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Depression in Parkinson's disease: an EEG frequency analysis study

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Abstract

Although depression is a common finding in Parkinson's disease (PD), its neurobiological mechanism is still unknown. The purpose of this study was to determine whether there are specific spectral electroencephalographic (EEG) characteristics that distinguish depressed from non-depressed PD patients. The study was performed in 24 patients with idiopathic PD whose antiparkinson medication was stopped 24 h beforehand. They were divided into two groups of 12 patients each, one with depressive symptomatology, and one without. The groups did not differ with respect to age, sex distribution, and disease severity and duration. All recordings were conducted using a 16-channel electroencephalograph, and artifact-free EEG was processed using a Fast Fourier Transformation. The EEG of depressed PD patients showed significantly less absolute and relative power in spectral band 7.5–10 Hz (alpha1), and slightly more relative power in spectral band 10.513 Hz (alpha2), while there was no difference in other spectral bands. Topographic analysis of the alpha1 absolute power revealed that, while in non-depressed patients this activity has a clear occipital maximum (and thus corresponds to the standard background activity), in depressed patients its maximum was shifted anteriorally toward the parietal region. Topographic analysis of the significance of the difference between the groups in the relative power of alpha1 and alpha2 bands revealed opposite gradients, posterior to anterior and anterior to posterior directions, respectively. The spectral EEG characteristics of the depressed PD patients not only differed from the spectral EEG characteristics of non-depressed PD patients, but they were also different from the usually reported spectral EEG characteristics of depressed patients without neurological disease. We propose that our data are sufficient to raise the possibility for the existence of a distinctive neurobiological substrate of depression in PD. This is not just a simple addition of two neurobiological substrata, one of depression (as it is determined in non-neurological patients) and one of PD, but rather a complex product of their interaction.

Keywords: Parkinson's disease; Depression; Electroencephalography; Frequency analysis

1. Introduction

Depression is a common finding in Parkinson's disease (PD). It has been reported in crosssectional samples that about 40% of patients have depression, of either major or minor type [1–4]. Although much data have been gathered in recent years, the exact mechanism of depression in PD is still a matter of debate.

Standard electroencephalographic (EEG) studies in PD have shown that while EEG is not consistently affected, the prevalence of abnormalities is greater than in the normal population [5,6]. Some association between pathological findings in EEG (i.e., slowing in occipital background activity) and greater movement impairment in mentally intact patients suggests that these EEG changes may be related to impairments in subcortical structures involved in motor control [6,7]. Quantitative EEG (QEEG) has only rarely been used for studying PD and the results have mainly confirmed previous findings [8,9]. However, there is no study that has specifically addressed the question of QEEG characteristics of depression in PD.

The purpose of the present study was to determine whether there are specific QEEG characteristics that distinguish depressed from non-depressed PD patients.

2. Patients and methods

2.1. Patients

The study was performed in 24 patients with idiopathic PD. They were divided into two groups of 12 patients each, one group with, and other without, depressive

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symptomatology. The groups did not differ with respect to age, sex distribution, and disease severity and duration.

Only patients aged 65 years or less were included in the study to minimize the major influence of age-related EEG changes. All patients presented with exclusively parkinsonian signs, dominated by at least two of its cardinal features (bradykinesia, tremor, or rigidity), and these had developed insidiously. Patients with evidence of focal lesions on CT scans and with a Hachinski ischemia score [10] greater than 4 were excluded. The stage of the disease was rated according to the Hoehn and Yahr scale (H & Y) [11]. The severity of motor disability was quantified by the Columbia University Rating Scale (CURS) [12], while the level of performance impairment of everyday activities was determined by the Northwestern University Disability Status Scale (NWUDSS) [13]. The Mini Mental State (MMS) exam [14] was used to screen for global cognitive decline and patients with a MMS score of less than 25 were excluded from the study. All patients underwent a standardized psychiatric evaluation (trained examiners supervised by D.L.) using the Schedule for Affective Disorders and Schizophrenia (SADS) [15], and were classified, according to the Research Diagnostic Criteria [16], as either depressed (major or minor depression) or non-depressed. Severity of depression was measured with the Hamilton Depression Scale (HAMD) [17]. All patients gave their informed consent for their participation in the study, and the study design was approved by the Ethical Board of the Faculty of Medicine.

