Article

Arq Neuropsiquiatr 2011;69(6):875-881

Alzheimer's disease

Relationship between cognitive aspects and power and coherence EEG measures

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ABSTRACT

Objective: To evaluate the relationship between specific cognitive aspects and quantitative EEG measures, in patients with mild or moderate Alzheimer's disease (AD). **Method:** Thirty-eight AD patients and 31 controls were assessed by CERAD neuropsychological battery (Consortium to Establish a Registry for AD) and the electroencephalogram (EEG). The absolute power and coherences EEG measures were calculated at rest. The correlations between the cognitive variables and the EEG were evaluated. **Results:** In the AD group there were significant correlations between different coherence EEG measures and Mini-Mental State Examination, verbal fluency, modified Boston naming, word list memory with repetition, word list recall and recognition, and constructional praxis ($p<0.01$). These correlations were all negative for the delta and theta bands and positive for alpha and beta. There were no correlations between cognitive aspects and absolute EEG power. **Conclusion:** The coherence EEG measures reflect different forms in the relationship between regions related to various cognitive dysfunctions.

Key words: dementia, cognition, Alzheimer's disease, electroencephalography.

Doença de Alzheimer: relação entre aspectos cognitivos e medidas de potência e coerência no eletrencefalograma

RESUMO

Objetivo: Avaliar as relações entre aspectos cognitivos específicos e medidas quantitativas do EEG em pacientes com doença de Alzheimer (DA) leve e moderado. **Método:** Trinta e oito pacientes com DA e 31 controles foram avaliados com a bateria neuropsicológica CERAD (Consortium to Establish a Registry for AD) e o eletroencefalograma. Foram realizadas medidas de potência absoluta e coerência do EEG, durante repouso, e avaliadas suas relações com variáveis do CERAD. **Resultados:** No grupo DA houve correlações significativas entre diferentes medidas de coerência e o mini-exame do estado mental, fluência verbal, teste de nomeação de Boston modificado, memória de lista de palavras com repetição, recordação e reconhecimento de lista de palavras e praxia construtiva ($p<0,01$). Essas correlações foram negativas para as faixas delta e teta e positivas para alfa e beta. **Conclusão:** As medidas de coerência do EEG em repouso refletem diferentes formas de organização nas relações entre regiões, relacionadas a várias disfunções cognitivas.

Palavras-Chave: demência, cognição, doença de Alzheimer, eletroencefalograma.

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Support
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Received 29 December 2010
Received in final form 20 July 2011
Accepted 27 July 2011

The EEG has been used as an aid in the evaluation of patients with cognitive deficits, especially when the diagnosis remains open after the initial clinical evaluations[1,2].

In addition to the visual EEG analysis, numerical representation of the digital EEG allows one to carry out various types of quantitative analyses (qEEG), amongst

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which the most used are the EEG band power and coherence analyses. In the EEG band power analysis, various band power ranges that constitute the electrical cerebral activity are calculated. In the analysis of coherence, the relationship between two regions with respect to their compositions in electrical cerebral activity is assessed, which makes it possible to evaluate the connectivity between them. This analysis reflects functional interactions between neural networks represented in the cortex[3].

In comparison with normal controls, there is increased activity in the theta band in subjects with Alzheimer's disease (AD), which is accompanied by an increase in delta activity and decreases in the alpha and beta bands[4]. In studies on coherence in AD, the most consistent finding has been a reduction in coherence in the alpha band[5-7].

There is still insufficient scientific evidence of the diagnostic utility of qEEG to establish this method for the initial evaluation of subjects with cognitive impairment in routine clinical practice[8]. There is thus a need for studies on other approaches using qEEG in order to improve its diagnostic value.

The literature has cited correlations between qEEG measures, such as increases in theta and delta power and alterations in the global scores of tests used in cognitive assessments, such as the Mini-Mental State Examination (MMSE)[9-13]. Cross-sectional studies with the coherence measures of the qEEG failed to show correlation with the MMSE, although only global coherence measures or those restricted to the alpha and beta bands were used in these studies[7,14,15].

