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Altered Sleep Brain Functional Connectivity in Acutely Depressed Patients

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Abstract: Recent evidence suggests that problems in information processing within neural networks may underlie depressive disease. In this study, we investigated whether sleep functional brain networks are abnormally organized during a major depressive episode (MDE). We characterized spatial patterns of functional connectivity by computing the "synchronization likelihood" (SL) of 19 sleep EEG channels in 11 acutely depressed patients [42 (20–51) years] and 14 healthy controls [32.9 (27–42) years]. To test whether disrupting an optimal pattern ["small-world network" (SWN)] of functional brain connectivity underlies MDE, graph theoretical measures were then applied to the resulting synchronization matrices, and a clustering coefficient (*C*, measure of local connectedness) and a shortest path length (*L*, measure of overall network integration) were determined. In the depressed group, the mean SL was lower in the delta, theta and sigma frequency bands. Acutely depressed patients showed a significantly lower path length in the theta and delta frequency bands, whereas the cluster coefficient showed no significant changes. The present study provides further support that sleep functional brain networks exhibit "small-world" properties. Sleep neuronal functional networks in depressed patients are characterized by a functional reorganization with a lower mean level of global synchronization and loss of SWN characteristics. These results argue for considering an MDE as a problem of neuronal network organization and a problem of information processing. *Hum Brain Mapp 30:2207–2219, 2009.*

Key words: neuronal networks; synchronization; small-world network; sleep; depression; insomnia

INTRODUCTION

Neurons form a dense network of connectivity spanning the entire thalamocortical system in the cerebral cortex [Sporns, 2002]. These brain networks are not random, but form highly specific pattern [Sporns, 2002]. A predominant feature of brain networks is that neurons tend to connect with other neurons in local groups. Because of the close relationship between neural connectivity and neural activity throughout the brain, it is important to consider structural connection patterns within the context of the specific patterns of dynamic ("functional") interactions that they support [Sporns, 2002]. Recent breakthroughs in modern

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TABLE I. Clinical and demographic measures

	Healthy controls (n = 14)	Depressed patients (n = 11)	P value
Demographic measures			
Sex, F/M	4/14n	2/11n	0.17
Age, y*	32.9 (27–42)	42 (20–51)	0.20
Marital status, No (%)			
Married	4 (28.57)	4 (36.36)	NA
Single-never married	1 (7.14)	1 (9.09)	NA
Divorced	5 (35.71)	4 (36.36)	NA
Cohabiting	4 (28.57)	2 (18.18)	NA
Employment status, No (%)			
Manager	7 (50)	4 (36.36)	NA
Employed	4 (28.57)	4 (36.36)	NA
Workman	3 (21.43)	3 (27.27)	NA
Clinical measures*			
24-Item Hamilton Depression score	0 (0–2)	27 (17–56)	<0.0001
Pittsburgh Sleep Quality Index	1.5 (1–8)	11 (1–20)	<0.0001

NA means "Non Applicable."
*Values are indicated as median with maximum and minimum range.

network theory now allow a better characterization and understanding of complex networks that is also relevant for understanding brain networks.

An important concept is that of a "small-world network" (SWN), which is a type of mathematical graph in which most nodes are not neighbors of one another (the network is sparsely connected), but most nodes can be reached from every other node by a small number of steps [Watts and Strogatz, 1998]. Social networks, spatial games, excitable media, the connectivity of Internet connectivity, and gene networks exhibit SWN characteristics [Watts and Strogatz, 1998].

There are empirical and theoretical a priori reasons why SWNs present an attractive model for brain network connectivity [Watts and Strogatz, 1998]: (i) The brain is a complex network on multiple spatial and time scales [Watts and Strogatz, 1998]; (ii) The brain supports both segregated and distributed information processing; and (iii) The brain likely evolved to maximize efficiency and/or minimize the costs of information processing. Network architecture is regarded as a key substrate for sensorimotor and cognitive processing, which may be localized discretely in specialized regions or represented by coherent oscillations in large-scale distributed systems. Small-world topology comprises both high clustering (compatible with segregated or modular processing) and short path length (compatible with distributed or integrated processing), and is associated with high global and local efficiency of parallel information processing, sparse connectivity between nodes, and low wiring costs. SWNs can operate dynamically in a critical state, facilitating rapid adaptive reconfiguration of neuronal assemblies in support of changing cognitive states [Watts and Strogatz, 1998].

In this study, our goal is to use computational models to explore how depressive disease behaviors relate to the general synchronization and connectivity of the underlying neuronal network during sleep. We propose to determine the patterns of neuronal functional connectivity during sleep using two methods that allow for the study of neuronal network behavior: the synchronization likelihood (SL) and the graph theory analysis. We hypothesized that acute depressive status will interfere with the optimal architecture of brain functional networks and could show functional connectivity reorganization as a "disconnection state" of the neural network. In this way, we want to confirm the fact that depression can be primarily viewed as an information processing problem in the brain.

MATERIALS AND METHODS

Participants: Patient and Control Selection

The present study included 25 subjects matched on age and education level: 14 healthy controls and 11 unmedicated inpatients with acute major depression according to DSM-IV-TR criteria [Amercian Psychiatric Association, 2000]. Descriptive clinical features of the acutely depressed patients and healthy control subjects are presented in Table I.

Healthy controls were recruited from the community by advertisements. On the basis of an extensive clinical interview, they were determined to be free of DSM-IV-TR axis I or evident axis II diagnoses and they had no family history of major psychiatric disorders. They reported a regular sleep–wake schedule and no current or past sleep disorders.

