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Composition of Brain Oscillations in Ongoing EEG During Major Depression Disorder

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Abstract
In the present study, we examined the composition of electroencephalographic (EEG) brain oscillations in 12 unmedicated major depressive outpatients and 10 healthy subjects during resting conditions (closed eyes). The exact composition of brain oscillations was assessed by the probability-classification analysis of short-term EEG spectral patterns. In contrast to previous studies of depression, the current study found that major depression affects brain activity in nearly the whole cortex and manifests itself in considerable reorganization of the composition of brain oscillations in a broad frequency range: 0.5-30 Hz. At the same time, the magnitude of the effect of depression was maximal in the posterior cortex of the brain. Interhemisphere asymmetry during major depression was also observed in the whole cortex with right hyperactivity in frontal, parietal and occipital brain areas. It is suggested that depressive brain is manifested in the superposition of distributed multiple oscillations. Our findings provide new insight on the relationship between major depressive disorder and cortical oscillatory activity.

Keywords: Major Depressive Disorder; Multiple brain oscillations; Short-term EEG spectral patterns; Interhemisphere asymmetry; Brain areas; Brain functions.

1. Introduction

Convergent neurophysiological data indicate that depression can be understood as re(dis)organization of the local and global oscillatory states in the cortex and may be interpreted in the context of the dynamical properties of a reorganized large-scale system (Fingelkurts et al., 2006c). Oscillatory states reflect the synchronization of neuronal assembles and a temporally ordered rhythmicity of activation (Lopes da Silva, 1991). Here, electroencephalogram (EEG) provides a satisfactory scale for accessing the large-scale dynamic of the brain's oscillatory states (with a temporal resolution in the order of milliseconds) associated with health and disease (Hughes and John, 1999; Basar et al., 2004).

To this day, the main analytical paradigm for EEG analysis remains spectral decomposition. Indeed, changes in the power spectrum have revealed important information about the electrical activity of the brain during major depressive disorder, MDD (Yamada et al., 1995; Davidson, 1998; Allen et al., 2004; Coan and Allen, 2004; just mention a few). It was demonstrated that depressed patients had more alpha and beta activity, and less delta activity than non-depressed controls (for alpha activity: Pollock and Schneider, 1990; Debener et al., 2000; for a review, see Hughes and John, 1999; for beta activity: Yamada et al., 1995; Knott et al., 2001; for delta activity: Lubar et al., 2003). Moreover, a link between relatively greater right frontal resting activity (or relatively lower left frontal resting activity) and depression has been reported (Henriques and Davidson, 1990, 1991; Kano et al., 1992; Gotlib et al., 1998; also see Cacioppo, 2004). In general it was reported that the incidence of abnormal EEG findings in mood disorders is ranged from 20% to 40% (Small, 1993). Specific patterns noted in mood-disordered patients include small sharp spikes and paroxysmal events (especially on the right hemisphere), increased alpha and/or theta power, interhemispheric asymmetry and decreased coherence (especially in anterior regions).

However, all previous studies have used averaged EEG parameters, based on extended periods of time and/or broad fixed frequency bands for a specific lead. But the averaging of the EEG signal may not only mask the dynamics of EEG characteristics, but may also lead to ambiguous data interpretation (Fingelkurts et al., 2002; 2004). When examining the average EEG parameters, it is ambiguous whether the observed phenomenon is (a) real (not the "virtual" result of averaging procedure), and (b) typical for the whole analyzed signal or for a small portion of it. In fact, and as explored in our previous work (Fingelkurts et al., 2003a; 2004) the total power spectrum does not characterizes each of the individual power-spectra for each EEG segment. Moreover, total EEG power may be affected by pink noise (polyrhythmic disorganized activity) (Dumermuth and

Molinari, 1987). In this case different indices and parameters of EEG may suffer from the influences of pink noise, instead of reflecting true rhythmic activity.

Additionally, in all of EEG-studies related to MDD the frequency bands were predefined and taken in isolation from each other. This does not permit researchers to examine a behavior of the actual/natural composition of brain oscillations involved. At the same time, it has been shown that brain functions are represented by superimposed multiple brain oscillations in many frequency bands (for the review, see Basar et al., 2004).

All these may contribute to numerous inconsistencies and contradictions in depression studies and in conceptualizations of affective disorders (Debener et al., 2000; Kempermann and Kronenberg, 2003; for the reviews see Sarbadhikari and Chakrabarty, 2001; Rotenberg, 2004; as an example, compare the works for alpha effect only: Henriques and Davidson, 1991; Gotlib et al., 1998; Davidson et al., 1999 with the works for other and/or many frequency bands effect: Brenner et al., 1986; Luthringer et al., 1992; Yamada et al., 1995; Pizzagalli et al., 2002, 2003; or compare the works for left-right frontal asymmetry: Kano et al., 1992; Davidson, 1998; Pizzagalli et al., 2002; Allen et al., 2004; Coan and Allen, 2004; with the works for NO left-right frontal asymmetry: Pollock and Schneider, 1990a,b; Reid et al., 1998). In order to overcome the limitations of conventional spectral analysis based on averaging procedures, it seems reasonable to examine the actual composition of brain oscillations and their percent ratio in ongoing EEG during MDD. To assess the exact composition of brain oscillations and their percent ratio, one can use the probability-classification analysis of short-term EEG spectral patterns (SP) which results in probability classification profile (PCP) (Kaplan et al., 1999; Fingelkurts et al., 2003a; for the initial idea, see Bodenstein and Praetorius, 1977, Jansen and Cheng, 1988). It was demonstrated that PCP is highly stable over time (Fingelkurts et al., 2006a) and provides adequate and detail description of electromagnetic brain activity (Kaplan et al., 1999; Fingelkurts et al., 2003a) during different cognitive tasks and states (Fingelkurts et al., 2002; 2003b). It is sensitive to drug effects on brain dynamics (Fingelkurts et al., 2004) and to pathological brain conditions (Fingelkurts et al., 2000; 2006b). Moreover, it was shown that distribution of spectral patterns in PCP is far from random (Fingelkurts et al., 2003b). Another advantage to using PCP is that pink noise is isolated in a separate class, and thus does not affect classes with true rhythmic activity (Fingelkurts et al., 2003a). At the same time, class with pink noise in its turn can be also subjected to analysis. This is justified since as explored in our previous work (Fingelkurts et al., 2003a; 2004) the amount of this activity in EEG is dependent on functional brain state and/or task.

