

Electroencephalographic frontal asymmetry and depressive symptoms in the elderly

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ABSTRACT

Although neurophysiological changes of aging are well known, there is still much to learn about cortical asymmetry in older depressed subjects. This study aimed at assessing differences between depressed and normal elderly subjects on alpha asymmetry, and to observe the correlations of this measure with depressive symptoms and quality of life. Thirty-six subjects (14 normal and 22 depressed) were assessed by EEG, depression rating scales, and SF-36. Despite the fact that compared to healthy elderly, depressive elderly subjects showed relatively greater right frontal activity (F4F3) and relatively greater left parietal activity (P4P3); this difference was not significant. The relationship between depression and frontal asymmetry was better observed in healthy elderly, where relatively greater left frontal activity was associated with less depressive symptoms.

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1. Introduction

Depression is a highly prevalent syndrome in the elderly. Its diagnosis is often difficult because of the multiple environmental, social, and biological factors involved with the clinical picture in late life. EEG and brain mapping have been used to study several electrophysiological variables related to brain metabolism and may be useful in the research of the aging process (Niedermeyer, 1993). Furthermore, some of the EEG features can be viewed as predictors of depression and anxiety in normal subjects. In fact, Blackhart et al. (2006) observed an association between depressive symptoms and temporoparietal asymmetry whereas anxiety symptoms were predicted by frontal asymmetry. The most observed EEG modifications in unipolar depression are located at the alpha band. The asymmetry of this band is closely related to

depressive symptoms and to the depressive disease itself. Over the last 20 years, research on this issue has been observing a model of hemispheric specialization associated with emotion proposed by Richard Davidson (to review, see Davidson et al., 1990; Davidson, 1992). According to this model, positive affect and approach behaviors are correlated with a greater relatively left frontal activity (Kline et al., 2000; Debener et al., 2000; De Raedt et al., 2008), whereas negative affect and withdrawal behaviors are related to a greater relatively right frontal activity (Lewis et al., 2007). In this sense, the depressed patients show a relatively greater right frontal activity (less right than left alpha) (Bruder et al., 1997; Allen et al., 2004a), associated with emotion and affective behavior. This phenomenon is related to greater negative affects (Coan et al., 2006; Davidson, 2004; Sutton and Davidson, 1997; Papousek and Schulter, 2002), and to an inverse relation with positive emotional stimuli (Pizzagalli et al., 2005).

The measurement of the EEG prefrontal asymmetry in depressed subjects has adequate internal consistency and test-retest stability (Sutton and Davidson, 1997; Allen et al., 2004a; Vuga et al., 2006). The model of frontal asymmetry and emotion may represent either a trait or a specific affective/cognitive status (Deldin and Chiu, 2005; Coan and Allen, 2004), given that no

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differences were observed on the EEG of depressed subjects who were on medication (Henriques and Davidson, 1991) or in diverse severity stages of depression (Vuga et al., 2006).

Albeit much is known about the changes in EEG due to the aging process, there is still much to learn about the difference between the frontal electric activity of normal and depressed elderly individuals. Changes in alpha asymmetry in depressed elderly may be linked to the specific aspects of aging, to symptoms of the disease and to negative affects, and may as well be influenced by life style and self-esteem. Quality of life and depression seem to have a mutual influence. Indeed, quality of life, physical, and social factors can exert some influence on the outcome of depression, whereas functional capacity, energy, vitality, and physical health are fundamental factors for a better quality of life in elderly subjects. Thus, the aim of this study is to assess the changes in frontal and parietal asymmetry of depressed elderly as compared to a control group of normal subjects. A secondary goal was to study the association of cortical asymmetry and depressive symptoms.

2. Methods

2.1. Subjects and study design

This is a cross-sectional study for which 36 subjects with more than 60 years of age were selected (normal = 14, depressed = 22). Subjects who were diagnosed with Major Depression according to the DSM-IV (American Psychiatric Association, 1994) criteria and with no other concurrent neurological or psychiatric disorders were included in this study. All the patients were under treatment at the Center for Alzheimer's disease and related disorders (CDA) and had been examined by trained psychiatrists in order to exclude dementia and other neuropsychiatric syndromes. They had been on antidepressants (fluoxetine and sertraline) [$n = 11$], anxiolytics (diazepam, lorazepam, and clonazepam) [$n = 8$], or both [$n = 3$] for at least 6 months at the time of the evaluation. The control group of normal elderly subjects was composed of volunteers who participated in a Fall Prevention Program at the same University. They were considered to be healthy according to a careful screening with a special focus on the past history of clinical or neurological disease, psychiatric illness, severe head injury or drug abuse, as well as according to the