Patients were recruited from both the Sleep Laboratory and an inpatient psychiatry ward at the Erasme Academic Hospital, where they were hospitalized for both MDD and sleep disturbances. Disturbances included difficulty falling asleep, difficulty staying asleep, and early morning awakening. Sleep self-reports were obtained by the Pittsburgh Sleep Quality Index (PSQI). The PSQI (range 0–21, higher values indicating greater sleep disturbances) is a self-rated questionnaire that assesses sleep quality and disturbances during the previous 1-month time interval [Buysse et al., 1989]. The 19 self-rated questions assess a wide variety of

factors relating to sleep quality, including estimates of sleep duration and latency, and the frequency and severity of specific sleep-related problems. A global PSQI score of ≥ 5 was found to correctly discriminate between "good" and "poor" sleepers [Buysse et al., 1989]. Patients were initially evaluated for a MDD by a psychiatrist using DSM-IV-TR criteria. Depressive symptom severity was assessed with the 24-item Hamilton Rating Scale for Depression (HAM-D). Patients were included in the present study if they fulfilled the following five criteria: (1) they suffered from major depression (unipolar without psychotic features); (2) they were free of all prescription and nonprescription psychotropic medications; (3) they had a HAM-D score of 20 or greater [Hamilton, 1960]; (4) they had a PSQI of five or greater; and (5) they did not suffer from untreated or poorly controlled conditions that may have confounded the sleep EEG results (e.g., Cushing's disease), or require treatment with agents that may affect results (i.e., β-blockers or corticosteroids). Both controls and patients were medically screened by way of physical examination (performed by an internist), chest X-ray, electrocardiography, electroencephalography, and laboratory tests such as liver and kidney function tests, hematology profile, thyroid function tests, and urinalysis. They did not show cardiovascular or endocrine abnormalities, or other systemic illness. Subjects with a BMI greater than 29 were excluded. We also excluded controls or patients who showed primary sleep disorders such as apnea–hypopnea syndrome, periodic leg movement syndrome, or parasomnia.

Before signing an informed consent, each subject received a detailed description and demonstration of the procedure involved in the study, and was deemed capable.

The study protocol was approved by the local ethics committee of the Erasme Academic Hospital-Free University of Brussels.

EEG Recordings and Experimental Conditions

EEG sleep studies were performed in the Sleep Laboratory of the Erasme Academic Hospital. In the patient group, sleep studies were conducted after a psychotropic medication-free evaluation period of at least 2 weeks. Polysomnographic recordings were obtained during three consecutive nights, of which only the latter two were examined because of the well-recognized "first night effect" on sleep measures [Agnew et al., 1966]. For the purposes of this analysis, one "artifact-free night" was chosen from the latter two nights. If both nights showed low levels of artifact, then one was randomly selected. Artifacts were detected by visual observation using the software Endymion (Endymion 1993–2008, Sleep laboratory, Erasme Hospital), which was developed in our laboratory for data analysis.

Patients and controls were instructed not to drink alcohol or coffee or use over-the-counter sleep aids during the same time frame. Subjects went to bed and got up at their usual times. During bedtime hours, controls and patients were supine with lights off. They awoke spontaneously in the morning, and daytime naps were strictly prohibited. Both controls and patients had a minimum of seven consecutive hours of recorded time in bed. Polysomnography was recorded with a 19-channel digital polygraph (Alice5^{TM}, Respironics, Murrysville, PA). The 19 electroencephalograms were recorded, according to the international 10–20 standard system, with a contralateral reference to the A1 or A2 mastoid derivation. Simultaneously, two electrooculograms (EOG), one submental electromyogram (EMG), and electrocardiographic activity (ECG) were recorded. Oxyhemoglobin saturation was measured using pulse-oximetry (Masimo MS-7, Irvine CA), oro-nasal airflow was detected with thermistors (Infinity^{TM}, Sleepmate Technologies, Midlothian, VA), thoracic and abdominal respiratory movements were recorded with piezoelectric sensors (Resp-EZ^{TM}, Sleepmate Technologies), and leg movements were detected with ankle piezoelectric movement strain gauges (Moving Images^{TM}, Sleepmate Technologies). All channels were sampled at 2,000 Hz—16 bits. For subsequent analyses, the EEG was stored at 200 Hz, the EOG at 100 Hz, the EMG at 100 Hz, and the ECG at 500 Hz. The Alice 5 device included adequate analog filters to eliminate low frequency artifacts, drifts, offsets, and aliasing. Also, adequate antialiasing filters were applied before down sampling. For example, a Bessel filter (Order 3) is applied to the EEG before digital sampling, with a bandpass from 0.32 to 106 Hz (−3 dB). To reduce the frequency to 200 Hz, two filters are applied: a least-squared FIR (Order 20) low-pass filter at 160 Hz followed by a Kaiser Window FIR (Order 88) low-pass filter at 95 Hz. The last step involves a 50-Hz notch filter (Order 30) with stop band at 43 and 57 Hz. The data were exported to the EDF format using Alice Sleepware (Respironics). All subsequent analyses, such as stage determination and spectrum calculation, were carried out on the sampled data, avoiding synchronization problems between the stages and the other calculations. Using the Endymion program, each 20-s epoch was visually scored according to standard criteria [Rechtschaffen and Kales, 1968].

The Synchronization Likelihood: Theory and Computation

The SL, introduced by Stam and van Dijk [2002], is a measure of the statistical interdependencies between a time series (such as an EEG channel) and one or more other time series within a dynamical system. This measure has already been used in several clinical neurosciences studies [Stam, 2005; Stam and Reijneveld, 2007]. For a detailed technical description of the method and its properties, we refer to Stam and van Dijk [2002]. Here we explain the general principles.