During the past two decades frontal asymmetry has been considered to be almost the only indicator of depression and emotional affect (Henriques and Davidson, 1991; Kano et al., 1992; Yamada et al., 1995; Davidson, 1998; Pizzagalli et al., 2002; for the review see Coan and Allen 2004). At the same time, the facts that (a) remission of depression symptoms associated with successful treatment is not accompanied by a normalization of activation asymmetry in frontal areas (Henriques and Davidson, 1990; Allen et al., 1993; Drevets et al., 1997) and (b) clinical severity of the disorder is unrelated to frontal asymmetry (Henriques and Davidson, 1991; Allen et al., 2004) indicate that frontal cortex is only a part of a larger overall neuro-network, other components of which are crucial for understanding the neural mechanisms of depression (Davidson, 2004). Support for this view comes from the work that demonstrated that the EEG activity of depressed subjects differs from that of healthy subjects in various brain areas, not only in the frontal region (Kano et al., 1992; Yamada et al., 1995), indicating that multichannel EEG recording is needed. Although the frontal EEG asymmetry literature has traditionally focused on alpha power (Henriques and Davidson, 1990, 1991; Gotlib et al., 1998; Davidson et al., 1999; Allen et al., 2004), it is important to examine actual brain oscillations carefully in a wide frequency range, as these may provide additional information not reflected in alpha band.

Hence, this study had multiple goals: (1) to investigate the actual composition of brain oscillations in ongoing multichannel EEG during MDD using broad frequency range: 0.5-30 Hz; and (2) to examine interhemisphere asymmetry of the composition of brain oscillations. Functional connectivity between different cortex locations during MDD analyzed from the same data has already been reported (Fingelkurts et al., 2006c). The present study extends previous report by investigating the local processes in the brain cortex.

2. Materials and Methods

2.1. Subjects

Twelve medication-free depressed outpatients (mean age 43 ± 14 years) participated in the study (Table 1). All underwent a Structured Diagnostic Interview (SCID) for DSM-IV (First et al., 1994) and all patients met the DSM-IV criteria for a Major Depressive Disorder (9 patients had a single severe episode, 3 patients had comorbidity). All patients had a score of at least 18 on the 17-item Hamilton Depression Rating Scale (HAM-D, Hamilton, 1960) at the time of the study procedure; mean HAM-D score was 24 ± 4. This means that all patients were depressed at the time of EEG recording which was done with delay of one to two days maximum after the interview. All

patients were in good physical health as determined by a physical examination and laboratory evaluation including a complete blood count, glucose, and hepatic enzymes, renal and thyroid analyses. Patients with a history of bipolar disorder, schizophrenia, alcohol, or drug dependence within last 5 years or significant suicidal ideation were excluded. Two patients have taken antidepressants for the extended periods, but not during the final two weeks (5 half lives of the longest acting agent).

Ten sex- and age-matched healthy control subjects (mean age 40 ± 13 years) were participated in the study (Table 1). Before inclusion the control subjects underwent a medical examination and were also screened for depression. The control subjects had no DSM-IV axis I diagnosis in the SCID evaluation, and none had a significant medical illness. All were free from psychotropic medication, and none had a history of central nervous system disease. The mean HAM-D score was 0.5 ± 0.8.

All depressive subjects in the present study demonstrated higher anxiety scores (30.1 ± 12), than control subjects (1.7 ± 1.4) ($p < 0.0001$; measured by The Beck Anxiety Inventory).

All the subjects studied gave informed written consent before enrolling in the study and the institutional ethical committee approval was obtained.

Table 1. Subjects' description

	ID	Sex	Age	Hand	HAM	BAI	Usage of anti-depressants	Medication during 2 weeks before study	Diagnosis	Comorbidity
PATIENTS	1	M	42	R	26	33	-	-	MDD, single episode	-
	2	M	25	R	22	29	-	-	MDD, recurrent	-
	3	M	57	R	26	34	-	-	MDD, single episode	-
	4	M	40	R	31	35	-	-	MDD, single episode	Panic attacks
	5	M	57	R	29	49	+	-	MDD, single episode	-
	6	M	56	R	23	16	-	-	MDD, single episode	-
	7	M	52	R	21	38	-	-	MDD, single episode	-
	8	F	31	R	18	37	-	-	MDD, single episode	-
	9	F	57	R	20	20	-	-	MDD, single episode	-
	10	F	24	R	24	11	-	-	MDD, recurrent	-
	11	F	26	R	18	16	-	-	MDD, recurrent	Anxiety Disorder
	12	F	56	R	27	42	+	-	MDD, single episode	Anxiety Disorder
	Aver.		43.5		23.7	30				
	St.D.		13.9		4.2	11.8				
HEALTHY SUBJECTS	13	M	60	R	0	3	-	-	-	-
	14	M	50	R	2	0	-	-	-	-
	15	M	25	R	0	2	-	-	-	-
	16	M	52	R	0	0	-	-	-	-
	17	M	43	R	2	2	-	-	-	-
	18	F	26	R	1	4	-	-	-	-
	19	F	51	R	0	1	-	-	-	-
	20	F	26	R	0	0	-	-	-	-
	21	F	36	R	0	2	-	-	-	-
	22	F	31	R	0	3	-	-	-	-
	Aver.		40		0.5	1.7				
	St.D.		12.9		0.8	1.4				

F - female, M - male, R - right, HAM - Hamilton Depression Rating Scale, BAI - The Beck Anxiety Inventory, MDD - Major Depressive Disorder

2.2. Trial design

The EEG recording was started 5 min after the subject adaptation in a chamber. To reduce muscle artifacts in the EEG signal, a subject was instructed (a) to assume a comfortable position, (b) to avoid movement and relax jaw muscles, (c) to look straight in front of him/her (even though the eyes were closed), and (d) to avoid unnecessary eye movements. Additionally, it was stressed to the subject the importance of maintaining an alert state. The behavior of a subject was observed on a TV monitor throughout the experiment. Each subject underwent EEG registration, 20 minutes in duration (eyes closed).

Vigilance of the subjects was controlled by (a) the presence in EEG of sleep spindles which naturally appear during drowsiness (Rechtschaffen and Kales, 1968), (b) occipital decrease of alpha activity, and (c) slow, pendular eye movements. Criteria for sleep spindles detection: frequency 13-15 Hz; time duration 0.5-2.5 sec., i.e. one should be able to count at least 6 or 7 distinct waves within the half-second period; peak-to-peak amplitude above 15 mkV (Rechtschaffen and Kales, 1968). Visual and spectral analysis of EEG did not reveal any sleep spindles or diminution of occipital alpha activity (Fig. 2, Table 1). Several EEG epochs contained eye movements, - they were rejected from the analysis.

2.3. EEG registration

All recordings were performed in a magnetically and electrically shielded room (Euroshield, Eura, Finland) in the BioMag Laboratory, Helsinki University Central Hospital. Electric spontaneous brain activity was recorded with a 60-channel EEG data acquisition system (Neuromag Vectorview, Helsinki, Finland) with a frequency band 0.06-86 Hz (sampling rate 300 Hz).

EEG was recorded with an electrode cap according to the International 10/20 extended system and the nose electrode was used as reference. The impedance of recording electrodes was always below 5 kΩ for each subject. Vertical and horizontal electro-oculograms were recorded.