2.2. EEG recordings and data analysis

All recordings were conducted using a 16-channel electroencephalograph (TECA Montage *II*). The brain electrical activity was recorded from Fp1, Fp2, F3, F4, F7, F8, T3, T4, C3, C4, T5, T6, P3, P4, O1, and O2 sites of the 10–20 International System, using an ''Electrocap'' [18]. Linked ears were used as a reference. Signals were filtered with 0.5 Hz high pass and 35 Hz low pass filters. All signals were digitized at a rate of 300 Hz (CED 1401 *plus*, Cambridge Electronics Design) and stored as two-second sequences on the hard disk using the ''CED EEG Measurement and Analysis System'' (Cambridge Electronics Design) software. At least 3 min of recorded EEG were stored. During the recording the patients were instructed to keep their eyes closed and to remain relaxed yet alert. The recording segments contaminated with artifacts because of eye movements, muscle tension, tremor, and drowsiness were excluded after a visual inspection ''off-line''. Finally, a minimum of 15 two-second epochs (i.e., 30 s) of artifact-free EEG were selected for further analysis. A Fast Fourier Transformation (FFT) was applied to each of the selected epochs. The epochs' power spectra obtained from the FFT were then averaged (CED EEG Measurement and Analysis System) to form a representative power spectrum that was used in further analysis. The frequency range analyzed was 2.5–29.5 Hz, and the absolute power was calculated for this frequency range as a whole, as well as the absolute and relative powers for delta (2.5–4.0 Hz), theta (4.5–7.0 Hz), alpha1 (7.5–10.0 Hz), alpha2 (10.5–13.0 Hz), beta1 (13.5–18 Hz), and beta2 (18.5–21.0 Hz) frequency bands. A logarithmic transformation was applied to absolute powers ($\ln x$) and relative powers ($\ln[x/(1-x)]$) to normalize their distribution [19]. In accordance with the suggestions of Jähnig and Jobert [20], for graphical presentations of the spectral data, the ''trimeans'' for each electrode for each of the groups were calculated. We define Trimean the following way: ''It combines the robustness of the median with quartile sensitivity for asymmetries in data distribution and it can be considered as a non-parametric measure of group location''. The formula for trimean (T) is: $T = 0.25Q^{1st} + 0.5M + 0.25Q^{3rd}$, where M corresponds to the median of the sample, and Q^{1st} and Q^{3rd} to the first and third quartile respectively.

The first step in data analysis was calculation of an analysis of variance (ANOVA), with DEPRESSION (present or absent) as a between-group factor, and EEG FREQUENCY BANDS (6) and ELECTRODE SITES (16) as the repeated factors. When a significant main effect of or interactions with FREQUENCY BANDS were found, a post-hoc analysis was conducted using the Tukey Honest Significant Difference (HSD) test. For frequency bands detected as significantly different between two groups, another ANOVA was performed, using only values from the selected frequency band. In these analyses DEPRESSION was the between-group factor and ELECTRODE SITES the repeated factor. Violations of sphericity were adjusted by the Huynh–Feldt correction. When a significant DEPRESSION × ELECTRODE SITES interaction was detected by ANOVA, in order to determine significance of difference for each of the electrodes, a separate repeated measures multivariate ANOVA (MANOVA) with single factor CONDITION was performed. Student's *t*-test was used for between-group comparisons in age, while Mann–Whitney *U* test was used for other demographic and clinical variables, apart from sex distribution where chi-square test was used.

To better appreciate the topographic characteristics of a certain parameters gray-scale coded brain-maps were constructed using the 64 × 64 grid matrix and an interpolation algorithm based on the data from all scalp electrodes.

3. Results

Patients were categorized according to the presence or absence of depression into two groups of 12 patients each: depressed (D +), and non-depressed (D −).