Table 1
Descriptive analysis

Characteristics	Depressed ($n = 22$)	Normal ($n = 14$)	F value	p value
Age (S.D.)	71.6 (1.2)	72.4 (1.7)	0.12	0.72
Female (%)	21(95)	13 (93)	0.75	0.74
SF-36 (S.E.)	55 (5.71)	81 (5.76)	0.37	0.01*
Beck (S.E.)	11.5 (1.75)	3.6 (1.17)	3.89	0.00*
Hamilton (S.E.)	9.4 (1.54)	1.1 (2.6)	3.91	0.00*
MADRS (S.E.)	10.7 (2.37)	1.57 (1.41)	9.92	0.00*
MMSE	26 (0.81)	27.28 (0.74)	1.26	0.35

(S.D.): standard deviation; (S.E.): standard error; MADRS: Montgomery–Asberg Depression Rating Scale; MMSE: Mini Mental State Examination.

* Significant difference between depressed and normal group.

results of the Short Form Health Survey (SF-36). Fig. 1 depicts the sample selection and Table 1 shows the descriptive analysis.

All the subjects were evaluated by a psychiatrist at the CDA for identifying possible psychiatric comorbidities. In case of any query regarding the case, a second psychiatrist reassessed the patient in order to confirm the diagnosis. Subjects who were left handed, were less than 60 years of age, were illiterate, and had any psychiatric or clinical comorbidity were excluded from the sample. Each participant signed the informed consent form and the experiment was approved by the Institutional ethics committee. Severity of cognitive impairment was evaluated by the Mini Mental State Examination (Folstein et al., 1975). Handedness was assessed by the Edinburgh Handedness Inventory (Oldfield, 1971).

2.2. Experimental procedures

All the participants were submitted to an EEG and completed three depression scales and a quality of life questionnaire.

2.2.1. Quality of life

The Short Form Health Survey-36 (SF-36) is a self-rating questionnaire which assesses eight domains, namely physical functioning, role limitations due to physical problems, pain, social functioning, mental health, role limitations due to emotional problems, vitality, and general health perceptions (Ware and Sherbourne, 1992). Higher scores represent better health appraisal and the scale ranges from zero to 100. A validated Portuguese version was used in this research (Ciconeli, 1997).