2.4. Data processing

Epochs containing artifacts due to eye movements, significant muscle activity, and movements on EEG channels were automatically rejected. The presence of an adequate signal was determined by visually checking each raw signal on the computer screen after the automatic artifacts rejection. A

full EEG stream, free from artifacts, contained 18-20-min of signal (eyes closed) for depressive and control subjects. EEG data were split into 2 distinct groups: "depressive" and "control." Further, data processing was performed separately for each 1-min portion of the signal (n = 206 for depressive and n = 182 for control groups). EEGs from fifty-nine standard EEG sites ($O_{1/2}$, Oz, $PO_{3/4}$, $PO_{7/8}$, POz, $P_{1/2}$, $P_{3/4}$, $P_{7/8}$, Pz, CPz, $CP_{1/2}$, $CP_{3/4}$, $TP_{7/8}$, $TP_{9/10}$, $C_{1/2}$, $C_{3/4}$, $C_{5/6}$, Cz, $T_{7/8}$, $FC_{1/2}$, $FC_{3/4}$, $FC_{5/6}$, FCz, $FP_{1/2}$, FPz, $FT_{7/8}$, $FT_{9/10,}$ $F_{1/2}$, $F_{3/4}$, $F_{7/8}$, Fz, $AF_{3/4}$, $AF_{7/8,}$ AFz) were analyzed with a converted sampling rate of 128 Hz.

After re-sampling and prior to the spectral analysis, the EEG signals were bandpass-filtered in the 0.5–30-Hz frequency range. This range was chosen because approximately 98% of spectral power lies within these limits (Thatcher, 2001) and the main depression effects on brain oscillations have been found in this frequency range (Marosi et al., 2002; Lubar et al., 2003; and others). Thereafter, individual power spectra were calculated in the range of 0.5–30 Hz with 0.5-Hz resolution (61 values), using FFT with 2-sec Hanning window shifted by 50 samples (0.39 s) (Fig. 1) for each EEG channel. These values revealed the best results in disclosing oscillatory patterns from the signal (Levy, 1987; Kaplan, 1998, for details, see Fingelkurts et al., 2006b). Sliding spectral analysis compensated for the effects of windowing, permitted us not to lose information from residual activity, and improves statistical confidence of the results.

As a result, the total number of individual SPs for each channel of 1-min EEG was 149 (Fig. 1). These SPs formed the multitude of the objects for further classification procedure. The compositions of brain oscillations (in terms of EEG SPs) were estimated with the help of a probability-classification analysis of the short-term EEG SPs (SPclass tool, see Fingelkurts et al., submitted). Considering that detail description of this analysis was published elsewhere (Fingelkurts et al., 2003a), here we are highlighting only the most important steps. In short, this analysis was undertaken in two stages (Fig. 1).

During the first stage, sequential single EEG SPs were adaptively classified in each channel of 1-min EEG using a set of standard SPs. The set of standard SPs was formed automatically from the EEG data itself using specially designed heuristics and Pearson's correlation coefficients (CC): A pool of SPs (n = 3 410 908) was built from all the SPs of the entire EEG signal (all locations) for all subjects. From this pool, all identical SPs with peaks in the same frequencies were counted. The set of identical SPs with the highest count was the most likely candidates to form the "set of standard SPs." Only those SPs with minimum cross-CC were selected. Basic procedure of adaptive classification was performed in three steps. During the first step, the initial matrix of cross-

correlations between standard and current individual SPs of analyzed EEG was calculated for each channel separately. On the basis of CC which were obtained at the first step, the current SPs were sorted: all current SPs that their CC passed the acceptance criteria of $r \geq 0.71$ were attributed to their respective standard classes. During the second step, the current SPs which were included in a particular class were averaged within this class. The same procedure was performed for all classes separately for each EEG channel. On the back of this, the standard spectra were reconstructed but this time taking into account the peculiarities of the spectral description of concrete channel of the particular EEG. In this way an "actualization" of the initial standard SP set was performed. In other words, they were converted into so-called actual spectral patterns. This actual SP set was in turn used for the third step - the final classification of the current SPs. As the result of this classification, each current SP was labeled according to the index of the class to which it belongs. Hence, each EEG signal was reduced to a sequence of individually classified SPs (Fig. 1).