3.1. Demographic findings

Our sample included 15 males (62.5%) and 9 females (37.5%) with a mean age of 50.0 (SD 9.7; range: 35–65)

Table 1
Demographic and clinical characteristics of the studied groups of patients. NWUDSS – the Northwestern University Disability Status Scale; CURS – the Columbia University Rating Scale; MMS – the Mini Mental State exam; HAMD – Hamilton Depression Scale

		Non-depressed (male/female: 8/4)		Depressed (male/female: 7/5)	
	N	Mean (SD)	[min.–max.]	Mean (SD)	[min.–max.]
Age (years)	12	47.8 (9.6)	[35–64]	52.3 (9.6)	[36–65]
Duration of disease (years)	12	2.9 (3.4)	[0.5–12]	2.3 (2.1)	[0.5–6]
Levodopa dose (mg/day)	4	275.0 (50.0)	[200–300]	350.0(173.2)	[200–600]
Duration of levodopa therapy (years)	4	2.4 (3.2)	[0.5–7]	2.4 (2.1)	[0.5–5]
Hoehn & Yahr stage	12	2.0 (0.8)	[1–4]	2.0(0.9)	[1–4]
NWUDS score	12	39.8 (4.4)	[29–45]	41.2 (6.9)	[25–48]
CURS score	12	34.6 (11.6)	[18–63]	35.8 (17.4)	[18–68]
MMS score	12	27.9 (2.1)	[25–30]	28.7 (1.8)	[25–30]
HAMD score	12	7.(2.8)	[4–12]	20.1(5.2)	[15–34]

years, and mean duration of disease of 2.6 (SD 2.7; range: 0.5–12) years. No significant between group differences were found in any of the demographic variables (Table 1).

3.2. Clinical findings

As expected, depressed patients showed significantly higher HAMD scores than non-depressed patients ($Z = 4.157$, $p = 0.000032$), but no significant difference in MMS scores, H & Y stages, CURS and NWUDSS scores, and duration of disease was found (Table 1). Four patients in each group were receiving levodopa therapy, which was discontinued 24 h before EEG recording, while the remaining patients had never received any antiparkinsonian therapy. The dosage of levodopa between two groups did not differ significantly. Four depressive patients were diagnosed as having minor depression, while the remaining eight had major depression. Three depressive patients started to display depressive symptoms (autobiographical data) before the onset of PD. No patient was on psychoactive drugs on a regular basis at least six months before EEG recording, and at the recording day no therapy of any kind was administered.

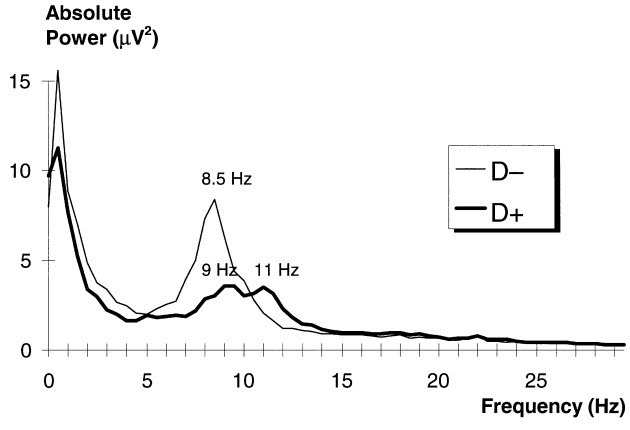

Fig. 1. The trimeans of the spatially averaged absolute power spectra for both patient groups; before trimean calculation, for each subject, the data from all 16 electrodes are collapsed to form a mean spectrum of the scalp EEG.

3.3. Neurophysiologycal findings

The trimeans of the spatial averages of the absolute power spectra for both patient groups is presented on Fig. 1. Before averaging across subjects, for each subject the data from all 16 electrodes were collapsed to form a mean spectrum of the scalp EEG (Fig. 2). The difference in power of the alpha1 and alpha2 frequency bands is obvious. The ANOVA with repeated design on absolute power values did not detect any significant influence of DEPRESSION as an isolated factor, but a statistically significant DEPRESSION × FREQUENCY BAND interaction was found (Table 2). Tukey HSD post-hoc test disclosed a significant difference between D + and D − patients in alpha1 band ($p = 0.001$) only (D + patients had less alpha1 activity) (Fig. 1), while differences in other bands were non-significant ($p > 0.25$). It should be noted that DEPRESSION × ELECTRODE SITE, as well as DEPRESSION × ELECTRODE SITE × FREQUENCY BAND interactions were also far from being statistically significant. Second ANOVA, on alpha1 values separately confirmed significant influence of DEPRESSION ($F[1,22] = 4.83$ [$p = 0.039$]), while DEPRESSION × ELECTRODE SITE interaction remained non-significant ($F[15,330] = 1.05$ [$p_{(\text{uncorrected})} = p_{(\text{corrected})} = 0.40$].