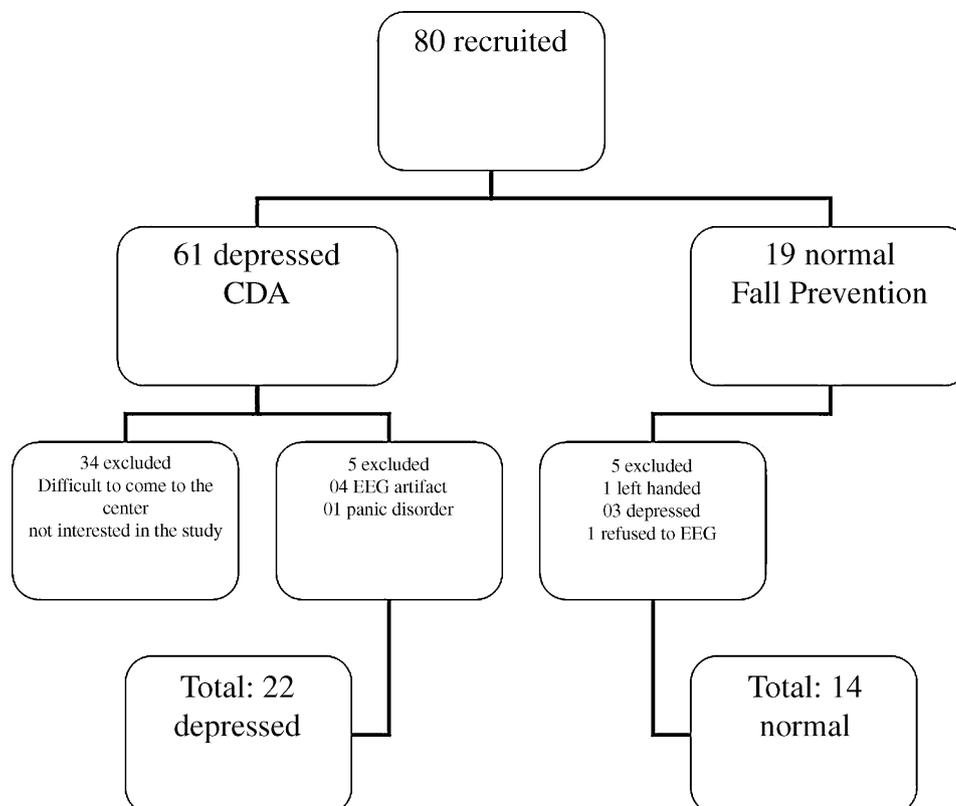


Fig. 1. Subject recruitment.

2.2.2. Depression scales

The validated Portuguese versions (Goreinstein and Andrade, 1996; Dractu et al., 1987) of the 17 item Hamilton Depression Scale (Hamilton, 1960), the Beck (Beck et al., 1961), and the Montgomery–Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) were used in our study. These scales assess the severity of depressive symptoms in normal and depressed subjects.

2.3. EEG recording, reduction and analysis

Patients and controls were seated in a comfortable sound and light attenuated room, while at least 8 min of eyes-closed alert/resting EEG data were collected from the 20 monopolar electrodes sites. International 10/20 System (referred to linked earlobes) for electrode placement was used with a Braintech-3000 (EMSA-Medical Instruments, Brazil). Eye-movement (EOG) artifact was monitored with a bipolar electrode montage using two 9-mm diameter electrodes attached superior to and on the external canthus of the right eye. Impedances for EEG and EOG electrodes were under 5 k Ω and 20 k Ω , respectively. Amplifier band-pass was 0.5–100 Hz (3 dB points), with a 60 Hz notch filter. Data were digitized at 200 Hz with a 12-bit resolution. EEG records were visually examined and the sites which contained the movement and muscle artifacts were marked. Independent Component Analysis (ICA) from EEGLAB was applied to remove possible sources of artifacts (Delorme and Makeig, 2004). For the ocular artifacts, the components with delta band activity were used with more projection on prefrontal areas (Fp1 and Fp2). As for the muscular artifacts, we used components with activity above 30 Hz and localized mainly in lateral frontal and temporal electrodes (F7, F8, T3, T4, T5, and T6) which cover the projections of the face and neck muscles. After the deletion of the components described above, the digital EEG was examined again in order to verify whether the removal of the artifacts was successful. When the removal of the Independent Components suggestive of the presence of artifacts did not properly correct the EEG, the contaminated epochs were manually excluded and ultimately only the artifact-free EEG was processed. Moreover, epochs containing bioelectric artifact greater than 100 μ V in any channel were rejected.

We used the linked ears reference given that this is the routine in our laboratory. Also, this reference has been used in other studies that have investigated alpha asymmetry (Kline et al., 1998, 1999, 2000; Debener et al., 2000) and may be more appropriate for the measurement of frontal resting asymmetry than the Cz reference. However, it must be noted that physically linking the ears may result in an electrical shunt across the head if the electrode impedances at A1 and A2 are very low and may also distort the EEG if the impedances at A1 and A2 are high but asymmetrical (Hagemann, 2004).

At least 2 min of artifact-free data were extracted from the EEG total record for quantitative analysis. A classic Power Spectral Density (PSD) estimator was used (i.e. based on the squared absolute value of the Fourier Transform) for artifact-free 4-s EEG epochs (spectral resolution: 0.25 Hz) with Hamming windowing. An overlapping factor of 50% (2 s) was used for consecutive epochs. Average alpha (8–13 Hz) power (microvolts squared) was then natural log transformed for normalization. A natural log (ln) transformation technique is used to normalize the distributions of power values, as these distributions tend to be positively skewed, and this is consistent with the recommendations of Davidson et al. (1990). Cortical asymmetry (ln[Right] – ln[Left]) was computed for alpha band. The difference in score thus provides a simple unidimensional scale representing the relative activity of the right and left hemispheres, with higher scores putatively indicate of relatively greater left frontal activity (assuming that alpha is inversely related to activity) (Allen et al., 2004b).