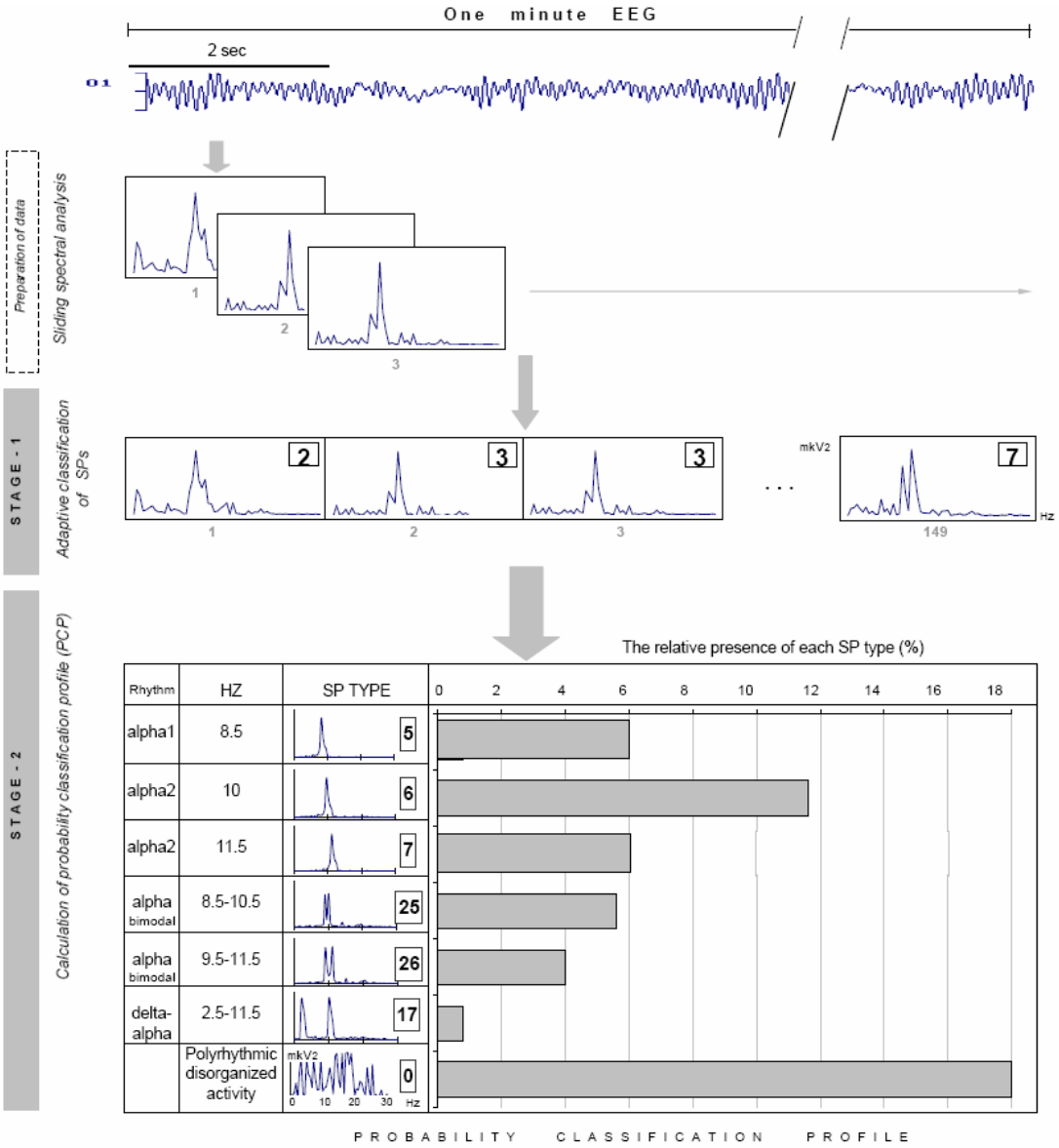

Figure 1. The scheme of the data processing. Sliding spectral analysis, adaptive classification of spectral patterns (SP) and calculation of the probability-classification profiles (PCP) were done separately for each subject and each channel of 1-min EEG. Modified from Fingelkurts et al., Int. J. Psychophysiol., 2006a. Gray small numbers under each SP represent the running numbers from 1 to 149. The numbers in the square represent the labels – types of classified SPs. Column "Hz" represents the main dominant peak(s) in particular SP. Presented PCP illustrates an example of the composition and percent ratio of brain oscillations.

At the second stage, PCPs of SPs for each channel of 1-min EEG in each subject were calculated (Fig. 1). These PCPs were calculated by taking the relative number of cases of an SP type as a percentage of the total amount of all SPs within each EEG channel – presented as the histogram of relative presence of each SP type. PCPs were averaged across 206 (for depressive group) and 182 (for control group) 1-min EEG signals separately for each EEG channel. It was expected that these PCPs would make it possible to portray (in SP description) the composition of brain oscillations and their percent ratio in detail.

2.5. Statistics

In order to reveal statistically significant differences in the relative presence of each SP type in PCPs between depressive and control subjects the Wilcoxon test was used separately for each type of spectral patterns presented in the PCP. Statistical significance was assumed when $P < 0.05$ (only statistically significant *P*-values are displayed). Since we intended to assess each variable in its own right, no Bonferroni correction was applied (for the problems associated with Bonferroni adjustments, see Rothman, 1990; Perneger, 1998).

However, in the case where we examined spatial distribution of significant differences a Bonferroni correction was made in order to control for repeated observations of the same measures. $P_{corrected}$ is the value required to keep the number of false positives at $P = 5\%$.

An asymmetry score was computed by estimating a statistically significant difference between SP type's relative presence in PCP for all sites that have symmetrical left and right locations (O1 and O2, and so on). The Wilcoxon test was used separately for each type of SP presented in the PCP in order to reveal statistically significant difference in the relative presence of each SP type in PCPs between each symmetrical left and right EEG location.

3. Results

3.1. General description of EEG for depressive and control subjects

For both depressive and control subjects all EEG channels were characterized by the same 9 SP types dominant in the PCPs (Fig. 2A,C). Spatial distribution of brain oscillations was generally consistent with those from earlier studies. Thus, a significant ($p < 0.001$) increase for alpha- and decrease for delta- and theta-rhythmic EEG segments in frontal-to-occipital direction was observed (Fig. 2A)

A

Rhythm	SP type	Hz	Relative presence of SP types	Spatial distribution of SP types presence
Alpha	SP5 SP6 SP7	8.5 10 11.5	5-15% for different groups of subjects and EEG channels	O — F
	SP26	9.5-11.5	2-11% for different groups of subjects and EEG channels	PO O — F
Theta2-Alpha1	SP22	4.5-9.5	5-9% for different groups of subjects and EEG channels	C O — F
Delta-Teta1-Alpha2 Delta-Theta1-Theta2	SP30 SP29	2.5-3.5-10 2.5-3.5-5	5-10% for different groups of subjects and EEG channels	PO O — F
Delta-Theta1	SP12	2.5-3.5	7-35% for different groups of subjects and EEG channels	O — F
Polyrhythmic disorganized activity	SP0	many	2-12% for different groups of subjects and EEG channels	O — F

B

Rhythm	SP type	Hz	Relative presence of SP types	Spatial distribution of SP types presence
Beta	SP8 SP9 SP10	16 19.5 22	2-3% for different EEG channels	CP1/2, CP3/4, FCz, FC1/2, FC3/4 All EEG channels from O to C All EEG channels from P to C

C

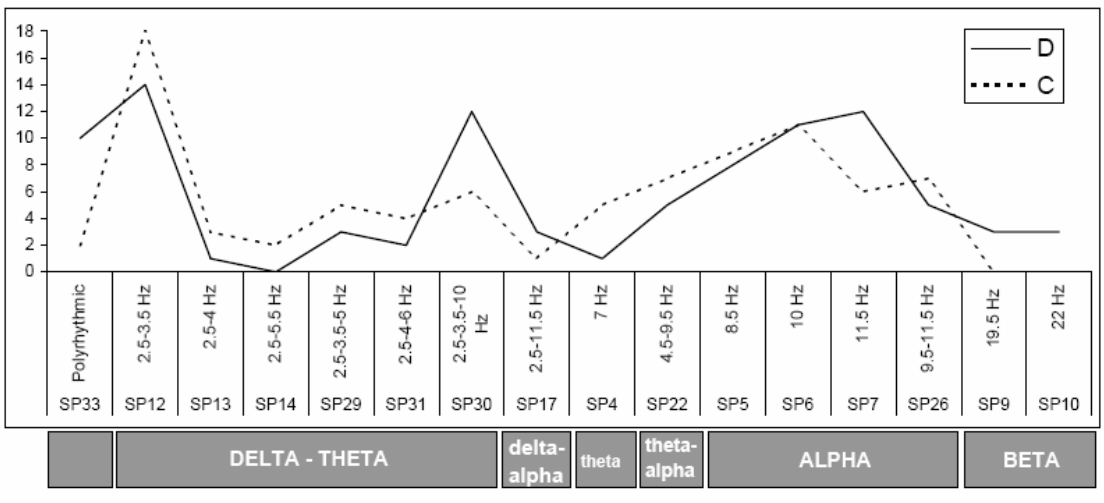

Figure 2. **Spectral pattern types dominant in all EEG channels for both depressive and control subjects (A) and unique spectral pattern (SP) types for depressive subjects (B).** Data averaged across 206 EEGs for depressive and across 182 EEGs for control subjects. SP - Spectral patterns; Hz - Frequency; O - Occipital EEG channels; PO - Parieto-Occipital EEG channels; PO - Parieto-Occipital EEG channels; P - Parietal EEG channels; C - Central EEG channels; F – Frontal EEG channels; "Rhythm" column represents the brain oscillations which contribute the most into a particular SP; "SP type" column represents the labels of spectral pattern types; "Hz" column represents frequency of the main peaks for each spectral pattern type. (C) Probability-classification profiles (PCPs) for O1 EEG of one subject: The x-axis displays the labels (numbers) of the standard SP and their main frequency peaks. The y-axis displays the share of the corresponding SPs in the percentage from the total number of the classified SPs. A line graphic was chosen instead of a bar for the ease of comparison. (Note that x-axis consists of discrete values, all the in-between values are meaningless). Only those SPs which were presented in PCPs are shown. C = Control subjects, D = depressive subjects.