The SL is sensitive to linear as well as nonlinear interdependencies and can be computed for each time sample, making it suitable for tracking time-dependent changes in the synchronization level. Hence, more accurate informa-

tion is given about functional interactions in a dynamical system [Stam, 2005; Stam and van Dijk, 2002]. The SL basic principle is that each time series is divided into a series of "patterns," which are searched for recurring patterns. Here, a pattern can be thought of as a brief part of the time series that contains at least one cycle of the characteristic frequency. More technically, the brief patterns are vectors constructed by time-delay embedding, using parameter settings [as described in Montez et al., 2006]. The SL is the chance that pattern recurrence in time series X coincides with pattern recurrence in time series Y. The SL takes on values between *P ref* (a parameter that was taken as *P ref* = 0.01 as in other SL studies), in the case of independent time series and one in the case of fully synchronized time series. The end result after computing SL for all pairwise channels combinations, is a square $N \times N$ matrix of size 19 (19 is the number of the EEG channels used in this study), where each entry N_{ij} contains the value of the SL for channels *i* and *j*. We computed the average synchronization by taking the mean of these values.

Structure of the Network and Connectivity: Computing the Clustering Coefficient (*C*) and the Characteristic Path Length (*L*)

An interesting approach to study the topographical characteristics of both local and long distance functional connectivity in complex networks is to apply a measure derived from graph theory [Sporns, 2002; Strogatz, 2001; Watts and Strogatz, 1998].

A graph is a basic representation of a network that is essentially reduced to nodes (vertices) and connections (edges) (see Fig. 1). Graphs are characterized by a clustering coefficient (*C*) and a characteristic path length (*L*), among other measures. *C* is a measure of the local interconnectedness of the graph, whereas *L* is an indicator of its overall connectedness. Watts and Strogatz have shown that graphs with many local connections and a few random long distance connections are characterized by a high *C* and a short *L*. Such near-optimal networks are designated as "small-world" networks [Watts and Strogatz, 1998]. Since then, many types of real networks have been shown to have small-world features [Strogatz, 2001]. Patterns of anatomical connectivity in neuronal networks are particularly characterized by high *C* and a small *L* [Watts and Strogatz, 1998]. It has also been suggested that small world-like network architecture may be optimal for synchronizing neural activity between different brain regions [Masuda and Aihara, 2004].

C and *L* were calculated following the methodology described in the studies of Newman [2003], Bartolomei et al. [2006], and Ponten et al. [2007]. The first step in applying graph theoretical analysis to synchronization matrices is to convert the $N \times N$ synchronization matrix into a binary graph (*N* is the number of EEG channels). A binary graph is a network that consists of elements (also called "vertices") and undirected connections between elements (also called "edges"). Edges between vertices either exist or do not exist; they do not have graded values. The synchronization matrix can be converted into a graph by considering a threshold (*T*). If the SL between a pair of channels *i* and *j* exceeds *T*, an edge is said to exist between *i* and *j*, otherwise, no edge exists between *i* and *j*.

Once the synchronization matrix has been converted to a binary, unweighted graph, the next step is to characterize the graph in terms of its *C* and *L*. A schematic explanation of graphs, *C*, and *L* is given in Figure 1.

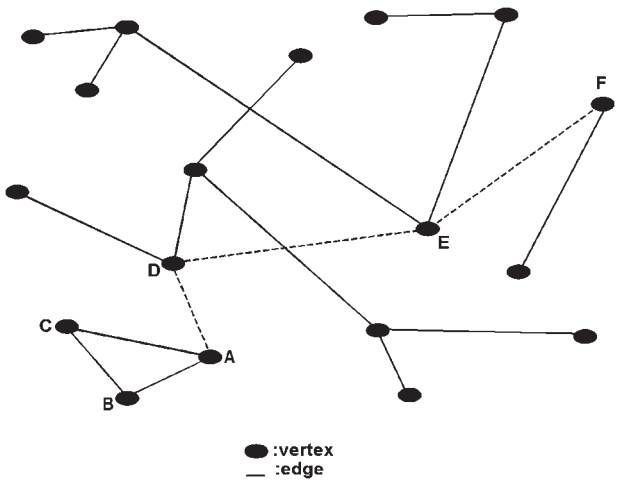

Figure 1.

Schematic explanation of a graph and graph theoretical measures. This figure is based upon Stam et al. [2007]. A graph consists of elements or vertices, denoted by black dots. If two vertices are connected a line is drawn between them. Such a connection is called an edge. The size of a graph is equal to the total number of vertices. The degree *K* of a graph is the average number of edge per vertex. In a graph all vertices need to be connected. The distance between two vertices is expressed by the number of edges that have to be traveled to get from the Vertex I to another. As an example, the shortest path from vertex A to vertex F has a length of three edges. The characteristic path length of a graph is the mean of all shortest paths connecting all pairs of vertices. *L* is a measure of how well connected a graph is. The cluster coefficient *C* is a measure of the existence of local densely connected clusters within a network. For example, to compute the cluster coefficient for vertex A, we first determine the other vertices to which it is directly connected. These neighbors are vertices B, C, and D. Then we determine how many edges exist in the set of neighbors. In this case, only B and C are connected. Next, we determine how many edges could have existed between the neighbors. In our example, this is three (B-C, C-D, and B-D). The cluster coefficient of A is the ratio of these two numbers: 1/3. The cluster coefficient can be determined for all vertices. This result is an average cluster coefficient for the entire graph. Optimal networks are characterized by a high *C* and a low *L*. Such networks are designated small-world networks [Watt and Strogatz, 1998].