Maps of the trimean absolute power in alpha1 frequency band were constructed to better appreciate characteristics of apha1 topography in two groups (Fig. 3). It can be seen that D − patients had an occipital maximum of alpha1 activity, that is actually their dominant/background activity, which corresponds to the typical topography of background activity in healthy subjects. In comparison to them, alpha1 activity in D + patients had different topographical features, although without statistical significance. The main difference was slight anterior shift of the activity peak, which is in this group in parietal region.

ANOVA on relative power values also failed to

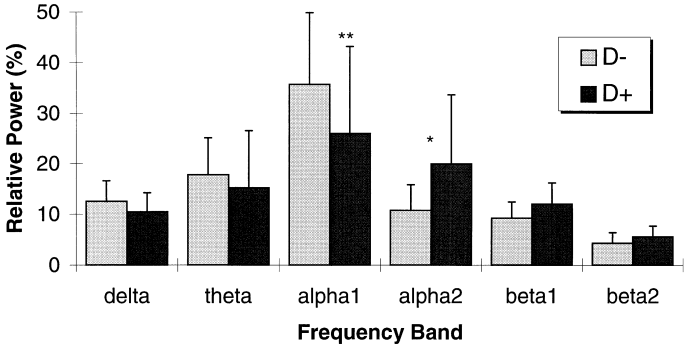

Fig. 2. The means (and standard deviations) of the relative power spectra in selected frequency bands for both patient groups. The spatially averaged data are presented before calculation of the group mean, for each subject and for each frequency band, the data from all 16 electrodes are collapsed to form a mean. The statistically significant differences were marked (*$p = 0.01$, **$p = 0.006$–ANOVA on individual frequency bands).

Table 2
Results of ANOVA on absolute power – summary of all effects [factors: 1—depression (2), 2—electrode site (16), 3—frequency band (6)]

Factors/Interactions	df effect	MS effect	df error	MS error	F	p-level
1	1	30.35305	22	28.79777	1.054007	0.316
2	15	4.213398	330	0.400583	10.51816	1.1E^{20}
3	5	133.6705	110	3.65782	36.54376	6.7E^{22}
12	15	0.243746	330	0.400583	0.608478	0.868
13	5	19.69018	110	3.65782	5.383037	0.0002
23	75	0.292602	1650	0.049397	5.92351	0
123	75	0.057922	1650	0.049397	1.172594	0.152

demonstrate any significant influence of DEPRESSION as an isolated factor, but again detected a significant DEPRESSION × FREQUENCY BAND interaction (Table 3). Tukey HSD post-hoc test disclosed that the only significant difference between D + and D − patients was in the alpha1 band ($p = 0.032$), with the D + patients having less alpha1 activity. In addition, differences in the alpha2 band were near the limit of significance ($p = 0.083$), with the D + patients showing slightly more alpha2 activity. Differences in other bands were non-significant ($p > 0.88$). A significant DEPRESSION × ELECTRODE SITE × FREQUENCY BAND interaction was also detected ($p = 0.0095$). Second ANOVA, on alpha1 and alpha2 values separately confirmed significant influence of DEPRESSION ($F[1,21] = 9.49$ [$p = 0.0057$], and 7.91 [$p = 0.01$], respectively)[1], while DEPRESSION × ELECTRODE SITE interaction behaved differently in two bands ($F[15,315] = 2.69$ [$p_{(\text{uncorrected})} = 0.0007$, $p_{(\text{corrected})} = 0.012$], and 1.92 [$p_{(\text{uncorrected})} = 0.021$, $p_{(\text{corrected})} = 0.115$], respectively).