On the other hand, there are a few studies assessing correlations between qEEG measures and specific cognitive aspects[15,16], but in these studies the coherence measurements were also limited with respect to the bands and locations studied. A study of relationships between the variables of the resting qEEG and specific cognitive aspects could contribute to knowledge concerning their physiopathology, and also contribute to the choice of variables to be used in qEEG studies during specific tasks with a view to diagnostic utility.

The objective of this study was to assess relationships between specific cognitive aspects and easy-to-use variables on the qEEG, such as EEG power and coherence analyses, in patients with slight and moderate AD, including not only the alpha and beta bands, but also the delta and theta bands and regional measurements.

METHOD

Thirty-eight patients were included, all attending the outpatient's clinic at the Department of the Neurology Clinic - PUC/Campinas and all with dementia according to the Diagnostic and Statistical Manual of Mental Disorders[17], and diagnosis of AD (mild or moderate stages) according to the criteria of the NINCDS/ADRDA (National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's disease)[18]. A control group was also set up, including 31 subjects with no history of cognitive decline or previous neurological or psychiatric disorders and of similar gender and age range. These were also submitted to the EEG and the same clinical-neurological assessments and cognitive tests as the AD patients.

The following exclusion criteria were applied: comorbidity with significant reduction in life expectancy; treatment with acetylcholinesterase inhibitors or any other modulator of cognitive functions or drugs with the potential to alter them.

The patients were submitted to the following procedures: a clinical-neurological assessment; routine laboratory testing and neuro-imaging to rule out other causes of dementia; CERAD neuropsychological battery (Consortium to Establish a Registry for Alzheimers Disease), Pfeffer questionnaire; Clinical Dementia Rating - *CDR* and the qEEG. The cognitive and behavioral assessments followed the recommendations of the National Consensus[19].

The standard CERAD neuropsychological battery used in the cognitive assessment was composed of a semantic verbal fluency assessment, abridged Boston Naming Test (15 items), the MMSE, word list memory with repetition, recall and recognition, and constructional praxis with copy and recall. Its applicability to the Brazilian population was previously verified[20] and the scores correspond to the right answers in all items. The Pfeffer questionnaire is a functional and cognitive assessment scale applied to the informants.

Electroencephalography

The EEG was recorded with a resolution of 12 bits, 0.5 and 35 Hz filters and 200 samples per second, using the Braintech 4.0 equipment (EMSA *Equipamentos Médicos*). Impedance was maintained below 10k. 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 inter-connected ear lobe electrodes served as the reference. The data were recorded during approximately 12 minutes, alternating resting periods with the eyes closed with awake periods when the eyes were open, each period lasting 2 minutes.

Eighteen to 26 epochs were selected for the qEEG while awake and resting (eyes closed), each lasting 2.56s. Epochs with more than 100 μV on the electro-oculogram were excluded from the means. After applying the Fast

Fourier Transform, the absolute powers 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 1 (8.2 to 9.8 Hz), alpha 2 (10.1 to 12.5 Hz) and beta (12.8 to 19.9 Hz). To obtain the normal distribution, the values for absolute power were substituted by their logarithms. The absolute power was analyzed for the various bands at all the individual electrode positions. The averages were also calculated for the electrodes of the left (F7, T3, T5, F3, C3, P3 & O1) and right (F8, T4, T6, F4, C4, P4 & O2) hemispheres and the global average of all the electrodes.

To analyze coherence, this was defined as:

$$\mathbf{Coh}_{xy}\,\mathbf{(f)} = [\mathbf{R}_{xy}\,\mathbf{(f)}]^2 = \frac{[\mathbf{G}_{xy}\,\mathbf{(f)}]^2}{\mathbf{G}_{xx}\,\mathbf{(f)}\,(\mathbf{G}_{yy}\,\mathbf{(f)}}$$

where **G** denotes the spectral estimate of two EEG signals x and y for a given frequency band **f**. The numerator contains the cross-spectrum for x and y ($\mathbf{G}_{xy}$), while the denominator contains the respective spectra for x ($\mathbf{G}_{xx}$) and y ($\mathbf{G}_{yy}$). A result of 0 corresponds to no coherence and a result of 1 to maximum coherence.

