = 0.001, respectively).

DISCUSSION

This study confirmed, in an original way, the hypothesis that a qEEG variable is associated with the QOL of AD patients regardless of cognitive and behavioral aspects. This association was not observed in the NC group or in a group with similar QOL deterioration, such as the PD group, whose physiopathology and qEEG differ from those of AD patients[10,19].

The present study corroborates the well-known fact that QOL is related to depression and the Neuropsychiatric Inventory scores of patients with PD and normal controls[21].

The present used the QOL-AD to investigate the patient's perception of his situation because it may differ from the caregiver's perception, and the latter can be biased by several factors[7,12,22].

The QOL-AD associated most significantly with the Hamilton Depression Rating Scale, Neuropsychiatric Inventory, neuropsychological test that assesses various aspects of orientation, memory, language, praxis, attention, and executive function, and Rating of Awareness Deficits, even though they clear differ between studies[7,12,23]. QOL is weakly correlated with cognition, and in some studies behavioral and psychological disturbances are more strongly associated with QOL than cognition or functional limitations[4,12,23]. The patient's QOL version also revealed associated factors that explain higher variance percentages (48.3%) than the carer-patient QOL ratings (37.5%)[7].

In this study the QOL-AD ratings of AD patients were lower than those of NC and similar to those of PD patients. As mentioned previously, the study included sociodemographic, cognitive, and behavioral variables associated with QOL to investigate factors possibly associated with QOL-AD.

The QOL-AD of the AD group correlated negatively with depression symptoms, in a way similar to other studies[4,12,23]. However, the QOL-AD correlated positively with verbal fluency, but this is hard to compare with other studies because other studies do not show cognitive their test results; correlations between cognitive aspects and QOL are uncommon[7,9].

Other studies have not found associations between QOL-AD and the Pfeffer functional activities questionnaire or the Neuropsychiatric Inventory[7].

The study AD group had smaller interhemispheric theta, alpha, and beta band coherences than the NC group, a finding corroborated by the literature[20,24,25,26,27]. Lower coherence in AD patients stems from the loss of long corticocortical tracts necessary for functional interactions or from low cholinergic coupling between cortical neurons[28]. Cortical areas would be functionally disconnected, which could be interpreted as neocortical "disconnection syndrome." In AD patients smaller alpha and beta band coherences are associated with worse cognitive performance[25].

The possible mechanisms behind the positive correlations between global interhemispheric coherence, specifically in the theta band, and QOL-AD deserve investigation. In a masterful review, Klimesh[29] found different correlations between absolute theta and alpha power oscillations in cognitive processing. Better performance in cognitive tasks is related to two types of phenomena: one tonic, regarding an increase in alpha and decrease in theta; and another phasic (event related), regarding a decrease in alpha and an increase in theta, depending on the type of memory used.

On the other hand, Stein and Sarnthein[30] emphasize that different electrical brain activity frequencies are associated with different scales of cortical integration. These authors found that local interactions during visual processing involve gamma frequency dynamics, semantic interactions between the parietal and temporal cortices involve beta frequency dynamics, and that long amplitude interactions during internal mental processes involve theta or alpha frequencies. The concept of QOL is speculated to depend on this broad and internal integration of components possibly related to theta coherence.

The limitations of the present study included the relatively small number of cases and the heterogeneous use of acetylcholinesterase inhibitors and antidepressants medications in the Group AD. Still, the present findings are important and based on simple and easily available qEEG methods.

In conclusion, this is the first report of a relationship between low global interhemispheric theta-band coherence and low QOL-AD, regardless of cognitive and behavioral variables. This interhemispheric coherence can be objectively measured, and its correlation with QOL scores also contributes to the knowledge about the physiopathology of AD, probably related to impaired functional connection between broad cortical areas.

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