2.4. Statistical analysis

Differences in Alpha absolute power (ln) were evaluated using analysis of variance (three-way ANOVA), with the variables of Group (depressive, normal control) as a between factor, and Hemisphere (left vs. right) and area [midfrontal (F3F4) vs. lateral frontal (F7F8) vs. posterior (P3P4)] as a within factor. Moreover, the independent Student's *t*-test was used to compare the metric value (F4-F3, F8-F7, P4-P3). The results of the scales of depression and of the quality of life questionnaire, together with the variables which did not have the log treatment, were compared using the non-parametric Mann–Whitney *U*-test. The association between asymmetry [Right(ln) – Left(ln)] and depressive symptoms was analyzed using Spearman's correlation. A three-way ANOVA was performed so as to compare drug treatment (anxiolytics vs. antidepressants vs. no drugs) \times hemisphere \times area. The groups were also compared with regard to the metric value of the asymmetry using a one-way ANOVA. The level of significance adopted for this study was 0.05.

3. Results

3.1. Quality of life and depression symptoms

3.1.1. SF-36

The depressed group showed lower scores on quality of life as compared to the normal elderly group (Table 1). As expected, the

Table 2

Correlation (rSpearman and *p* value) between EEG alpha asymmetry, depressive symptoms (Beck scale) and quality of life (SF-36) in normal and depressed elderly subjects

	F4F3	F8F7	P4P3	SF-36
Beck				
Normal (<i>n</i> = 11)	–0.54 (0.08)*	–0.19 (0.56)	–0.28 (0.39)	–0.90 (0.00)**
Depressed (<i>n</i> = 20)	0.00 (0.99)	0.35 (0.12)	0.27 (0.24)	–0.28 (0.29)
SF-36				
Normal (<i>n</i> = 11)	0.33 (0.31)	–0.10 (0.74)	0.43 (0.18)	–
Depressed (<i>n</i> = 15)	–0.33 (0.21)	–0.30 (0.27)	0.13 (0.63)	–

* Significant correlation (*p* < 0.1).

** Significant correlation (*p* < 0.05).

SF-36 scores were inversely correlated ($r_s = -0.610$, $p = 0.03$) with depressive symptoms as measured by the Beck scale. The higher were the scores on the quality of life scale, the lower the scores on Beck scale. However, the significant findings only remained for the control group when observed within the groups (Table 2). Yet, no correlation was found between SF-36 and alpha asymmetry.

3.2. Depression scales

As expected, there was a significant difference in the severity of depressed and normal groups on all the three scales used to measure depression. The demographic and clinical characteristics of the subjects in the two groups are shown in Table 1.

3.2.1. Alpha asymmetry

The ANOVA of alpha absolute power showed no significant difference between the hemispheres and among the groups (Fig. 2). As expected, there was a main effect of area ($F = 19.837$; $p = 0.000$), where $F7F8 < F4F3 < P4P3$. Moreover, a main effect of hemisphere ($F = 18.111$; $p = 0.000$) showed left > right. However, no interaction was observed. Although the results point to a difference between groups (control and depressed) regarding the behavior of the hemispheric activation, no statistical significance was found. Fig. 3 shows all the asymmetry values (ln Right – ln Left) just aiming to show an overall view of the difference in hemispheric activity in both groups.

3.2.2. Medication status

The medication exerted no influence on any of the performed analysis. The groups (anxiolytics \times antidepressants \times no drugs) did not show any significant difference either on the metric value of the asymmetry or on the absolute power at the hemispheres (Fig. 4).

3.2.3. Asymmetry and depressive symptoms

The correlation between depressive symptoms and frontal asymmetry was not significant in the depressed group, and there was a trend for an inverse correlation between midfrontal asymmetry (F4F3) and depressive symptoms in the healthy control group. This finding suggests that relatively greater left midfrontal activity (greater metric value) is correlated to less symptoms of depression. The correlations between asymmetry, mood symptoms, and quality of life are depicted in Table 2.

4. Discussion

This study aimed at investigating the difference of frontal and parietal asymmetry between normal and depressed elderly subjects. We also looked into the correlation between asymmetry, depressive symptoms, and quality of life. The findings showed a different pattern of cortical activity between the normal and depressive

