



Research report

EEG frontal asymmetry in the depressed and remitted elderly: Is it related to the trait or to the state of depression?

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ABSTRACT

Background: Over the last 30 years, frontal EEG asymmetry has been investigated with regards to the study of emotion, motivation, and psychopathology.

Method: We analyzed the frontal alpha asymmetry, depressive symptoms with a Beck Depression Inventory (BDI) and quality of life with a Short Form Health Survey-36® (SF-36®) in depressed ($n = 12$), remitted ($n = 8$) and non-depressed ($n = 7$) elderly subjects. We also evaluated the correlation between the frontal EEG asymmetry and physical and mental aspects of SF-36®.

Results: The groups showed no difference regarding the frontal alpha asymmetry ($F = 0.37$; $p = 0.69$). Moreover, there was no significant correlation between frontal asymmetry and quality of life (mental and physical aspects).

Conclusion: The results showed no evidence of a relationship between frontal asymmetry, quality of life and depression in the elderly. Future studies on frontal asymmetry should carefully consider the effects of age.

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1. Introduction

Depression along with dementia is the most common mental illness in elderly adults. The World Health Organization (World Health Organization, 1992) predicts that by 2020, depression will become the second leading cause of disease worldwide, as measured by disability-adjusted life years. Making the diagnosis of depression in the elderly is often difficult because symptoms may be confused as physical complaints, particularly among frail older adults (Chapman and Perry, 2008). Risk factors for depression among elderly community subjects include sleep

disturbance, disability, prior depression, sedentary life style, and female gender (Cole and Dendukuri, 2003; Deslandes et al., 2009). Furthermore, depression in the elderly is associated with physical disability and cognitive deficits (Russo et al., 2007; Bierman et al., 2007), which render an additive problem in differentiating depression from dementia.

Neuroimaging studies have shown neurobiological changes in a variety of brain regions, neurotransmitter systems, and genetic factors related to major depressive disorder (MDD) (Southwick et al., 2005; Maletic et al., 2007). Electroencephalography alpha asymmetry has also been used as a measure of cortical activity linked to emotional process, mood, and psychopathology. Several studies have shown that positive emotions (i.e., approach-related) are associated with greater relative left frontal activity, whereas negative emotions (i.e., withdrawal-related) are associated with higher relative right frontal activity (Schaffer et al.,

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1983; Henriques and Davidson, 1990; Henriques and Davidson, 1991; Bruder et al., 1997; Putnam and McSweeney, 2007). Experiments using asymmetry as a measure suggest that it can be associated either to a trait or to a state of depression (Coan and Allen, 2004). The first hypothesis (trait) is in agreement with studies which observed persistent asymmetry after clinical remission (Kwon et al., 1996; Vuga et al., 2006; Allen et al., 2004). The second hypothesis (state) suggests that changes in clinical state or emotions are related to changes in frontal asymmetry (Papousek and Schulte, 2002). Additionally frontal asymmetry is also correlated to other factors usually seen in depression, such as anxiety (Blackhart et al., 2006; Smit et al., 2007), rumination (Putnam and McSweeney, 2007), low self-esteem (Putnam and McSweeney, 2007, De Raedt et al., 2007), defensive style (Kline and Allen, 2008), and poor physical activity (Hall and Petruzzello, 1999). So, it is conceivable to hypothesize that mental and physical aspects of quality of life might be related to frontal asymmetry as well. Higher left frontal activity could be related both to mental or physical aspects. Moreover, an inverse correlation between quality of life and depressive symptoms is expected, since MDD is associated with poor perception of physical and mental aspects of quality of life.

Albeit an extensive literature has been produced for investigating asymmetry and depression in young adults, few studies have hitherto focused on frontal asymmetry in the elderly (Hall and Petruzzello, 1999; Thibodeau et al., 2006; Silveira et al., 2010; Kline et al., 2000; Deslandes et al., 2008; APA, 1994). Numerous experiments employed young adults and children, leaving a dearth of knowledge on asymmetry in the elderly. In one experiment performed with elderly subjects, Kline et al. (2000) examined the changes in anterior asymmetry in response to pleasant, unpleasant, and neutral odors. Although they found that pleasant odor produced relative left frontal activation, elderly subjects did not show relative right frontal activation in response to unpleasant odor. A study published by our laboratory has shown that compared to healthy control group, depressive elderly subjects showed relatively greater right frontal activity, but this difference was not significant (Deslandes et al., 2008). It is possible however that the heterogeneity of depressive symptoms in the MDD group have influenced the results. Recently, we verified that depressed elderly showed increased EEG alpha asymmetry only in the posterior areas which was associated with better treatment response (Deslandes et al., 2010). Noteworthy, we did not find any difference in anterior areas as depression decreased. Although several studies point out to frontal asymmetry as a possible marker of depression (trait) or as a dysfunction associated with the presence of symptoms in depression (state), the results are conflicting. Furthermore, the frontal asymmetry in elderly adults needs to be systematically analyzed, since it has been suggested that aging promotes changes in asymmetry (Smit et al., 2007). A recent meta-analysis which comprised 37 studies did not include any with elderly subjects (Thibodeau et al., 2006). Our latest study (Deslandes et al., 2008) found little difference between depressed and normal elderly, whereas some other authors found that never-depressed individuals can be distinguished from remitted individuals (Henriques and Davidson, 1990).