The comparative analysis of PCPs for depressive and control subjects demonstrated that there were unique SP types associated only with major depression: SP8 (main peak at 16 Hz), SP9 (19.5 Hz), and SP10 (22 Hz) which comprise $beta_1$ and $beta_2$ oscillations (Fig. 2B). However, these SP types were presented in PCPs not more than 2-3%.

Although EEGs for both depressive and control subjects were mostly characterized by the same dominant SP types (Fig. 2A,C), depressive and control subjects differed from each other according to the probability estimation of the occurrence of these SP types in PCPs.

3.2. Characteristics of depression-induced EEG changes

In general, MDD affected all EEG channels: there was no a single EEG channel without statistically significant differences in the relative presence of at least 24% of SP types in PCPs between depressive and control subjects. At the same time, different cortical areas were characterized by different number of SP types which demonstrated statistically significant difference in their relative presence in PCPs, thus indicating the magnitude of the effect of depression. The posterior part of the cortex (Oz, $O_{1/2}$, POz, $PO_{3/4}$, $PO_{7/8}$, Pz, $P_{1/2}$, $P_{3/4}$, $P_{7/8}$, CPz, $CP_{1/2}$, $CP_{3/4}$ EEG channels) was maximally ($p < 0.001$–$p < 0.00001$) affected by MDD – the number of SP types which demonstrated statistically significant difference in their relative presence in PCPs between depressive and control subjects reached in these areas up to 72% from all observed SP types. $TP_{7/8}$, $TP_{9/10}$, $T_{7/8}$, Cz, $C_{1/2}$, $C_{3/4}$, $C_{5/6}$, F_8, $FT_{7/8}$, $FT_{9/10}$, AFz, $AF_{3/4}$, $AF_{7/8}$, FPz, $FP_{1/2}$ EEG channels were affected by depression moderately (up to 52%, $p < 0.001$–$p < 0.0001$). Minimum ($p < 0.0001$–$p < 0.00001$) number of SP types (up to 40%) which demonstrated statistically significant difference in

their relative presence in PCPs between depressive and control subjects was observed in FCz, $FC_{1/2}$, $FC_{3/4}$, $FC_{5/6}$, Fz, $F_{1/2}$, $F_{3/4}$, F_7 EEG channels. At the same time, each from all observed SP types (n = 24) revealed statistically significant difference in its relative presence in PCPs between depressive and control subjects in at least 22% of EEG channels.

Comparative analysis of the PCPs demonstrated that EEG during MDD was characterized by a larger percentage of delta–$alpha_1$- [SP17 (main peaks at 2.5 and 11.5 Hz)], delta–$theta_1$–$alpha_2$- [SP30 (2.5, 3.5 and 10 Hz)], $alpha_2$- [SP7 (11.5 Hz)], $beta_2$- [SP9 (19.5 Hz)] and poly-rhythmic segments, and by a smaller percentage of delta–theta- [SP12 (2.5 and 3.5 Hz), SP13 (2.5 and 4 Hz), SP14 (2.5 and 5.5 Hz), SP29 (2.5, 3.5, and 5 Hz), SP31 (2.5, 4, and 6 Hz)], $theta_2$- [SP4 (7 Hz)], and $alpha_1$-$alpha_2$- [SP26 (9.5 and 11.5 Hz)] rhythmic segments when compared with control subjects ($p_{corrected} < 0.001$–$p_{corrected} < 0.000001$ for different channels) (Table 2, see also Fig. 2C). Conventional 'energetic' estimation (mean spectral power) of the depression-related EEG spectral changes revealed a simplified "picture": increase power in the alpha (9-13 Hz) and beta (15-23 Hz) frequency bands in the occipital and parietal EEG channels and decrease power in the delta (2-3 Hz), theta (4-7 Hz), and alpha (8-11 Hz) frequency bands in the frontal EEG channels when compared with control subjects ($p < 0.05$).

The main effects of depression described above were detected in the majority (36-100%) of EEG channels and were observed either in the whole cortex, or in the posterior region of the cortex, or in the posterior and anterior regions of the cortex (Table 2).

3.3. Interhemisphere asymmetry in the EEG for depressive and control subjects

In general, for both depressive and control subjects, interhemisphere asymmetry (indexed by relative presence of SPs in PCPs) was observed in all homologous EEG-channel pairs (n = 25) for at least 4% of SP types. At the same time, all observed SP types (n = 24) showed interhemisphere asymmetry in their relative presence in PCPs for at least 4% of EEG-channel pairs. Only polyrhythmic activity did not reveal any interhemisphere asymmetry.

The total number of asymmetric homologous EEG-channel pairs was larger ($p < 0.01$) for depressive subjects when compared with control subjects (Fig. 3. I.a, I.b). Additionally, depressive subjects had more EEG-channel pairs with right-side-dominance asymmetry than EEG-channel pairs with left-side-dominance asymmetry ($p < 0.05$), whereas control subjects had the opposite results (Fig. 3. I.b).

Table 2. Spectral pattern types which demonstrated statistically significant (*Pcorrected* < 0.001–*Pcorrected* < 0.000001) difference in relative presence in probability-classification profile between depressive and control subjects in more than 36% of EEG channels. Data averaged across 206 EEGs for depressive and across 182 EEGs for control subjects.