The inter-hemispheric EEG coherences between the following homologous electrode pairs were measured: left-right frontal (F3-F4), left-right centrals (C3-C4), left-right parietals (P3-P4), left-right anterior temporals (F7-F8), left-right midtemporals (T3-T4), left-right posterior temporals (T5-T6) and left-right occipitals (O1-O2). The mean of the inter-hemispheric coherences between the frontal, temporal, central and parietal regions, corresponding to the F3-F4, F7-F8, T3-T4, C3-C4, P3-P4 and T3-T4 pairs (FTCP inter-hemispheric coherence), was calculated. For the intra-hemispheric coherences, the coherences between the frontal-occipital, central-parietal and midtemporal-posterior temporal pairs were measured both on the left (F3-O1, C3-P3 and T3-T5) and right (F4-O2, C4-P4 and T4-T6) hemispheres. All of these measurements were carried out for each of the four bands (delta, theta, alpha, beta).

Considering that the measures of coherence depend on the distance between the electrodes, coherences between electrodes with different distances were not compared. Only equivalent coherences were compared between the AD and control groups.

Statistical analysis

AD patients and controls were assessed with respect to the relationships between the variables of the CERAD neuropsychological battery and the global absolute power means and those of the left and right hemispheres in the 4 frequency bands. The relationships of the CERAD neuropsychological battery with the mean inter-hemispheric coherences between the frontal, temporal, central and parietal regions (FTCP inter-hemispheric coherence), between the frontal and temporal regions (frontal-temporal inter-hemispheric coherence) and the coherences between the occipital regions (O1-O2), as also with the means of the left (F3-O1, C3-P3 and T3-T5) and right (F4-O2, C4-P4 and T4-T6) intra-hemispheric coherency measurements were studied. The partial correlation coefficients, corrected for schooling level, were computed to assess independent relations between EEG measures and the CERAD neuropsychological battery parameters.

The Statistical Packages for Social Sciences statistical program (SPSS 10.0.1) was used, applying both parametric and nonparametric tests according to the data distribution. In order to minimize the possibility of errors due to the multiple comparisons, means of measurements involving various areas were used and not isolated electrode positions. In view of the exploratory nature of the study the level of significance was fixed at $p \leq 0.01$, despite the relatively large number of tests.

Ethical aspects

The Ethics Commission for Research with Human Beings of PUC-Campinas approved the project, and the subjects signed informed consent forms.

RESULTS

Clinical aspects

Table 1 shows the socio-demographic data and the results of the CERAD neuropsychological battery for the 38 patients of the AD group and the 31 controls.

Electroencephalogram

Table 2 shows the global means for the absolute powers in the 4 frequency bands, as well as in the left and right hemispheres for delta and theta bands. It should be noted that, in the theta band, the global amplitude and those of the right and left hemispheres were significantly greater in the AD group, whereas in the delta band they were greater in the AD group, but there was only a trend significance.

With respect to coherence, there was only a trend significant difference with respect to the frontal-temporal coherence (means for coherence for F3-F4 and F7-F8) in the alpha and beta bands (Table 2).

EEG relationships with the results of the CERAD neuropsychological battery

Global group constituted of AD patients and controls – Table 3 shows the partial correlation coefficients, corrected for schooling level, between the EEG variables and the results of the CERAD neuropsychological battery for this group, and also the degree of statistical significance. Negative correlations for the absolute

Table 1. Clinical characteristics of the study sample.

Clinical characteristics	Alzheimer (n=38)	Controls (n=31)	p value
Age (years)	73.82 (6.60)	71.39 (4.36)	0.083[a]
Male/female	14/24	8/23	0.328[b]
Education (years)	3.22 (3.18)	5.66 (4.77)	0.018[c]
Verbal fluency	8.31 (3.45)	16.58 (5.23)	0.000[a]
Abridged Boston naming test	8.37 (2.68)	13.35 (2.0)	0.000[c]
Mini-Mental State Examination	17.28 (3.48)	26.74 (2.08)	0.000[b]
Word list memory with repetition	7.19 (3.99)	16.71 (3.52)	0.000[a]
Constructional praxis	3.28 (1.25)	4.58 (0.56)	0.000[c]
Word list recall	1.00 (1.37)	5.16 (1.77)	0.000[c]
Word list recognition	3.54 (4.04)	8.48 (1.91)	0.000[c]
Constructional praxis recall	1.14 (1.46)	3.30 (1.32)	0.000[c]

When mean values are shown, the standard deviations (SD) are given in parentheses. [a]t test; [b]χ^2 test; [c]Mann-Whitney test.