To compute the C of a certain vertex, we first determine to which other vertices it is directly connected; these other vertices are called "neighbors." The C is the ratio of all existing edges between the neighbors and the maximum possible number of edges between the neighbors. It ranges between 0 and 1. This C is computed for all vertices of the graph and then averaged, and it measures for the tendency of network elements to form local clusters.

The characteristic L is the average shortest path that connects any two vertices of the graph. The length of a path is indicated by the number of edges it contains. The L is an emergent property of the graph that indicates how well its elements are integrated/interconnected.

Because C and L are computed as a function of T, the results may be influenced by differences in the mean level of synchronization between the two groups. The SL is expected to be significantly lower for acutely depressed patients than for controls. Therefore, depressed patient's graphs will have fewer edges than control subject's graphs for a given T value and this will influence the differences in C and L between the two groups. To control for this effect, we used an individual-adapted T such that we get a number of connections per vertex K (which is the average number of edges per vertex) for each individual graph with the same K for all subjects and filter settings. In this way, graphs studied in both groups are guaranteed to have the same number of edges, so any remaining differences in C and L between the groups reflect only differences in graph organization.

The choice of K is somewhat arbitrary. We followed the suggestion of Watts and Strogatz for the minimal K value necessary for a network with size N (here 19 channels), such that a random network generated from it will still be guaranteed to be fully connected: N [dmt] K [dmt] Ln (N) [Watts and Strogatz, 1998]. Here, K number greater than 3 fulfils these conditions. In our study we used $K = 5$, with which we obtained the most striking findings. K is fixed in order to compare the topological structure of the networks without any bias from differences in the mean SL [Ferri et al., 2007]. By fixing K, all of the graphs have the same number of vertices and edges; the only differences are in the spatial arrangement (which are reflected by C and L) [Bartolomei et al., 2006].

To avoid the problem of the disconnected graph, we used an alternative approach based on the global efficiency [Latora and Marchiori, 2001], where L is calculated as the reciprocal of the average of the reciprocals. Infinite values of L (when two edges are not connected) contribute nothing to the sum [Newman, 2003]. For the clustering coefficient C of the graph, disconnected points are assigned a value of 0.

Then, the values of C and L were compared to theoretical values of random networks generated following the procedure described by Sporns and Zwi, which preserves the degree distribution exactly [Sporns and Zwi, 2004]. For a K value of 5, for each EEG, 50 random networks were generated, and the mean C-s and L-s of all of these networks were calculated as a reference value for C and L. The ratios C/C-s and L/L-s were considered. SWNs are characterized by the simultaneous presence of values of C/C-s values significantly greater than 1.5 and values of L/L-s values around the value one [Micheloyannis et al., 2006; Stam et al., 2007; Watts and Strogatz, 1998]. In the randomization procedure, the degree distributions of the original networks were preserved. The mean L/L-s ratio in the different epochs was above 1, whereas the mean C/C-s ratio was greater than 1.5.

EEG Signal Analysis

All EEG channels were down sampled to 200 Hz. Using the Endymion program, all 20-s windows were visually scored according to standard criteria [Rechtschaffen and Kales, 1968]. For each of the three sleep stages [Stage 2, SWS (Stages 3 and 4), and REM sleep], we randomly selected 25 artifact-free (no eye blinks, slow eye movements, excess muscle activity, electrocardiogram artifacts, etc.) 20,48-s epochs. The number of epochs (25) was arbitrarily chosen to obtain a common quantum in order to carry out our study despite the great disparity in the number of epochs during the different sleep stages.

EEG epochs were converted to ASCII files, resulting in times series of 4,096 samples for further analysis. Digital, zero-phase shift filtering of the EEG in three frequency bands (delta: 1–4 Hz, theta: 4–8 Hz, and sigma: 12–16 Hz), SL computation and the two graph theoretical measures [cluster coefficient (C) and characteristic path length (L)] were done off-line with the DIGEEGXP software written by one of the authors [C.J. Stam]. Graph theoretical analysis was based on the full 19 × 19 matrix of all possible pairwise combinations of electrodes.

Statistical Analysis

Mann–Whitney nonparametric U-tests were used to examine group (controls vs. depressed) differences in clinical, demographic, and sleep measures as well as in SL values and graph parameters (C, L, C/C-s, and L/L-s) within the different frequency bands (delta, theta, and sigma). This test was deemed most appropriate because of the sample size and data distribution. Qualitative data were compared by means of the Fisher Exact test, because expected frequencies were less than 5. Correlations were studied with the Spearman's rank correlation coefficient.

All analyses were performed with α (Type I error) set at 0.05 using the statistical software program SPSS for Windows, version 14.0.