Rhythm	SP type	Hz	Number of EEG channels for: D > C	D < C	Total	Relative presence of SP types in PCPs	Spatial distribution of SP types in PCPs
Delta-Alpha2	SP17	2.5-11.5	46	1	47	up to 4%	nearly whole cortex
Delta-Theta1-Alpha2	SP30	2.5-3.5-10	22	7	29	up to 10%	nearly whole cortex besides AF, FP, FT EEG channels
Alpha2	SP7	11.5	29	13	42	up to 15%	D>C, posterior part of the cortex; D<C, anterior part of the cortex
Beta2	SP9	19.5	31	-	31	up to 2%	posterior and central parts of the cortex
Polyrhythmic disorganized activity	SP0	many	59	-	59	up to 12%	whole cortex
Delta-Theta	SP12	2.5-3.5	6	29	35	up to 35%	D<C, posterior part of the cortex; D>C, anterior part of the cortex
	SP13	2.5-4	5	30	35	up to 5%	nearly whole cortex besides FC and F EEG channels
	SP14	2.5-5.5	-	21	21	up to 2%	posterior part of the cortex
	SP29	2.5-3.5-5	7	25	32	up to 10%	nearly whole cortex besides TP, FC, F EEG channels
	SP31	2.5-4-6	2	43	45	up to 8%	nearly whole cortex
Theta2	SP4	7	-	28	28	up to 6%	nearly whole cortex besides CP, C, FC EEG channels
Alpha1-Alpha2	SP26	9.5-11.5	-	48	48	up to 10%	nearly whole cortex besides TP, T EEG channels

SP - spectral pattern; D - depressive subjects; C - control subjects; PCP - probability-classification profile. "Rhythm" colomn represents the brain oscillations which contribute the most into a particular SP. "SP type" column represents the labels of spectral pattern types; "Hz" column represents frequency of the main peaks for each spectral pattern type.

The total number of SP types which demonstrated interhemisphere asymmetry for each homologous EEG-channel pairs was also larger ($p < 0.001$) for depressive subjects when compared with control subjects (Fig. 3. II.a, II.b). Depressive subjects had more EEG-channel pairs with right-side-dominance asymmetry than EEG-channel pairs with left-side-dominance asymmetry ($p < 0.05$), whereas control subjects had the opposite results (Fig. 3. II.b).

Detailed analysis of asymmetric homologous EEG-channel pairs revealed that for depressive subjects $PO_{7/8}$, $P_{3/4}$, $P_{7/8}$, $TP_{9/10}$, $T_{7/8}$, $FC_{3/4}$, $FC_{5/6}$, $F_{7/8}$, $FT_{9/10}$ EEG-channel pairs had the highest asymmetric rate, meaning that statistically significant ($p_{corrected} < 0.002$–$p_{corrected} < 0.0001$) interhemisphere asymmetry, indexed by relative presence of SP types in PCPs, was observed for more than 38% of SP types. Whereas, for control subjects the most asymmetric homologous EEG-channel pairs were found only for $P_{3/4}$, $P_{7/8}$ EEG channels.

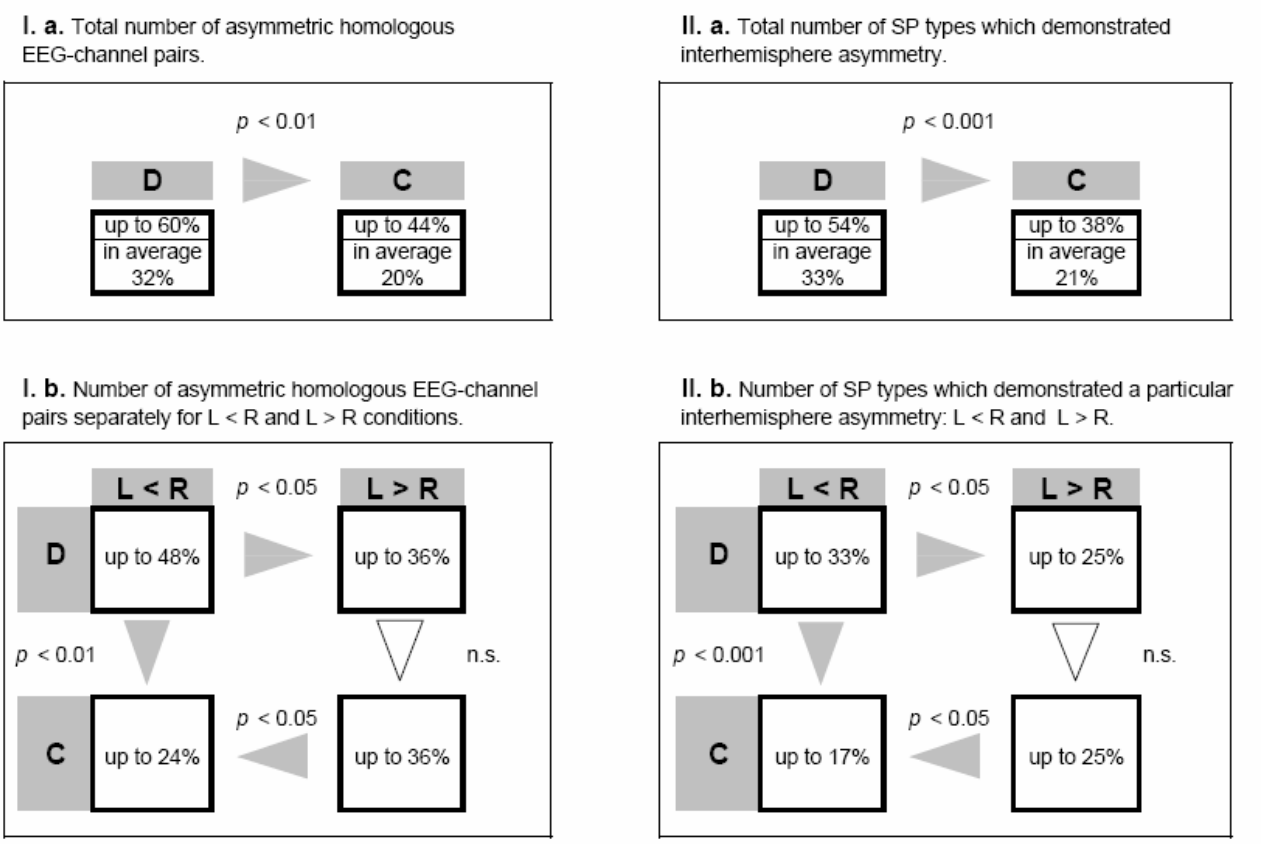

Figure 3. Number (in %) of homologous EEG-channel pairs and spectral pattern types which demonstrated statistically significant ($P < 0.05$-$P < 0.0001$) interhemisphere asymmetry indexed by relative presence of each spectral pattern type in probability-classification profiles. Data averaged across 206 EEGs for depressive and across 182 EEGs for control subjects.
L - Left brain hemisphere; R - Right brain hemisphere; D - Depressive subjects; C - Control subjects; ▼ - Statistically significant difference; ▽ - Nonsignificant difference

At the same time, eleven (for depressives) and three (for controls) SP types demonstrated statistically significant ($p_{corrected} < 0.002$–$p_{corrected} < 0.0001$) interhemisphere asymmetry, indexed by relative presence of them in PCPs, for more than 40% of homologous EEG-channel pairs.