Table 2. EEG measures: comparison between patients with Alzheimer's disease and the controls.

	Alzheimer group (n=31)		Control group (n=38)		
EEG measures	Mean	SD	Mean	SD	p value
Absolute power					
Global delta power	32.51	6.41	29.77	5.48	0.060
Right hemisphere delta power	33.37	6.37	30.74	5.97	0.082
Left hemisphere delta power	32.11	6.59	29.14	5.60	0.047*
Global theta power	38.50	9.81	32.90	9.45	0.019*
Right hemisphere theta power	38.28	10.36	32.77	9.91	0.028*
Left hemisphere theta power	38.49	10.07	32.53	9.70	0.015*
Global absolute alpha power	42,77	10.56	40.71	11.78	0.446
Global absolute beta power	27.09	9.41	26.94	6.96	0.944
Coherence					
Frontal-temporal alpha inter-hemispheric	0.493	0.080	0.542	0.091	0.021*
Frontal-temporal beta inter-hemispheric	0.421	0.057	0.454	0.055	0.020*

T test, *p <0.05.

powers of the delta and theta activities can be observed in the results of the CERAD neuropsychological battery.

Significance was found for the left hemisphere absolute delta and theta powers with the word list recognition.

For MMSE there was a negative correlation with the left delta intra-hemispheric coherence and positive with frontal-temporal alpha inter-hemispheric coherence. Negative left delta intra-hemispheric coherence also occurred for abridged Boston naming test and word list recognition.

Positive correlations were observed for word list recall and praxis recall, respectively, with frontal-temporal beta inter-hemispheric coherence and frontal-temporal alpha inter-hemispheric coherence.

There were no significant correlations between the EEG measurements and those of CERAD for the verbal fluency, word list memory with repetition, and constructional praxis.

AD group – In this group there were no significant correlations between EEG power measures and CERAD results.

It should be noted that the correlations were negative with the coherences for the slow activities delta and theta of the left hemisphere, and that the correlation coefficients for these same coherences in the right hemisphere, were low. With respect to the inter-hemispheric coherences, it can be seen that the correlations were differentiated according to the CERAD item under study, and that the negative correlations referred to delta activity and positive correlations to alpha or theta activities (Table 4).

Table 3. EEG measures: corrreleation coefficients for the global group constituted of Alzheimer's disease and controls.

EEG measurements	MMSE[a]	Verbal fluency[a]	Abridged Boston naming test[a]	Word list memory with repetition[a]	Word list recall[b]	Word list recognition[b]	Constructional praxis[b]	Praxis recall[b]
EEG absolute power								
Left hemisphere delta	–0.22	–0.20	–0.14	–0.27*	**–0.33****	**–0.33****	–0.21	**–0.36****
Right hemisphere delta	–0.12	–0.13	–0.10	–0.16	–0.224	**–0.316****	–0.12	–0.25*
Left hemisphere theta	–0.17	–0.21	–0.10	–0.21	**–0.31****	**–0.41*****	–0.13	–0.27*
Right hemisphere theta	–0.12	–0.17	–0.08	–0.21	–0.24*	**–0.35*****	–0.08	–0.19
Intra-hemispheric EEG coherence								
Left delta	**–0.35*****	–0.25*	**–0.32****	–0.28*	–0.19	–0.16	–0.21	–0.08
Right delta	0.10	0.05	–0.13	0.05	0.10	–0.00	0.11	0.19
Inter-hemispheric EEG coherence								
Frontal-temporal alpha	**0.32****	0.12	0.27*	0.22	0.26*	0.11	0.12	**0.33****
Frontal-temporal beta	0.25*	0.11	0.26	0.25*	**0.33****	0.21	0.02	0.27*

[a]Partial correlation coefficients; [b]Spearman's rank correlation coefficients; *p<0.05; **p<0.01, ***p<0.005. Significant correlations are marked in bold; MMSE: Mini-Mental State Examination.