Maps on Fig. 4 summarize the significance of differences between D + and D − patients in the alpha1 and alpha2 bands for each of the electrodes, as revealed by an independent MANOVA. The difference in alpha1 band was most expressed over the posterior part of the scalp with a clear posterior to anterior gradient. There was also an asymmetry in the occipital region where the difference between patient groups was higher on the left than on the right (MANOVA $F[1,21] =$ {O1} 15.28 [$p = 0.0008$], and {O2} 7.57 [$p = 0.012$]). Differences in the alpha2 band were more evenly distributed, with slight anterior to posterior gradient and asymmetry at frontal sites where the between-group difference is more expressed on the right (MANOVA $F[1,21] =$ {Fp2} 9.07 [$p = 0.0066$], {F4} 8.34 [$p = 0.0088$], {Fp1} 6.87 [$p = 0.016$], and {F3} 6.97 [$p = 0.015$]).

4. Discussion

This is the first study to compare QEEG findings between depressed and non-depressed PD patients. We have found a distinctive spectral pattern of depressed PD patients that differs from the spectral pattern of non-depressed PD patients with equal levels of parkinsonian symptomatology. The main differences were a significant diminution of slower alpha activity (alpha1), especially over the posterior regions, and a slight surplus of faster alpha activity (alpha2), especially over right frontal regions, in depressed PD patients. Aside from being different from the pattern seen in non-depressed PD patients, this pattern was also different from the spectral pattern usually described in the literature for depressed non-PD patients suggesting, therefore, the

[1] Interestingly, separate ANOVA on relative power in whole alpha band taken together (i.e., from 7.5 Hz to 13 Hz) did not disclose any significant effect for depression factor nor depression × electrode site interaction ($F[1,21] = 0.51$, and $F[15,315] = 0.57$ [$p > 0.40$in both cases], respectively).

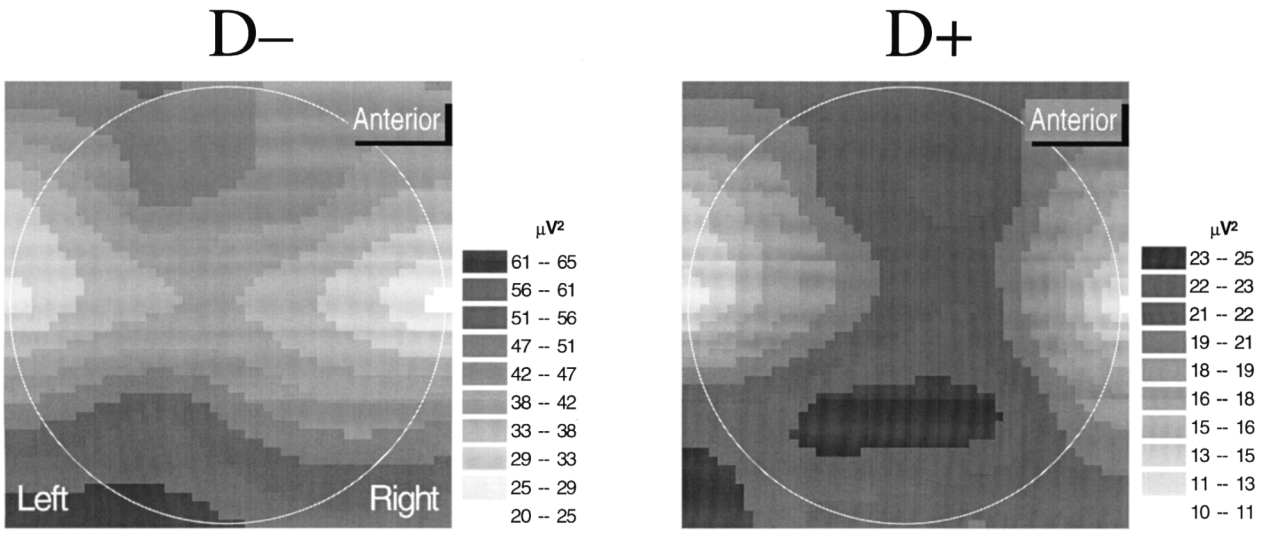

Fig. 3. Topographic maps of the trimeans of the absolute power in alpha1 frequency band for non-depressed (D −) and depressed (D +) PD patients' groups. The adjusted gray scale ranges were used for each map in order to better emphasize topographic features.

existence of a distinctive neurobiological substrate for depression in PD.