To try and answer these issues the objective of the present study is to compare the frontal asymmetry of three groups of elderly subjects: remitted depressive, currently depressed, and normal ones. Furthermore, we intend to examine the correlation between physical and mental aspects of quality of life and frontal asymmetry. Two alternative results might be found with regards to asymmetry as a trait- or state-related measure, and the other hypothesis is related to quality of life, as follows: i) Frontal asymmetry is a trait marker for depression: both depressed and remitted would show the same asymmetry pattern, as opposed to that observed in non-depressed individuals; or ii) Frontal asymmetry is a state-related finding in a current depression: depressive group would show relatively greater right frontal activity or relatively lower left frontal activity, whereas remitted and non-depressed group would exhibit relatively greater left frontal activity or relatively lower right frontal activity; and iii) frontal asymmetry could be positively correlated to quality of life.

2. Methods

2.1. Subjects

The sample consisted of three groups aged 65 years or more ($n=27$): depressed ($n=12$), remitted ($n=8$), and control ($n=7$). The depressive and remitted subjects were on treatment at the Psychiatric Institute and had been diagnosed according to DSM-IV (American Psychiatric Association, 1994) criteria as Unipolar Depression by a trained psychiatrist. A consensus meeting with two other psychiatrists took place whenever a doubt was raised about the diagnosis. All the patients had been on antidepressants (fluoxetine or sertraline) and anxiolytics (diazepam, lorazepam or clonazepam) for at least six months. The control group consisted of non-depressed volunteers who participated in a Fall Prevention Program at the same University, and had never experienced a depressive episode. Only individuals with a Beck Depression Inventory (BDI) score below 10 were included in this group. Exclusion criteria for the study were illiteracy, cognitive impairment suggestive of dementia, other concurrent neurological or psychiatric disorder, and left-handedness (assessed with the Edinburgh Handedness Inventory) (Oldfield, 1971). Written informed consent was obtained from each volunteer and this study was approved by the Ethics Committee of Psychiatric Institute.

2.2. Procedures

The evaluation consisted of: EEG recording, Beck Depression Inventory (BDI) (Gorestein and Andrade, 1996), Mini Mental State Examination (Folstein et al., 1975), and a quality of life questionnaire (SF-36) which were administered at the same day and none lasted more than one hour. Subjects were classified according to diagnosis and depressive symptoms as follows: I) a depressed group (clinically diagnosed as depression and with $BDI > 10$); II) a remitted group (clinically diagnosed as depression and with $BDI < 10$); III) a non-depressed group (clinically diagnosed as non-depressed and with $BDI < 10$).

2.3. Depression scale

The Portuguese validated version of the Beck Depression Inventory (BDI) was used in our study. This scale is a self-report measure and contains 21 questions, including symptoms and attitudes, each answer being scored on a scale value of 0 to 3. The cutoff to distinguish the level of depression is below 10 for non-depressed, 10 to 18 for mild to moderate depression, 19–29 for moderate to severe depression, and 30–63 for severe depression (Gorenstein and Andrade, 1998).

2.4. Quality of life

The Portuguese validated version of the Short Form Health Survey-36® (SF-36®) was used (Ciconeli, 1997). SF-36® is a self-rating questionnaire which assesses eight domains of physical health (physical functioning [PF], role physical [RP], bodily pain [BP] and general health [GH]) and mental health (social functioning [SF], mental health [MH], emotional role [RE], vitality [VT]). Higher scores represent better health appraisal and the scale ranges from zero to 100%.