Table 4. EEG measurements: correlation coefficients for the group with Alzheimer's disease.

EEG measurements	MMSE[a]	Verbal fluency[a]	Abridged Boston naming test[a]	Word list memory with repetition[a]	Word list recall[b]	Word list recognition[b]	Constructional praxisb
Intra-hemispheric EEG coherence							
Left delta	**–0.62*****	–0.41*	**–0.60*****	–0.47*	–0.22	**–0.53****	–0.39*
Right delta	–0.24	–0.10	–0.42*	–0.01	0.11	–0.19	–0.17
Left theta	**–0.44****	**–0.49*****	**–0.49*****	**–0.49*****	–0.13	**–0.48****	–27
Right theta	0.045	–0.22	–0.30	–0.11	0.17	–0.04	–0.05
Inter-hemispheric EEG coherence							
FTCP delta	–0.36*	–0.13	**–0.46****	0.04	0.22	–0.20	**–0.47****
O1-O2 theta	0.21	–0.07	–0.12	0.32	**0.42****	0.26	–0.07
O1-O2 alpha	0.30	0.03	0.01	0.37*	0.38*	0.38*	0.07

[a]Partial correlation coefficients; [b]Spearman's rank correlation; *p <0.05; **p<0.01; MMSE: Mini-Mental State Examination.

Control group (data not shown) – For the control group significant correlations between EEG measures and CERAD results were not observed.

DISCUSSION

In the present casuistic, the finding of an increase in the theta power and to a lesser degree in the delta band in the AD group is in agreement with the literature[4,21].

In this survey the alterations in coherence were limited to the alpha and beta bands and the frontal and temporal regions (F3-F4 and F7-F8), similarly to that described in the literature[5-7]. The present casuistic can be considered typical of mild and moderate AD from the point of view of the qEEG.

Relationships between absolute power and cognitive aspects

With respect to MMSE, elevated negative correlation between delta and theta activities and the MMSE score was reported for patients with dementia[9], whereas in other studies they were not found[21]. On analyzing together normal elderly subjects and those with cognitive compromise, Onishi et al.[12] found a significant regression model to forecast the MMSE score using theta and alpha 1 powers.

In the present study, correlations were found for the slow activities delta and theta in the left hemisphere with MMSE, but they did not reach statistical significance.

The differences found in the relationship between the

slow activities and MMSE in the various surveys were probably due to the composition of the series with respect to the proportion and severity of the cognitive dysfunctions, and to the different EEG measures used.

Studies evaluating the relationship between EEG power measures and specific cognitive aspects are scarce[15]. In agreement with those studies, trend significant relationships were found in the present study between slow band powers and activities linked to memory, such as word list recall and recognition and praxis recall. Also, similarly to this study, the relationship between aspects of the EEG and the Boston naming test was not significant[15].

The association of an increase in slow activity with cognitive deficit could be explained by the hypothesis that basal forebrain neurons are severely affected in AD, resulting in a cerebral cholinergic deficit which, for its part, is involved in the genesis of memory loss and of other cognitive symptoms[22], as also in slowing of the EEG.

Relationships between coherence and cognitive aspects

Various studies have failed to find any relationship between EEG coherence and MMSE[7,14,15], but those studies used global coherence measurements that did not include the delta band or did not have any normal controls.

In the present study, in addition to the short distance intra-hemispheric measurements (for example C3-P3, T3-T5 for the left hemisphere) as used in other studies[14,15], long distance measures such as F3-O1 or F4-O2 were also used. Thus C3-P3, T3-T5 and also F3-O1 entered the mean for left coherence, resulting in both long and short distance measurements being represented, which could contribute to more ample knowledge of the functional relationships between areas of the brain. It is known that distance is a factor that interferes with coherence, and direct comparisons were not made between the long and short coherence measurements.