Additionally, eight SP types, – which comprised five brain oscillations, – demonstrated statistically significant ($p_{corrected} < 0.002$–$p_{corrected} < 0.0001$) interhemisphere difference opposite for depressive and control subjects in ten homologous EEG-channel pairs (Table 3). It can be seen that for depressive subjects the left hemisphere was characterized by more delta-$theta_2$-$theta_3$, $theta_2$-$theta_3$, and $theta_3$ brain oscillations in parietal cortex areas and by more $alpha_1$, $alpha_2$, and $alpha_1$-$alpha_2$ brain oscillations in frontal and occipital cortex areas when compared with the right hemisphere, whereas right hemisphere was characterized by more delta-$alpha_2$ brain oscillations in

fronto-temporal, parieto-temporal, central and occipital cortex areas and by more $theta_2$-$alpha_1$ brain oscillations in temporal cortex areas when compared with the left hemisphere. For control subjects described interhemisphere asymmetry was the opposite (Table 3).

Table 3. Spectral pattern types which demonstrated statistically significant (*Pcorrected* < 0.002–*Pcorrected* < 0.0001) interhemisfere difference opposite for depressive and control subjects.Data averaged across 206 EEGs for depressive and across 182 EEGs for control subjects.

Rhythm	SP type	Hz	EEG-channel pairs C	D
Delta-Theta2-Theta3	SP31	2.5-4-6	P1 < P2	P1 > P2
Theta2-Theta3	SP19	4--6	P3 < P4	P3 > P4
Theta3	SP4	7	P7 < P8	P7 > P8
Delta-Alpha2	SP16	2.5-10	TP9 > TP10	TP9 < TP10
			FT9 > FT10	FT9 < FT10
			C1 > C2	C1 < C2
			C5 > C6	C5 < C6
			O1 > O2	O1 < O2
Theta2-Alpha1	SP22	4.5-9.5	T7 > T8	T7 < T8
Alpha1	SP5	8.5	F7 < F8	F7 > F8
			O1 < O2	O1 > O2
Alpha2	SP6	10	F1 < F2	F1 > F2
			F3 < F4	F3 > F4
			F7< F8	F7 > F8
			O1 < O2	O1 > O2
Alpha1-Alpha2	SP25	8.5-10	F1 < F2	F1 > F2
			F3 < F4	F3 > F4
			F7< F8	F7 > F8
			O1 < O2	O1 > O2
			T7 > T8	T7 < T8

SP - spectral pattern; D - depressive subjects; C - control subjects.
"Rhythm" colomn represents the brain oscillations which contribute the most into a particular SP; "SP type" column represents the labels of spectral pattern types; "Hz" column represents frequency of the main peaks for each spectral pattern type.

4. Discussion

4.1. Composition of multiple brain oscillations for depressive and control subjects

The PCPs obtained for both depressive and control subjects revealed that all EEG channels were predominantly characterized by the same five brain oscillations (indexed by 9 SP types) in multiple frequency bands, several of which were superimposed: delta, theta$_1$, theta$_2$, alpha$_1$, and alpha$_2$ (Fig. 2A,C). At the same time, MDD was characterized by unique (but infrequent) brain oscillations in beta$_1$ and beta$_2$ frequencies (Fig. 2B). Additionally, depressive subjects differed from control subjects according to the probability estimation of the occurrence of particular brain oscillations and/or their compositions (indexed by relative presence of SP types in PCPs): several SP types were more or less probable for depressive than for control subjects (Fig. 2C, Table 2). This means that MDD affects brain activity in the whole cortex (various areas to different degrees), and it is reflected in the reorganization of the probability of the occurrence of several brain oscillations and/or their composition.

In contrast to the previous data that emphasize the main role of the anterior cortex in depression (for the reviews see Allen et al., 2004; Coan and Allen 2004; and others), the present results (Fig. 2, Table 2) demonstrated that the effect of the MDD was most pronounced in the posterior cortex of the brain. This may indicate that depressive subjects had increased arousal (Heller and Nitschke, 1998) which may reflect a prolonged stress and may serve as a background for psychopathology development. This idea is supported by the fact that the whole posterior region of the cortex in the present study was characterized by beta brain oscillations (together with other oscillations) in depressive subjects only. Additionally, the greater effect of MDD on the posterior cortex may be explained by the contribution of comorbid anxiety (Heller and Nitschke, 1998). Indeed, all depressive subjects in the present study demonstrated higher anxiety scores, than control subjects (see Materials and Methods). Recent study (Fernandez et al., 2005) also demonstrated that posterior part of the brain was significantly related to depression.

Results of the present study that depressed patients had more alpha and distributed beta activity, and had less distributed delta activity than non-depressed controls (Fig. 2, Table 2) conformed earlier findings (for alpha activity: Pollock and Schneider, 1990; Debener et al., 2000; for a review, see Hughes and John, 1999; for beta activity: Yamada et al., 1995; Knott et al., 2001; for delta activity: Lubar et al., 2003). At the same time, findings in the present study substantially extend the results of conventional spectral analysis: our analysis revealed changes in the total amount of time (percentage of EEG segments) that the particular type of brain oscillations was on, rather than

the changes in its amplitude or power. This can explain contradictions between some of our results and previous studies (for beta activity: Brenner et al., 1986; Luthringer et al., 1992; Pizzagalli et al., 2002; for delta and theta activity: Nyström et al., 1986; Fernandez et al., 2005). Moreover, the present study demonstrated that EEG during MDD has more segments with polyrhythmic/disorganized activity than EEG in control subjects (Table 1). This is in agreement with our previous work (Fingelkurts et al., 2000; 2006b), where we reported that increased amount of polyrhythmic/disorganized activity in EEG is a sign of brain pathology. EEG polyrhythmic/disorganized activity indicates a mixture of activity of small neuronal subpopulations each with its own mode (Tirsch et al., 2000).

Since theta and slow alpha oscillations represent the activity in the thalamo-cortical network and fast alpha oscillations reflect the activity in the cortical networks (Lopes da Silva et al., 1980; Klimesch, 1996), the fact that MDD affected the percentage of EEG segments with theta, slow alpha, and fast alpha brain oscillations indicates that depression may alter the activity in both thalamo-cortical and cortical circuits. This idea is supported by the work of Lindgren et al. (1999) where researchers have demonstrated that during MDD the activity of thalamo-cortical circuits is affected. Present study suggests that the dysfunction in these neurocircuits is reflected in the reorganization of the probability of the occurrence of several brain oscillations and/or their compositions in both frequency ranges. This explanation is supported by the neurophysiologic abnormalities in thalamus (along with other brain regions) that were identified during depression (Drevets, 2000). Considering (a) the hypothesis that alpha band activity in the human EEG may reflect a resting or “idling” state (Adrian and Matthews, 1934), (b) the well-known significant decrease in whole (and multi-regional) brain metabolism during depression (Sackeim et al., 1990; Bonne et al., 2003), and (c) the inverse relationship between EEG alpha amplitude and BOLD signals in primary and secondary visual areas (Feige et al., 2005), an increase in cortical alpha in depressed patients (the present study) may suggest a decreased activation in thalamo-cortical networks (however, see Lindgren et al., 1999).