2.5. EEG recording

Because previous research has shown that sleep disturbance alters frontal alpha power (Ferreira et al., 2006), the subjects were inquired about fatigue state and hours of sleep previous the EEG acquisition. Moreover, they also abstained from coffee, smoking or other mood-altering substances before testing. Subjects were seated in a comfortable sound and light attenuated room, while at least eight minutes of eyes-closed alert/resting EEG data were collected from the 20 monopolar electrodes sites (Fz, Cz, Pz, Oz, Fp1, Fp2, F3, F4, F7, F8, C3, C4, T3, T4, T5, T6, P3, P4, O1, and O2). International 10/20 System (referred to linked earlobes) (Jasper, 1958) for electrode placement was used with a Braintech-3000 (EMSA-Medical Instruments®, Brazil). The eye movement artifact was monitored (by electrooculogram) with a bipolar electrode montage using 2 electrodes of 9 mm diameter attached superior to, and on the external canthus of, the right eye. The vigilance of the subjects was controlled by the presence of an occipital decrease in alpha activity and of sleep spindles in the EEG, which naturally appear during drowsiness (Fingelkurts et al., 2006). The impedances for the EEG and electrooculogram electrodes were under 5 and 20 kΩ, 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. Visual inspection was employed for detection and elimination of artifacts. Biologic artifacts (i.e., eye movements, forced eye closure, forced jaw closure, and tongue movements) were removed through visual analysis (Anghinah et al., 2006). Moreover, epochs containing bioelectric artifacts greater than 100 μV in any channel were rejected. Independent Component Analysis (ICA) from EEGLAB was applied to remove other possible sources of artifacts and only the artifact-free EEG was processed.

2.6. EEG data analysis

At least two minutes of artifact-free data were extracted from the EEG total record for quantitative analysis. Power-spectral analysis was performed with Fast Fourier Transform (FFT). For each of the 20 monopolar derivations, absolute spectral power (μV^2) was computed for alpha (8–12.9 Hz) frequency bands. EEG measures were log-transformed (i.e., $X' = \log_n X$) to acquire Gaussianity (i.e., to obtain a normal distribution). Frontal Asymmetry ($\ln [\text{Right}] - \ln [\text{Left}]$) was computed for alpha band (prefrontal Fp2–Fp1, medial frontal F4–F3, and lateral frontal F8–F7). The difference score thus provides a simple unidimensional scale representing the relative activity of the right and left hemispheres, with higher scores putatively indicate of greater left frontal activity (assuming that alpha is inversely related to activity) (Allen et al., 2004).

2.7. Statistical analysis

To compare for statistically significant differences in depressive symptoms and in quality of life among groups (control vs. remission vs. depression), the Kruskal–Wallis test was used. Mann–Whitney test was used to compare duration of disease (years) and ANOVA was used to compare age (years) among groups. For the EEG variable, Log Absolute Alpha Power, three-way ANOVA was computed. Groups (control vs. remission vs. depression) were established as a between-subject factor and hemisphere (right vs. left) and area (prefrontal vs. medial frontal vs. lateral frontal) as within-subject factors. One-way ANOVA was used to compare the metric value ($\ln \text{Right} - \ln \text{Left}$) among groups at each area. Moreover, we computed the separate correlation (Spearman) between alpha asymmetry metric scores, depression scale and physical and mental aspects of SF-36. Significance levels were set at $p \leq 0.05$ for all statistical analyses.

3. Results

The sample characteristics are shown in Table 1. There was no significant difference in age between groups. As expected, depressive symptoms and physical and mental aspects (SF-36) showed statistically significant differences among the groups. Three-way ANOVA analysis showed a significant main effect to hemisphere ($F = 15.33$; $p = 0.001$) and to area ($F = 8.02$; $p = 0.002$), expressed as greater alpha power in left hemisphere and to medial frontal F3–F4 area on the EEG. However, there was no significant difference among groups ($F = 0.37$; $p = 0.69$). One-way ANOVA also indicated no significant difference in metric asymmetry among groups for F8–F7 ($F = 1.04$; $p = 0.36$), Fp2–Fp1 ($F = 1.88$; $p = 0.17$) and F4–F3 ($F = 0.86$; $p = 0.43$) (Fig. 1).

No significant correlation was found between asymmetry and physical or mental aspects of quality of life (Table 2). There was no significant correlation between frontal asymmetry and Beck scale as well. The Beck Depression Inventory was negatively associated with SF-36 physical aspects ($R_s = -0.50$; $p = 0.01$) and mental aspects ($R_s = -0.53$; $p = 0.01$), showing that the higher the depression score the worse the perception of quality of life (Fig. 2).

Table 1
Subject characteristics.