The first EEG studies of PD patients, performed in the late 1930s by Jasper and Andrews [21], suggested the existence of specific 4–5 Hz rhythmic activity synchronous with the tremor. However, further studies with simultaneous EEG and EMG registration [22], revealed that this activity was actually an artifact introduced into the EEG by head tremor, and that real EEG activity in PD patients did not differ from normal. This was the generally accepted opinion for the next 20 years, and there was no study that specifically addressed this problem over this time. With the advent of the stereotaxic procedures in the early sixties the interest in EEG in PD re-emerged. However, the great majority of the studies performed suffered from serious methodological drawbacks, such as imprecise diagnostic criteria, undefined therapeutic and clinical status, vague criteria for ''pathological'' findings, and variable recording conditions. Summarizing the results of these studies, Markand [23] concluded that the majority of patients had normal EEGs, and that in only a minority of patients, usually in later phases of the disease and/or with more serious motor derangement, slowing of the occipital background activity below 8 Hz and an increase in the percentage of the generalized theta–delta activity was encountered.

In one of the rare methodologically correct studies, Neufeld et al. [6] found ''pathological'' EEG in 16% of non-demented PD patients, stating that the main pathological finding was slowing of the background activity and an increase in diffuse theta activity. Additionally, they noted a statistically significant relationship between the frequency of pathological findings and the degree of motor impairment. Later on, same group [9] using this time QEEG, but on a relatively small sample of 10 PD patients and 10 control subjects, failed to find any significant difference between patients and controls, although a trend toward a higher percentage of slower activity with greater motor deficit was again noted. However, using also the QEEG, Soikkeli et al. [8] demonstrated a significant increase of absolute and relative theta activity, decrease of relative alpha and beta activity, as well as slowing of the mean and dominant frequency of the background activity, in a group of 18 non-demented PD patients. Our results for the non-depressed patients do not differ much from the studies mentioned. The pattern of the average spectral profile of D − patients closely matches the pattern of the standard ''normal''

Table 3
Results of ANOVA on relative power – summary of all effects [factors: 1—depression (2), 2—electrode site (16), 3—frequency band (6)]

Factors/Interactions	df effect	MS effect	df error	MS error	*F*	*p*-level
1	1	1.226984	21	1.042465	1.177003	0.290
2	15	0.372939	315	0.035607	10.47367	$2.14E^{20}$
3	5	174.9441	105	5.856534	29.87161	$9.12E^{19}$
12	15	0.031512	315	0.035607	0.884998	0.581
13	5	33.22	105	5.8565	5.6723	0.0001
23	75	0.429288	1575	0.076951	5.578743	0
123	75	0.1106	1575	0.077	1.4375	0.0095