RESULTS

Clinical and Demographic Measures

Depressed and healthy groups did not differ on age or sex (Table I). As expected, the depressed subjects showed

TABLE II. Electroencephalographic sleep measures

	Healthy controls (n = 14)	Depressed patients (n = 11)	P value
Sleep continuity			
Total sleep time (min)**	479.5 (439–541)	375.5 (204–485)	0.001
Sleep latency (min)	31.5 (5–51)	25.7 (5–186)	0.58
Sleep efficiency (%)	84.7 (78.2–94.1)	72.4 (35.8–89.3)	0.08
No. of awakenings	62 (38–90)	73 (25–115)	0.76
Awake (min)	62.7 (20–90)	89.3 (18.3–180.7)	0.35
Awake (% SPT)	11.8 (3.8–15.9)	18.5 (3.7–47)	0.17
Non rapid eye movement (NREM)			
% Stage 1	7.2 (3.5–11)	10.4 (2.9–22.3)	0.71
% Stage 2*	59.5 (50.6–73.1)	54.5 (34.8–65.8)	0.049
% Slow wave sleep	15.15 (1.5–23.7)	12.1 (2.3–21)	0.55
Rapid eye movement (REM)			
% REM	22 (15.3–27.3)	22.7 (9.5–32.1)	0.91
REM latency**	71.8 (50–131)	48 (5–98)	0.003
REM density (unit/min)	1.68 (1.1–3.2)	1.74 (0.6–7.9)	0.68

Values are expressed as median with minimum–maximum range.
*P-value < .05
**P-value < .01

significant elevations in depressive symptoms, as measured by the total score on the HDRS [Hamilton, 1960]. According to the insomnia questions on the HRSD [Hamilton, 1960], sleep disturbances were moderately severe and distributed evenly throughout the night (initial, middle, and delayed). Sleep disturbance, as measured by the PSQI, was significantly higher in the depressed patients who reported difficulty falling asleep, early waking, and many awakenings. Seven depressed patients had recurrent major depression [average age at onset 29 ± 6 years (mean ± SD)], while four had single-episode major depression [average age at onset 28 ± 6 years (mean ± SD)].

Conventional Sleep Characteristics

A Mann–Whitney U-test revealed a significant decrease in total sleep time as well as in REM latency onset among the patients group (Table II).

The depressed patient group also showed several of the well-known pathognomonic sleep changes, such as

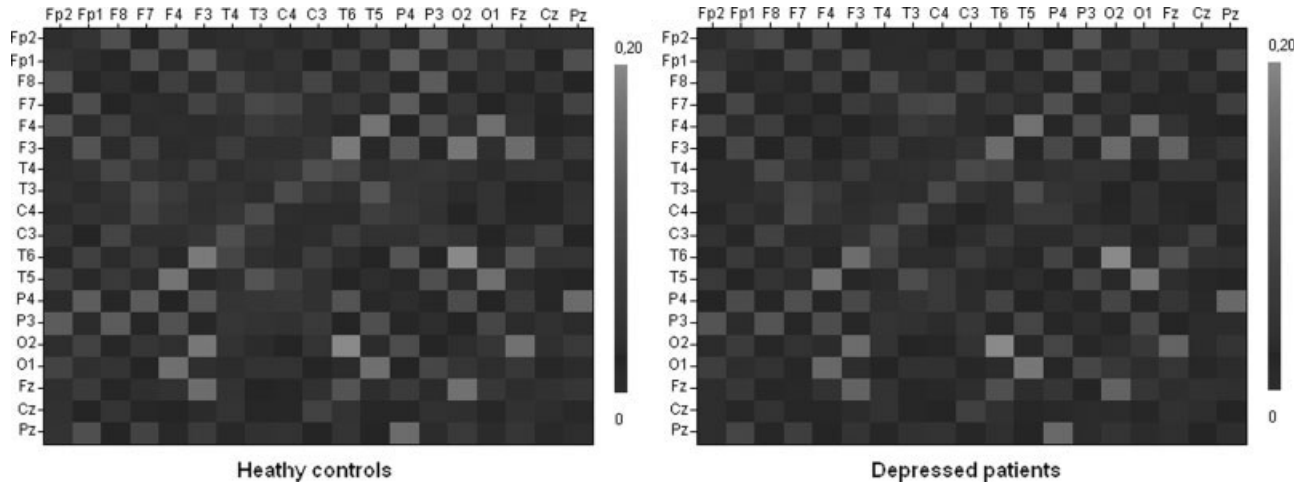

Figure 2.

Mean synchronization matrices for healthy controls (n = 14) and acutely depressed patients (n = 11) in the delta frequency band. The synchronization matrix is a 19 × 19 square matrix, where X axis and the Y axis correspond with the channels numbers, and where the entries indicate the mean strength of the SL between specific pairs of channels. The strength of the SL is indicated with a black-grey scale, from black (SL = 0) to light gray (SL → 1). The diagonal running from the upper left to the lower right is intentionally left dark gray. The names of the corresponding electrodes according to the 10–20 electrode placement system have been indicated respectively on the X and Y axis.

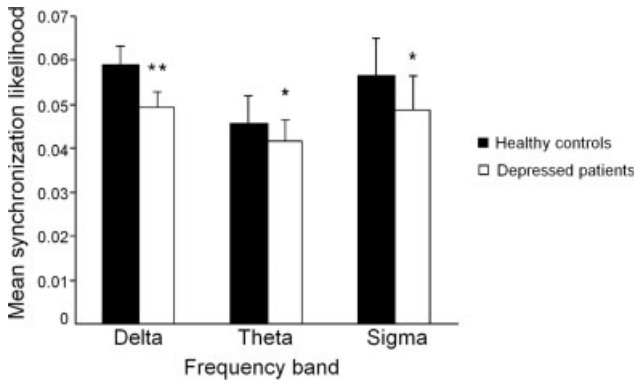

Figure 3.
Mean synchronization likelihood (error bar denote standard deviations) of healthy controls and depressed patients for the different frequency bands. * indicates $P < 0.05$. ** indicates $P < 0.001$.

decreased sleep efficiency and decreased Stage 2 percentage. We also observed increased sleep onset latency, Stage 1 percentage, awakenings throughout the night (in terms of number and percentage), REM sleep percentage, and REM density. We also observed a decreased percentage of SWS. However, the above-mentioned parameters did not differ significantly between the two groups in our sample, but were significantly different in a large number of previous reports [Kerkhofs et al., 1991; Kupfer, 1995].