N	Depressed group		Remitted group		Non-depressed group	
	12 (6 females)		8 (6 females)		7 (6 females)	
	Mean	SD	Mean	SD	Mean	SD
Age (y)	71	7.8	71	3.7	72	9.2
Disease (y)	13.2	11.5	10.8	9.4	–	–
BDI (score)**	16.4	4.4	4.5	3.5	2	2.3
MMSE	25.2	3.9	27.5	2	26.5	3
SF-36 physical (%)*	47.9	26.9	70.4	28.4	88.4	20.4
SF-36 mental (%)*	41.4	28.5	64.4	31.6	95.2	12.2

BDI (Beck Depression Inventory); MMSE (Mini Mental State Examination).
SF-36 (Short Form Health Survey-36®); ** $p \leq 0.01$; * $p \leq 0.05$.

4. Discussion

This study aimed to compare depressive symptoms, quality of life, and frontal asymmetry among depressed, remitted and non-depressive elderly subjects. Contrary to our hypothesis, the frontal asymmetry did not display any differences among groups and was not correlated with other variables. As expected, there was a significant difference between the depressed and the other groups with regards to the depressive symptoms and physical and mental aspects of quality of life. The physical and mental aspects of quality of life showed a statistically significant negative correlation with depressive symptoms.

Our results seem to corroborate those found in other studies that also showed no differences in EEG frontal asymmetry between depressed, remitted, and controls individuals. For instance, some studies observed no differences in frontal asymmetry between depressive and normal controls (Bruder et al., 1997; Reid et al., 1998). Another neuroimaging study did not present any significant difference in asymmetry in depressive and remitted subjects either (Navarro et al. 2002). In turn, some other studies observed an association between asymmetry with anxiety symptoms, but not with depression symptoms (Blackhart et al., 2006; Bruder et al., 1997). Different methodologies in EEG recordings, lack

of a clinically structured diagnosis, comorbidity of depression with anxiety and post traumatic stress disorder might be factor to explain some discrepancies between the studies (Thibodeau et al., 2006; Bruder et al. 1997; Reid et al., 1998; Metzger et al., 2004).

Smit et al. (2007) examined the genetic and environmental contribution to the relationship between frontal asymmetry and risk for anxiety and depression in young and middle-aged adults. Interestingly, they found that asymmetry was heritable only in young adults. As in our study, the negative results could be related to the right hemi-aging hypothesis, whereby the right hemisphere ages more rapidly than the left and the older brain responds in a homogenous or global manner (Cabeza, 2002). Pleasant and unpleasant stimuli were found to be associated to frontal asymmetry in the elderly. The subjects who were exposed to unpleasant odors did not present an increase in right frontal activity, whereas left frontal increase was increased in response to pleasant odors (Kline et al., 2000). This is line with Davidson's hypothesis (Henriques and Davidson, 1990; Henriques and Davidson, 1991). It may thus be very difficult to relate the frontal asymmetry as a trait or state in depressed elderly, as both the aging process and major depression may influence this measure. Findings from functional neuroimaging studies in elderly people tend to find in most cases a weaker and more diffuse cortical activation, with reduced hemispheric asymmetry (Minati et al., 2007). A possible explanation is a structural and functional impairment of the right hemisphere with the aging process. Thus, possible changes in neural connections are associated with compensatory mechanisms and bilateral activation. This would result in a reduced hemispheric asymmetry in the elderly compared with younger subjects (Li et al., 2009). Another model proposed by Wolkowitz et al. (2010) states that depression in the elderly would trigger structural and functional changes in the brain,

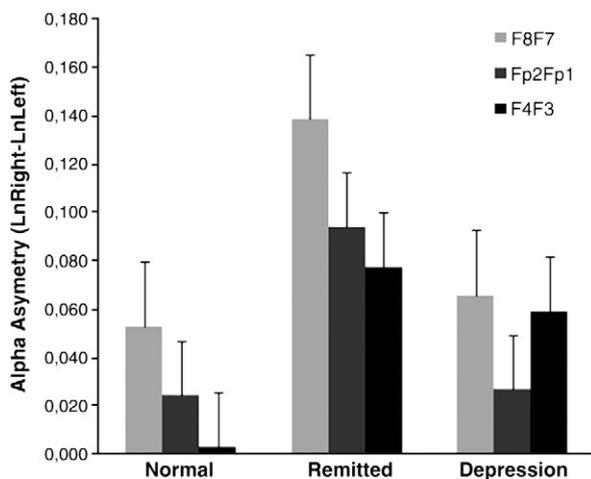


Fig. 1. Frontal asymmetry (mean and sd) in normal, remitted and depressed elderly subjects.