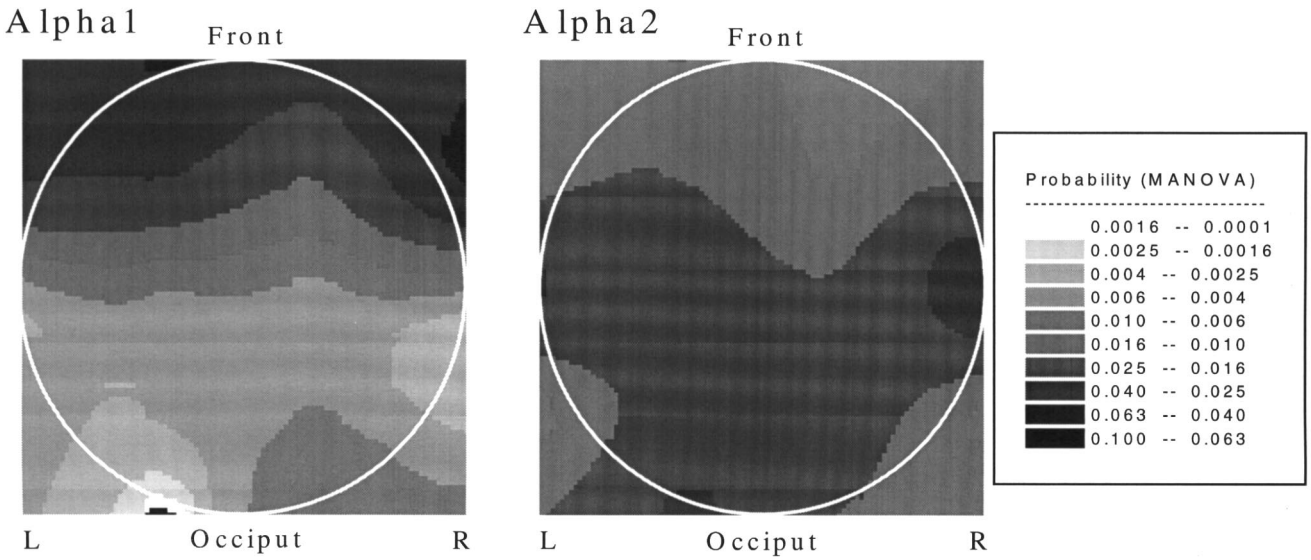

Fig. 4. Topographic maps of the results of the MANOVA on relative power in alpha1 and alpha2 frequency bands – presented are the probabilities of the significance of difference between depressed and non-depressed patients.

spectral profile described in the literature [24,25]. The only difference is the slight shift of the main body of spectral power toward slower frequencies, with abundance of activity in fast theta and slow alpha spectral regions, but this corresponds well with described findings in PD patients from the aforementioned studies.

A number of functional imaging studies have reported evidence of cerebral hypoactivity, manifested mainly as reduction of global cerebral blood flow and metabolism, in patients with depression [26–29]. This global cerebral hypoactivity in depression may account for the reduced power in the alpha1 band (dominant/background activity of the D − patients) displayed by our D + PD patients. However, our findings do not fit well with the published data about EEG characteristics of depression.

The main body of data from EEG studies of depressive non-neurological patients stresses the association between psychomotor retardation in depression and slowing of EEG. For example, Monakhov and Perris [30] found that, among depressive patients, symptoms associated with the ''anxiety–depression'' psychometric construct were related to fast activity in the EEG, whereas symptoms associated with the ''retardation'' construct showed a significant relationship with slow EEG activity. Nyström et al. [31] also found that major depressive disorder was associated with an increase of delta amplitude, and in particular, retarded depression was associated with an increase of delta and theta amplitudes and EEG variability. Brenner et al. [32] found that, although the EEG was usually normal or only mildly abnormal in patients with depression or depressive pseudodementia, these groups did show a significant slowing of the dominant posterior rhythm and had a higher percentage of generalized abnormal EEGs compared to controls. Nieber and Schlegel [33] specifically examined the associations between severity of depression, psychomotor retardation, and EEG spectral analysis in a large group of 63 depressed patients. According to their data, slow EEG activity (fast theta–slow alpha bands) was positively, and fast activity (fast alpha–beta bands) negatively, correlated with the observed retardation. Out of the four retardation sub-items they examined (motor, verbal, intellectual and emotional), motor retardation correlated most closely with slow EEG activity. In contrast to these findings that generally associate motor retardation in depression with slow EEG activity, our D + PD patients did not show any particular increase in theta–delta activity in comparison to D − patients. In addition, there was no increase in beta activity that can be also inferred from the aforementioned data that associate anxiety with fast EEG activity.

It has been repeatedly demonstrated that the profile and evolution of depressive symptoms in PD are not identical to those reported in idiopathic depression [34–37]. The profile of cognitive impairments of depressed PD patients does not completely match the profile of non-PD depressed patients, and is different from the profile of non-depressed PD patients [38]. Depressed PD patients, in contrast to non-depressed PD patients and non-PD depressed patients, do not express euphoriant responses to the central stimulant methylphenidate, aimed at testing functional integrity of mesocorticolimbic dopaminergic circuits [39]. Functional imaging studies have reported evidence of a bilateral caudate, prefrontal, and anterior temporal reduction of metabolism in depressed PD patients in comparison to both non-depressed patients and control subjects [40,41]. Although this pattern of hypometabolism is consistent with the pattern of hypometabolism described in neurologicaly normal depressed patients [42,43], the two are not completely identical [44,45]. For example, while the majority of studies on