Synchronization Likelihood Per Frequency Band

As seen in the delta frequency band (see Fig. 2), the synchronization matrices of both groups show a complex but, nonetheless, rather similar pattern, with various regions of high (light grey: SL → 1) and low (black) level of synchronization. These graphs revealed global SL that occurred at all channels. Our results show that the mean SL (averaged over all pairwise combinations of channels and time points) was significantly lower in the depressed group in all of the frequency bands that we have investigated (see Fig. 3): delta (NREM sleep—slow wave sleep), theta (REM sleep), and sigma (NREM—Stage 2).

To render the differences between groups more clearly, we also computed SL over all channels, comparing each channel with all others for the three frequency bands of interest (see Fig. 4). The loss of synchronization observed in the depressed group is global in the theta band, whereas it localized more specifically in the frontal, parietal, and temporal areas of the delta and sigma frequency bands.

Small-World Network Parameters

The synchronization $N \times N$ matrices were converted to graphs using an individual-adapted threshold which resulted in a value of $K = 5$ for all graphs. As an example, Figure 5 shows the graphs that correspond to the mean synchronization matrices of Figure 2, in both groups and for delta frequency band. As shown in Figure 5, the organization of the neuronal network differed between the acutely depressed patients and healthy controls. Compared with the depressed group, the control group graph shows a large number of edges between the central, temporal, parietal, and frontal regions of the delta band (see Fig. 5).

The most striking SWN parameter values in the delta (NREM sleep—SWS), theta (REM sleep), and sigma

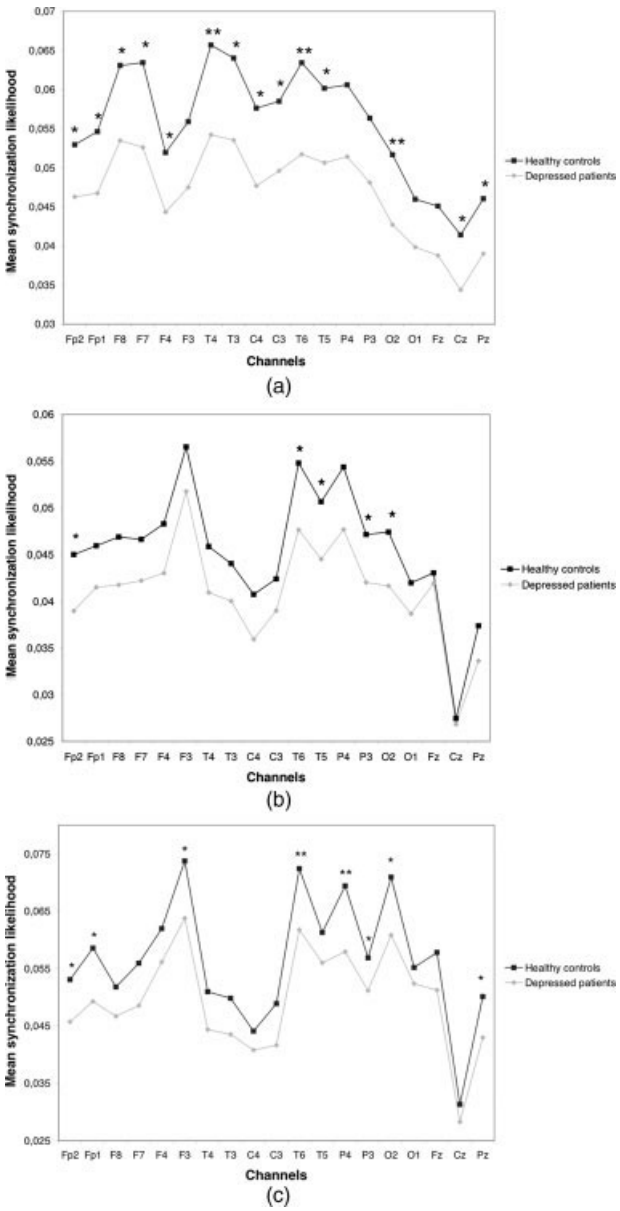

Figure 4.
Mean synchronization likelihood in the different channels in sigma (**a**), theta (**b**), and delta (**c**) frequency bands. * indicates $P < 0.05$. ** indicates $P < 0.001$.