The fact that, in the present study, frontal theta increased during MDD indicates the possible involvement of anterior cingulate cortex (ACC) in the psychopathology of depression (for a review, see Pizzagalli et al., 2003): Indeed, the ACC had been proposed as a possible neuronal source of frontal theta activity in the human brain (Asada et al., 1999; Ishii et al., 1999). At the same time, observed in the present study distributed theta decrease may reflect a hippocampal dysfunction.

Indeed, it was suggested that MDD psychopathology involves hippocampal symptoms (Kempermann and Kronenberg, 2003).

4.2. Distributed property of brain oscillations in major depression

Because the main effects described in the present paper have been observed in more than 36% of EEG channels, it appears that distributed neuronal networks were affected by MDD. These results are in agreement with a study by Fingelkurts et al. (2006c; analyzed from the same data), in which the authors also demonstrated the involvement of distributed cortical network in MDD.

Distributed EEG effects during MDD can be explained through the "monoamine concept," which proposes that depression is related to a deficit of monoamines, particularly norepinephrine and serotonin, at critical synapses (Delgado, 2000; Moreno, 2000). It has been shown that activation of serotonin signaling can suppress the $GABA_{ergic}$ inhibition (Feng et al., 2001). Thus, in serotonin deficit diseases such as MDD, $GABA_{ergic}$ signaling in the cortex may be overly potent. Because serotonin is one of the widely distributed neurotransmitters in the central nervous system (Mann, 1999), it is likely that a disturbance of serotonergic neurotransmission would lead to an increase in the $GABA_{ergic}$ signaling in many different brain regions.

Another factor contributing to the distributed effects of MDD that were observed in the present study is the well-known significant decrease in whole (and multi-regional) brain metabolism during depression (Sackeim et al., 1990; Bonne et al., 2003).

For all the reasons just described, MDD might be considered to be a disorder distributed over large-scale cortical (and subcortical) systems including functionally connected areas in the frontal, temporal, parietal and occipital lobes (LeDoux, 1996; Rolls, 1999; see also Davidson, 2004) which optimize the signal transmission in multiple resonant frequency channels (Basar et al., 2004). These different regions forming interconnected distributed neural network with pathologic patterns of neurotransmission and multiple brain oscillations are involved to a greater or lesser extent, depending on the imbalance in monoamines and neuropeptides at a particular moment of the time, the type of input (external or internal), the nature of the task, and additional physiological and cognitive demands.

4.4. Interhemisphere asymmetry in depressive and control subjects

Analysis of the interhemisphere asymmetry indexed by the relative presence of each SP type in PCPs for each homologous EEG-channel pair demonstrated that subjects with MDD had significantly more asymmetric homologous EEG-channel pairs and more SP types that showed interhemisphere asymmetry than control subjects (Fig. 3. I.a, II.a). Additionally, such asymmetry was predominantly right-sided for depressive subjects and predominantly left-sided for control subjects (Fig. 3. I.b, II.b). The homologous EEG-channel pairs most involved in the interhemisphere asymmetry (meaning that significant difference in relative presence of SP types was observed for more than 38% of all SP types) were from posterior, temporal, and frontal regions of the cortex in depressive subjects, and only from posterior area for control subjects. This indicates that MDD increases interhemisphere brain asymmetry and changes it from relatively left-sided (which is species-specific for humans – in general, normal subjects demonstrate greater alpha activity in the right hemisphere than in the left, see Graae et al., 1996; Annett, 1999) to strong right-sided dominance.

Detailed analysis of homologous EEG-channel pairs and brain oscillations involved in interhemisphere asymmetry revealed opposite tendencies in depressive and control subjects (Table 3). Thus, during MDD anterior and posterior regions of the right cortex exhibited hyperactivity (they had significantly less EEG segments with delta, $theta_2$, $theta_3$, $alpha_1$, and $alpha_2$ brain oscillations than in the left hemisphere), whereas central and temporal parts of the right cortex showed hypoactivity (they had significantly more EEG segments with delta, theta, $alpha_1$, and $alpha_2$ brain oscillations than in the left hemisphere). At the same time, control subjects had the opposite results (Table 3). These findings are consistent with identified link between relatively greater right frontal resting activity (or relatively lower left frontal resting activity) and depression (Henriques and Davidson, 1990, 1991; Kano et al., 1992; Gotlib et al., 1998; also see Cacioppo, 2004). Perhaps, in depression the physiological overactivation of the right hemisphere reflects the unsuccessful effort to overcome its functional insufficiency (Rotenberg, 2004).

The fact that depressive subjects in the present study showed right-sided activation in both frontal and parietal scalp regions may indicate that these subjects have elevated anxiety as one of their symptoms (Heller, 1993; Heller and Nitschke, 1998; Davidson et al., 2000). This is supported by significantly higher anxiety scores in depressive, than in control subjects in the present study. The involvement of central and temporal regions in interhemisphere asymmetry during depression was also demonstrated by Perris et al. (1981) and Tucher and Dawson (1984): In the central and temporal

regions, depressed patients displayed a relatively higher activation on the left brain side than on the right brain side. Thus, although the frontal cortex is clearly a significant component of the affective network (Allen et al., 2004; Cacioppo, 2004), it appears that affective systems are implemented in circuits, only some of which are in frontal areas.

Before coming to the final conclusions, an alternative attribution of the results obtained in the present study should be considered. It could be suggested that these results may be attributed primarily to the anxiety rather than to depression. This view seems unlikely for the following reason: Buchsbaum et al., (1975) demonstrated that anxiety disorder is characterized by diminished alpha activity. This contradicts to the results of the present study (see Table 2, Fig. 2).

Conclusions

Taken together, all results in the present study revealed that the overall picture of the composition of brain oscillations and asymmetric brain activations involved in MDD is more complicated than might be expected from the literature. This may result from the microstructural approach to EEG analysis used in the present study, which is sensitive to the actual composition of brain oscillations.

In particular, the present study demonstrated that MDD affects brain activity in nearly the whole cortex, rather than in only the frontal and/or parietal areas. This was reflected in the considerable reorganization of the composition of brain oscillations in multiple frequencies (not in the alpha frequency only) in a broad frequency range: 0.5-30 Hz in majority of EEG channels. At the same time, the magnitude of the effect of depression was maximal in the posterior cortex of the brain. Interhemisphere asymmetry during MDD also was characteristic for the whole cortex, with right hyperactivity in frontal, parietal, and occipital brain areas.

Perhaps interactions among the various brain oscillations of the network we described are likely to play an important role in determining behavioral output of MDD. However, the present study cannot show if any of the abnormalities discussed above precede the onset of the depression, co-occur with it, or follow the expression of the disorder. Further study of a relationship between severity of depression and level of abnormality in the EEG with a larger number of patients is needed.

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