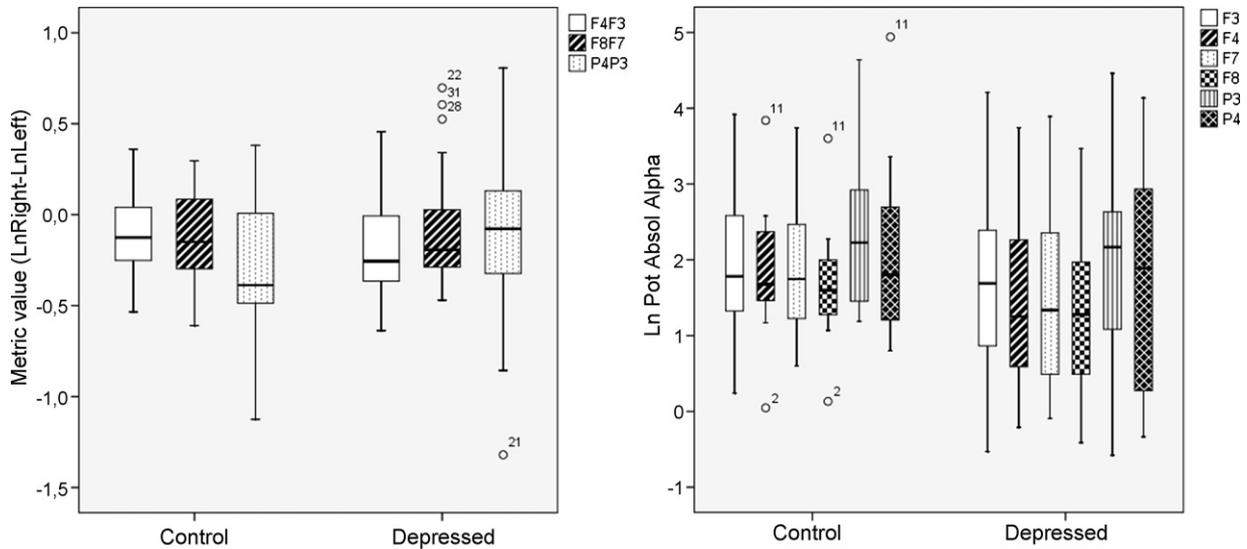


Fig. 2. Alpha absolute power according to group, area and hemisphere (right boxplot), and frontal and parietal asymmetry (left boxplot). Higher positive metric value is indicative of greater left activity. Vertical lines indicate the minimum and maximum data values.

groups. The midfrontal asymmetry showed a better correlation with depressive symptoms in normal than in the depressive group. Moreover, depressed elderly subjects presented relatively greater left parietal activity (P4P3) and relatively greater right frontal activity, although this difference was not significant. In this line, Reid et al. (1998) did not show significant differences in frontal asymmetry between depressed and nondepressed individuals. Henriques and Davidson (1991) reported significant group differences, both when testing single sites with hemisphere as a factor and when using asymmetry metrics from homologous sites. However, when the data was referenced to average ears, the group (depressed vs. nondepressed) × hemisphere (left vs. right) interaction was not significant. The methodology (e.g. reference) and the statistical tests may influence the interpretation of the frontal asymmetry findings. In addition, the subjects from that study were not elderly, a fact that could have influence the results. A recent meta-analysis on the relationship of frontal asymmetry and depression and anxiety (Thibodeau et al., 2006) concluded that younger infant samples showed larger effect than older ones. Having been unable to present

any theoretical or factual explanation for this difference, the issue remains as an exploratory finding.

Several studies have shown a relatively greater right frontal activity in depression (Sutton and Davidson, 1997; Allen et al., 2004a; Bruder et al., 1997; Henriques and Davidson, 1991). A number of brain areas are involved in the emotion circuitry, namely the dorsolateral and ventro-medial prefrontal cortex, the nucleus accumbens, basal ganglia areas, the amygdala, the temporal and the parietal cortex, and the hippocampus. Lesions in the left prefrontal area and in the left basal ganglia are related to the increased severity of depression and depressive symptoms. Moreover, a greater right prefrontal activity and lower left activity in depressed states are corroborated by metabolic and neuroimaging studies (Fregni et al., 2006), and are thought to be associated with negative emotions (Davidson, 1992). Nonetheless, changes occurring due to the aging process might influence the cortical electrical activity and the hemispheric asymmetry independent from the mood symptoms or from the presence of mental disorders. Studies that investigated cortical asymmetry during