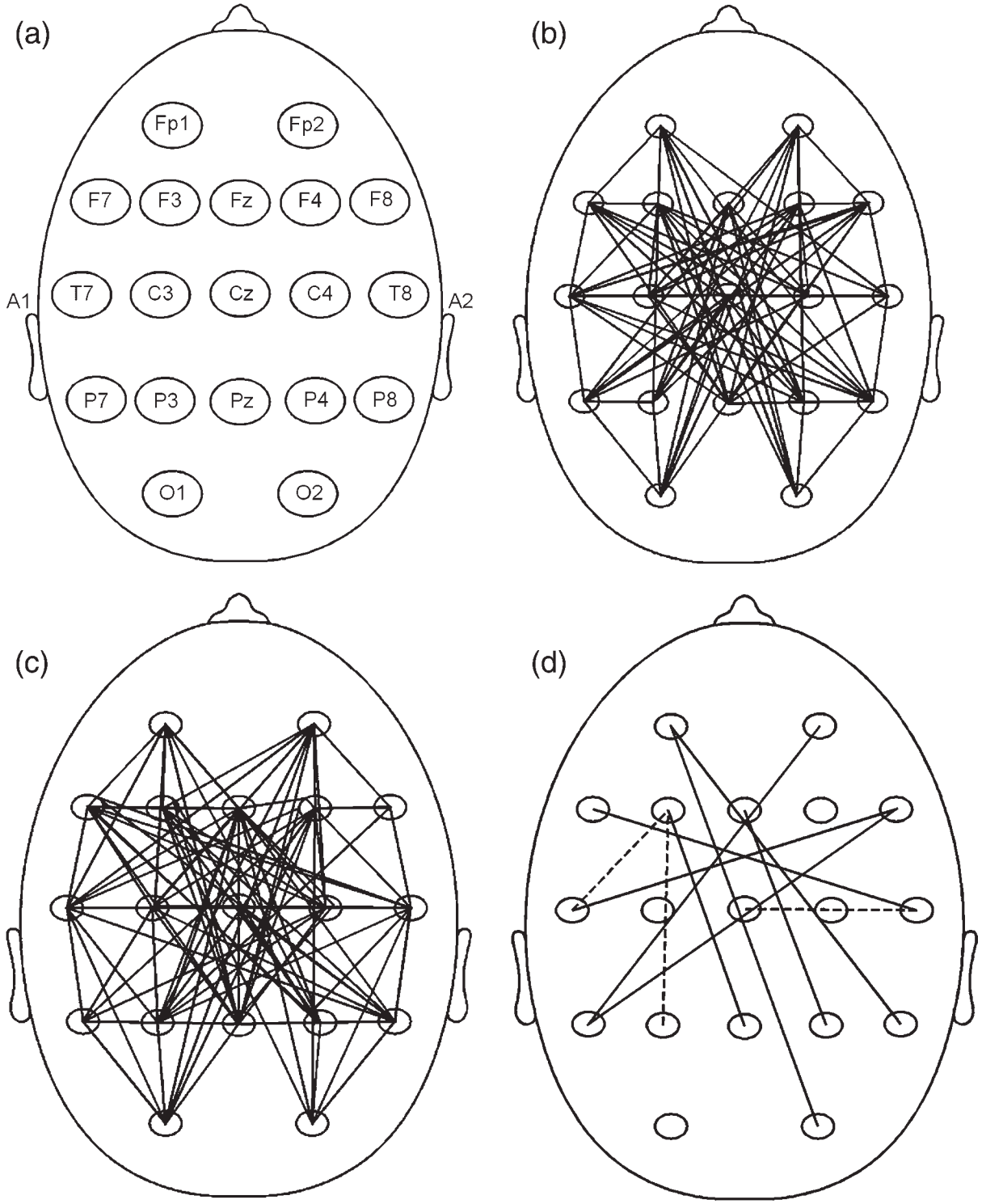

Figure 5.

Mean synchronization matrices of Figure 2 converted to graphs using individual thresholds for controls and depressed patients. Schematic image of the head seen from above, with the positions of the electrodes indicated by small circles and numbered according to the 10–20 electrode placement electrode (**a**). Graph of the control subjects in the delta frequency band (**b**). Graph of the acutely depressed patients in the delta frequency band (**c**). Differences between the two groups in the delta frequency band (**d**): Co–De: edges only present in control group (solid lines); De–Co: edges only present in depressed group (dotted line).

TABLE III. Small-world network parameters

	Healthy controls (n = 10)	Depressed patients (n = 11)	P value
C			
Delta	0.48 (0.45–0.52)	0.48 (0.43–0.49)	0.33
Theta	0.55 (0.49–0.58)	0.52 (0.46–0.56)	0.1
Sigma	0.54 (0.50–0.58)	0.54 (0.50–0.58)	0.29
L			
Delta*	2.1 (2.03–2.16)	2.06 (2.03–2.14)	0.03
Theta*	2.12 (2.04–2.22)	2.08 (2.05–2.12)	0.01
Sigma	2.09 (2.05–2.15)	2.09 (2.05–2.15)	0.89
C/C-s			
Delta	2.17 (1.97–2.31)	2.13 (1.94–2.22)	0.27
Theta	2.41 (2.18–2.53)	2.3 (2.03–2.55)	0.19
Sigma	2.43 (2.2–2.6)	2.37 (2.17–2.57)	0.17
L/L-s			
Delta*	1.24 (1.19–1.26)	1.21 (1.19–1.25)	0.03
Theta**	1.26 (1.19–1.3)	1.21 (1.2–1.24)	0.005
Sigma	1.21 (1.2–1.26)	1.22 (1.2–1.25)	0.95

Values are expressed as median with minimum–maximum range.
*P-value < .05
**P-value < .01.

(NREM sleep—Stage 2) frequency bands are presented in Table III.

There were no significant clustering coefficient differences between the depressed patients and the healthy controls in the frequency bands that were investigated. However, the C tends to show a greater value in controls than in the patient group in the theta band. In contrast, the characteristic L is significantly lower in the depressed group in the theta and delta frequency bands.

The C and L values were compared with the values for random graphs, using the procedure described by Sporns and Zwi [2004]. In the randomization procedure, the degree distributions of the original networks were preserved. As expected in SWN organization, the mean L/L-s ratio was slightly above 1 in the different frequency bands, whereas the mean C/C-s ratio was significantly greater than 1 (Table III). In the different frequency bands that were investigated, there were no statistically significant C/C-s differences. In the delta, especially, theta bands, L/L-s was significantly lower in the depressed group.