idiopathic depression emphasize changes in dorsolateral and medial prefrontal cortex, Mayberg et al. [40] found selective hypo-metabolism in the orbital-inferior part of the frontal lobes of their depressed PD patients. In another study, Ring et al. [41] found hypometabolism in the medial prefrontal cortex of depressed PD patients that was similar to their findings in primarily depressed patients, but some small albeit statistically significant difference existed between the two groups in the same region. Taken together, all these observations indicate that depression in PD may have different patho-physiological mechanisms from idiopathic depressive disorders. This might explain discrepancies between our EEG findings and those reported in the literature regarding neurological normal depressed subjects.

The finding of a slight increase in relative alpha2 power in D + PD patients in our study may well be a methodological artifact. Compared to absolute power measurements, relative power and its logarithmic transformation have the disadvantage that all bands are interrelated. A decrease in absolute power in one frequency band may cause an apparent increase in relative power of other frequency band, even if the amount of absolute power in that band has not changed. This might be the case for the slight anterior to posterior gradient displayed by differences between two patient groups in alpha2 relative power that may be just the simple counterpart of the posterior to anterior gradient displayed by alpha1 relative and absolute power differences. However, an alternative explanation is possible in the light of the aforementioned imaging data about metabolic changes in frontal lobes in depression. Nevertheless, some other topographic features of alpha1 and alpha2 relative powers in our D + patients seem to be more than methodological artifacts. In particular, this relates to the clear alpha1 occipital and alpha2 frontal asymmetry in the level of significance of difference in relative power between D + and D − patients (Fig. 4).

Lateralized dysfunction in depression have been repeatedly reported based on functional imaging methods. Using rCBF technique, Uytdenhoef et al. [46] reported left frontal hyper-vascularization and right posterior hypo-vascularization in depression. Using SPECT, Devous [47] reported a reduced flow in the right temporal and parietal lobes in depressed patients, while Rush et al. [26] found that depressed patients exhibit a greater flow to the left hemisphere. Systematically studying the age associated alteration in cortical blood flow in depression, Devous et al. [48] have demonstrated that the greatest difference between groups of patients with endogenous depression and a control group was in the left inferior temporal flow. We found that the greatest difference in alpha1 band, which is the frequency band of the dominant/background activity in our non-depressed PD patients, was located over the left posterior cortex. This suggests that the left hemisphere, and especially its posterior cortex, might be the site of the greatest dysfunction (most probably hyperfunction) typical for depression in PD. In contrast, the finding that the greatest difference in alpha2 band, which is the frequency band of EEG activity that is characteristic for our depressed PD patients, was located over right frontal cortex suggests some sort of right hemisphere, probably frontal or anterior temporal, dysfunction. Whether this pattern has a direct causative relationship with depressive symptomatology, or the frontal or anterior temporal dysfuntion are just a concomitant result of the impairment in some other structures or circuits is an open question.

Before concluding, some limitations of our study should be pointed out. First, as a result of the rather small sample, we collapsed patients with major and minor depression into one group. It is possible that these two types of depression have different neurobiological mechanisms and therefore different QEEG characteristics. Future studies should examine QEEG characteristics in PD patients with major and minor depression separately. Second, few of our patients had depression that was present before the onset of parkinsonian symptoms, and in sensu stricto they may not represent true ‘‘depression in PD’’. Nevertheless, since the presumed pathological process in PD starts well before the onset of the first motor parkinsonian symptoms [49], it is impossible, on clinical grounds alone, to determine whether the depression in those patients shares some common pathological features with PD or not. Finally, the analysis concentrated on possible differences in power only, while other modalities of QEEG analysis were not evaluated (e.g., coherence analysis). Nevertheless, we propose that our data are suggestive enough to raise the possibility for the existence of a distinctive neurobiological substrate of depression in PD. This is not just a simple addition of two neurobiological substrata, one of depression (as it is determined in neurologically normal patients) and one of PD, but rather a complex product of their interaction. Future studies, using QEEG and other methods, should elucidate this question in more detail.

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