Table 2

Correlation (rSpearman and *P* value) between EEG alpha asymmetry, depressive symptoms (BDI) and physical aspects and mental aspects of quality of life (SF-36).

	FP2–FP1	F4–F3	F8–F7	BDI
BDI	–0.29(0.13)	0.12(0.95)	–0.14(0.46)	–
Physical aspects	0.19(0.32)	0.09(0.64)	0.31(0.10)	–0.50(0.00)
Mental aspects	–0.12(0.52)	0.11(0.57)	–0.18(0.36)	–0.53(0.00)

* $p \leq 0.01$.

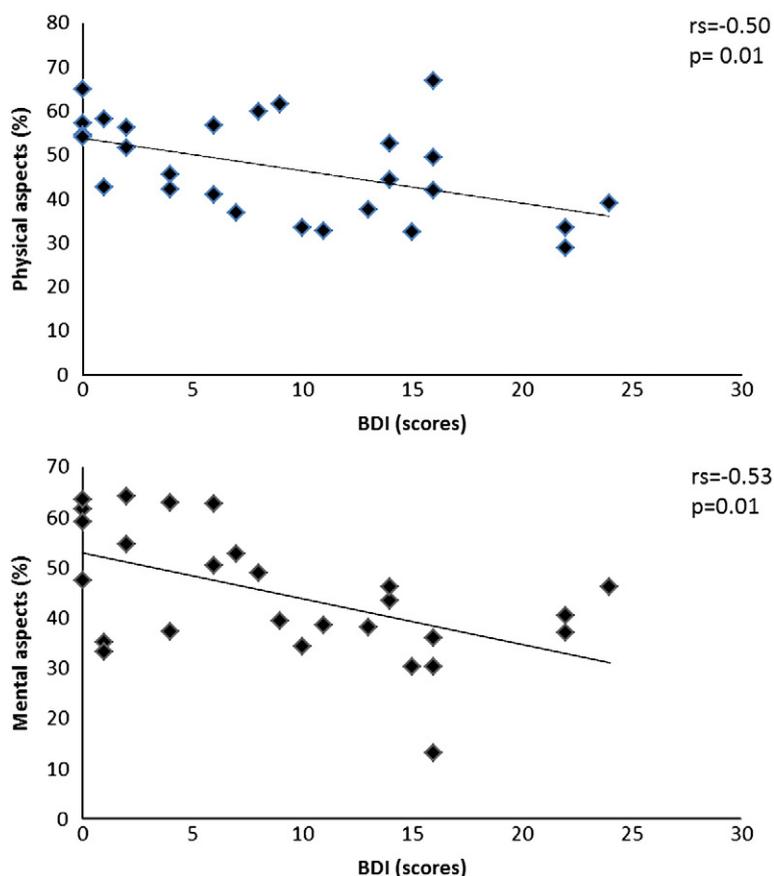


Fig. 2. Scatter plot of the correlation between SF-36 aspects (%) and Beck Depression Inventory (BDI) scores of Depressed, Remitted and Normal Elderly subjects.

somehow speeding up cell aging. Ultimately, changes in frontal asymmetry would appear as a result of the aging process derived from this mechanism.

The results from the present study should be examined with a grain of salt. First, the cross-sectional design is not appropriate to study these effects due a possible instability in frontal asymmetry measure across time. It should be noted however that some studies found moderately long-term stability (Vuga et al., 2006; Allen et al., 2004). Also, it is not possible to ascertain whether a trait is present just in a cross-sectional study. Second, our research focused only on depressive symptoms and quality of life. Several studies have shown that asymmetry could be influenced by other factors, such as anxiety (Bruder et al., 1997), self-esteem (De Raedt et al., 2007), and level of physical activity (Hall and Petruzzello, 1999). Only mild and moderate depressed patients were examined. Finally, the small sample size may have influenced our results.

This study was not able to confirm that frontal asymmetry is either related to a trait or to a state of depression in elderly subjects. A positive finding, however, would be of clinical relevance since if frontal asymmetry were to be a trait in depression, i.e., a neurophysiological marker of the disease, then EEG would be a useful and easy tool for early diagnosis of depression. Future research with longitudinal design should continue to examine the changes in asymmetry associated

with aging. These experiments will have to determine if the frontal asymmetry is a sensitive tool to determine trait or state of depression.

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Conflict of interest

No conflict declared.

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