In the joint group of AD plus the controls, a negative correlation was found between MMSE and the delta coherence of the left hemisphere, and positive correlation with the inter-hemispheric frontal-temporal alpha coherence. The inter-hemispheric coherences also showed positive correlation with word list recall and praxis recall.

Adler et al.[7] also observed a decreased alpha coherence associated with immediate verbal recall performance, which could suggest that in the organization of the electrical activity of the brain, the sub-cortical control of alpha activity has a relationship with working memory mechanisms.

Both in the global group and in AD group theta, and particularly delta intra-hemispheric coherences on the left, were inversely and strongly correlated with various types of cognitive aspects. Also negative was the correlation between delta frontal-temporal-central-parietal coherence with the abridged Boston naming test in the AD group. On the other hand, the occipital inter-hemispheric coherences in alpha and theta bands showed positive correlation with word list recall.

With respect to the physiopathological interpretation, the association of less coherence in the alpha band with worse cognitive performance in AD would be a result of reduced functional connections between areas of the brain beneath the electrodes, or reduced control of two areas by a third area, supporting the hypothesis that Alzheimer's disease is, in part, a disconnection syndrome. This could be the result of a loss of the cortico-cortical association fibers necessary for functional interactions, or to reduced cholinergic coupling interactions between cortical neurons[23].

With respect to coherence in the slow bands, a decrease in acetylcholine can cause an inverse effect with respect to alpha and beta bands, that is, an increase in coherence. In fact, in healthy subjects anti-cholinergic drugs induce an increase in coherence in slow bands[24] and there are reports of an increase in slow coherence in AD[25]. It is also possible that the association of greater coherence in the slower bands with a fall in cognition could also be due to a decrease in acetylcholine in AD subjects.

The predomination of correlations between the slow coherences in the left hemisphere and cognitive aspects could be related to the preponderant representation of language, whose compromise would affect performance in the tests[7]. In patients with AD there would also be preponderant metabolic and morphological alterations in the left hemisphere[26].

EEG profiles and cognition

The MMSE showed correlations with left delta and theta intra-hemipheric EEG in common with other more specific items from CERAD. In patients with AD, verbal fluency showed correlations that were restricted to the theta coherence of the left hemisphere that involved short (C3-P3 and T3-T5) and long (F3-O1) distance coherences, with participation of the frontal and temporal areas, in accordance, respectively, with their executive functions and connected to the semantic fluency for animals[27].

Positive correlations with the coherence of the alpha and beta activities appeared in the tests involving memory, specifically the word list recall, and praxis recall, for both the general casuistry and in the Alzheimer group. Connections between alpha rhythm and memory have already been pointed out in the literature[28], especially for immediate memory[7,16]. These relationships would be supported by physiological aspects in which the alpha

rhythm is mainly modulated by thalamo-cortical and cortico-cortical interactions, facilitating or inhibiting the transmission of information amongst the sub-cortical and cortical pathways and the retrieval of semantic information from brain storage[29].

The abridged Boston naming test showed correlations with both inter- and intra-hemispheric coherences in the delta band, which could be related to two categorical stages of object recognition: a perceptual stage in the right hemisphere and a semantic stage that depends on the left hemisphere[30].

Although the analysis carried out in this research was for resting EEG, the differences in the aspects of the EEG for the different cognitive aspects indicated the existence of varied aspects of organization and control of the composition of the electrical activity related to the various cognitive aspects. The original aspect of the present work was to evaluate the relationships among specific cognitive aspects in AD subjects using simple EEG coherence and power measures involving delta, theta, alpha and beta bands, available in the majority of equipments. With this information one can arrive at the value of the study with the delta coherences of the cerebral hemispheres together with other measures of coherence and power, in the relationships with various cognitive aspects.

A practical and relevant aspect of this study is being a basis for the use of specific variables of the EEG for the study of the registers made during specific functional activations, which could eventually provide a greater diagnostic value to the EEG in clinical practice, in assessing cognitive dysfunctions.

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