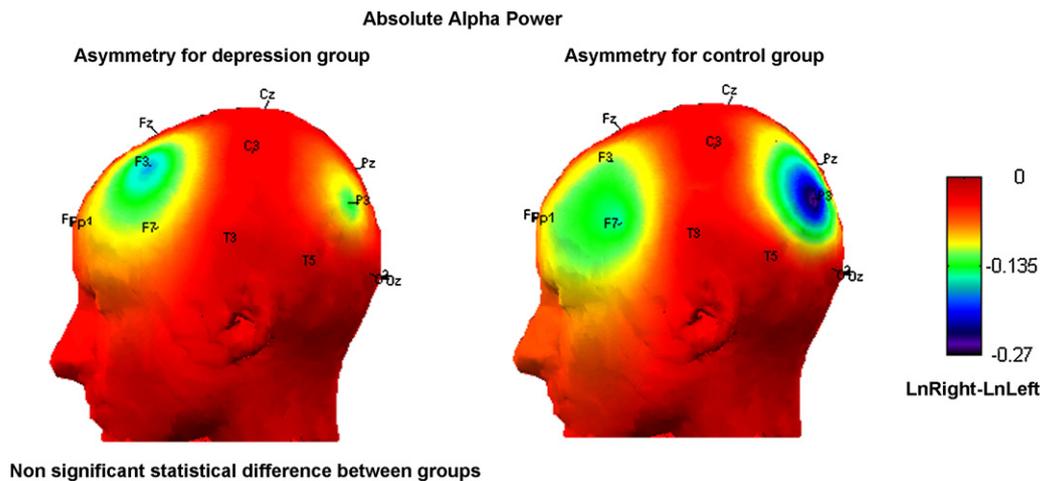


Fig. 3. Cortical maps of asymmetry values in depressed (left) and normal elders (right). The cortical maps represent the difference (Right – Left) only in frontal (F4-F3, F8-F7) and parietal (P4-P3) areas. Greater values (red, yellow and green) represent relatively left activity and lower values (blue) represent relatively right activity. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

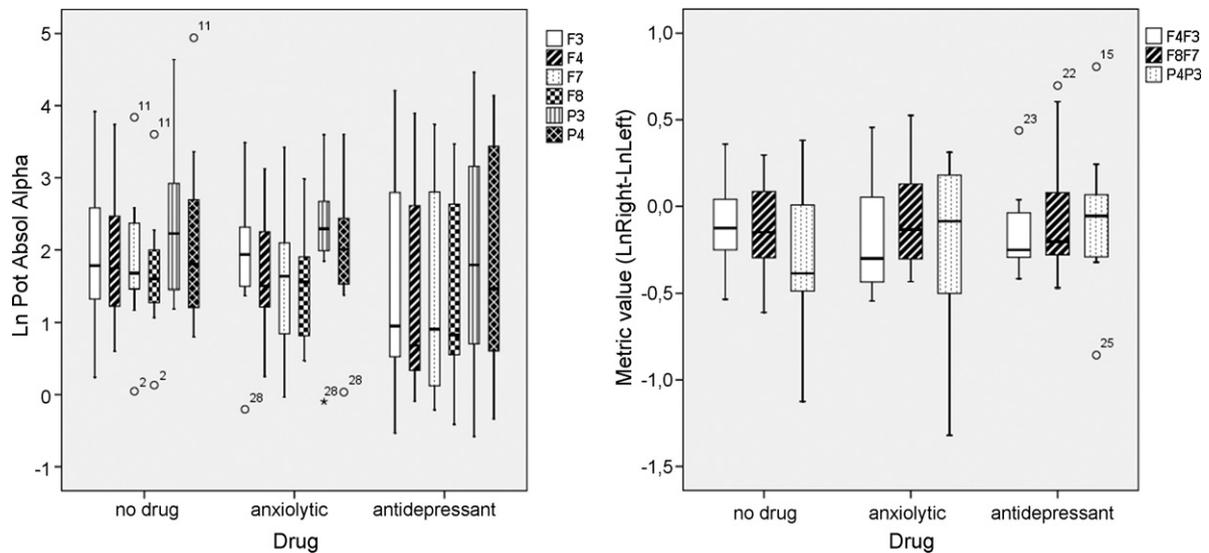


Fig. 4. Boxplot of the alpha asymmetry according to used medication (no drug vs. anxiolytics vs. antidepressants). Vertical lines indicate the minimum and maximum data values.

cognitive processes observed that the frontal activity seems to be less lateralized in older adults than in young adults (Bellis et al., 2000; Cabeza, 2002). The decreased asymmetry in the aging process is observed by two models: the right hemi-aging model and the HAROLD model (Hemispheric Asymmetry Reduction in Older Adults). Both present the hypothesis of a decreased lateralized activity with aging, either because of a greater degeneration of the right hemisphere or because of a greater global activity during the cognitive process (Dolcos et al., 2002). Most studies which investigated the relationship between asymmetry, emotion and depressive symptoms were carried out with younger subjects. One of the few studies in the literature that observed the asymmetry associated with the approach and withdrawal-related emotion in elderly subjects (Kline et al., 2000) showed a relatively greater left frontal activity related to pleasant smells (vanilla). However, the opposite was not observed, that is, relatively greater right frontal activity related to unpleasant smells (valerian).

Our results show a different response in depressed and normal groups regarding the relationship between depressive symptoms and frontal asymmetry. A relatively greater left frontal activity is expected to be related to a lower score on the Beck scale. However, we observed a trend for this correlation only for the normal group. Henriques and Davidson (1991) did not observe a significant correlation between the Beck and Hamilton scales and the frontal asymmetry in normal or depressive adults. These results would be due to a slight variation of the intra-group results. Our results regarding the correlation of the Beck and asymmetry were also not significant, despite their wide variation (0–27). Although a study with young depressive subjects also showed no correlation between the Beck scores and the frontal asymmetry (Blackhart et al., 2006), a correlation was observed between frontal asymmetry and anxiety scores. Moreover, they showed a correlation between posterior asymmetry and depression scores 1 year later, suggesting that EEG asymmetry could be used to predict the chance of developing psychopathology such as anxiety and mood disorders. In our results, the relationship between depressive symptoms and midfrontal asymmetry in the normal group was greater than in the depressed group. The greater correlation in the normal group might be explained by other factors, such as defensiveness. Several studies verified that defensiveness correlates positively with left frontal activity in women (Tomarken and

Davidson, 1994) and this result may vary as a function of gender (Kline et al., 1998, 1999). Interestingly, Kline and Allen (2008) demonstrated that defensiveness is correlated positively with depression in highly defensive individuals who are right frontally active. However, we did not evaluate this kind of self-enhancing cognitive style (defensiveness) in our study. The better physical and mental health observed in normal subjects as compared to the depressed patients is another issue that might have influenced asymmetry in our results. Hall and Petruzzello (1999) found the expected inverse correlation between frontal asymmetry and dispositional affect only in elderly with high physical activity, not observed in low activity elderly. They suggested that the relationship between dispositional affect and asymmetry is influenced by the physical activity in older adults. However, these results were not replicated.

Our data did not show any significant difference on the frontal and parietal asymmetry among the drug groups (no drugs, anxiolytics and antidepressants). Accordingly, Henriques and Davidson (1991) did not observe any difference on the frontal asymmetry in groups who were on tricyclics and serotonin reuptake inhibitors (imipramine and fluvoxamine). As for the effects of benzodiazepines on asymmetry, Davidson et al. (1992) showed that diazepam reduces relatively right frontal asymmetry in monkeys, especially in the 4–8 Hz band. However, the cross-sectional design of our study did not enable a deeper analysis of this evidence. We also assessed physical health and the perception of well being with the SF-36. Despite the fact that the control group presented significant higher scores on the SF-36 than the depressive elderly, this measure did not show the correlation with the asymmetry in either groups.

Our study has some limitations that need to be addressed. Our control group referred having regular physical activity (twice a week), which may not only have contributed for the low scores for depression and high scores for quality of life on the scales, but also for the EEG pattern. Although scarce and with some methodological limitations, the studies that assess the brain electric activity as a function of exercise point to a greater total alpha activity (Crabbe and Dishman, 2004) and to an association of positive feelings, practice of physical activity, and greater left frontal activity (Petruzzello et al., 2001). It should be noted, however, that these studies assessed younger subjects, and the response in the elderly is not well known. Future studies designed to observe the

EEG of elderly subjects before and after the commencement of a routine training might enhance the knowledge regarding this relationship. The depressed group was under pharmacological treatment. Despite the fact that there was no significant difference in asymmetry between the groups treated with anxiolytics or antidepressives, it is still possible that the drugs might have influenced the observed values of the depressed patients in our study. Another limitation is the reference used (linked ears). When compared to other studies, our results should be interpreted minding the linked earlobes reference, since this reference method might influence the EEG data.

To conclude, this study found that when compared to normal subjects, clinically depressed elderly adults show alpha asymmetry similar to that of younger depressed subjects reported in other studies (relatively right frontal activity and relative left parietal activity), although not statistically significant.

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