As a summary, the most obvious changes occurred in the depressed group, in which a decrease of both the L and L/L-s ratio were observed during delta and theta bands. Thus, alterations in graph architecture were found to only affect L (except in sigma band).

Mean SL, Small-World Network Parameters and the Severity of Depression

We also tested whether the mean level of SL, C, and L were related to the severity of depression. Linear correlations were observed between the global SL, C, L, and the HDRS as: the more depressed the patient, less are the global level of SL, C, and L in theta and delta frequency bands. These correlations were significant for SL in the sigma and delta frequency bands and for L in the delta and theta frequency bands. Then, in these frequency bands and with the specific parameters (SL or L), the more depressed are the patients, the less are the values of SL and L.

This observation was contrasted by an inverse relation (without statistical significance) in the sigma frequency band for L (Table IV).

DISCUSSION

The principal findings of the present study are twofold. First, we demonstrated that the acute state of depressive disease is characterized by a decrease in the global mean levels of the sleep EEG synchronization. Second, we showed that a major depressive episode (MDE) displays a significant reorganization of the neuronal brain networks.

Sleep Brain Rhythms and Cortical Synchronization

Studying the functional connectivity of the different frequency bands is important, because it has been postulated that synchronous oscillations between the different cortical areas play a role in various aspects of brain function, specifically cognitive functioning [Klimesch, 1999]. Moreover, because sleep is not simply a suspension of waking activities, there must be a good reason why complex brains have developed an elaborate dynamic choreography during sleep [Buzsáki, 2006].

To the best of our knowledge, with the exception of a few studies performed specifically on the slow-wave EEG and cycling alternating pattern synchronization [Ferri et al., 2005, 2006; Stam, 2004], this is the first study that shows a global decreased level of cerebral synchronization in the sigma, theta, and delta frequency bands during sleep in depressed patients. In the sigma and delta bands, this loss of synchronization is more specifically localized in the frontal, temporal, and parietal areas. A generally agreed upon view among the scientific community is that depression may be a disorder that shows disturbed large-scale cortical (and subcortical) systems that include a number of functionally connected cortical regions, such as the temporal, frontal, and parietal lobes [Davidson, 2004].

TABLE IV. Correlation values between the score in the Hamilton Depression Rating Scale, the global level of SL and the small-world measures

		Global synchronization	C	L
Theta	Rs	−0.305	−0.216	−0.414
	P value	0.138	0.3	0.04
Sigma	Rs	−0.5	−0.286	0.191
	P value	0.011	0.166	0.36
Delta	Rs	−0.662	−0.119	−0.42
	P value	0.001	0.572	0.036

Rs, Spearman's rank correlation coefficient.

Moreover, a malfunction of limbic-cortical networks is currently the leading systems-level candidate for mediating major depression, based on an extensive literature on blood flow, metabolism, EEG dynamics, and histological findings [Drevets, 2000; Linkenkaer-Hansen et al., 2005]. The frontal cortex is also clearly a significant component of the disturbed system related to major depression [Drevets et al., 1997]. Thus, the topographic synchronization abnormalities found in this article (in both the delta and sigma frequency bands) in terms of loss of synchronization are in agreement with the current literature [Drevets, 2000; Drevets et al., 1997; Linkenkaer-Hansen et al., 2005].

Slow-wave activity synchronization during sleep may be one factor that plays a role in the recently hypothesized importance of EEG slow-waves during sleep for cognitive processing [Huber et al., 2004]. The roles of sleep slow-wave activity and synchronization in memory consolidation, and learning processes are the subject of different animal and human studies [Steriade, 2006]. Presumably, networks that are activated during the learning of a new task are reactivated during sleep, which improves performance on the same task the next day [Huber et al., 2004]. Moreover, the surface-positive half-waves of sleep slow-waves have been reported to be associated with distinctly enhanced coherence after learning in the slow-oscillatory, delta, sigma, and gamma bands [Mölle et al., 2004]. The loss of delta mean synchronization activity observed in this study could have a part in the cognitive dysfunctions that are classically found in patients suffering from depression [Porter et al., 2003].

Sleep spindles are initiated by a deep brain structure, the thalamic reticular nucleus, in connection with principal thalamic nuclei and are synchronized by corticortical, corticothalamic, and thalamocortical loops [Steriade, 2006]. Both intrinsic thalamic conductances and reticulothalamic/cortico-thalamo-cortical loops are involved in spindle generation, amplification, and synchronization of spindles [Steriade, 2006]. Of importance, abnormalities in these thalamocortical structures have been implicated in the neurobiology of schizophrenia [Andreasen et al., 1994]. Neuromodulatory systems that affect the function of these thalamocortical circuits and the generation of these sleep rhythms (such as norepinephrine, serotonin, acetylcholine, and γ-aminobutyric acid) are altered in schizophrenia as well, but also and mostly in major depression [Belmaker and Agam, 2008]. A few previous works have studied the sleep spindle activity in patients suffering from major depression with different and contradictory results [de Maertelaer et al., 1987; Ferrarelli et al., 2007]. Because our study clearly shows a defect in the mean synchronization of the sigma frequency bands in depressed patients, we can argue that thalamocortical system abnormalities may play a role in MDE.

Theta rhythm, which is one of several electroencephalographic waveforms associated with various sleep (REM sleep) and wakefulness states, is one of the main rhythms in the hippocampus, and has been associated with cognitive processes and memory [Buzsáki, 2006]. The hippocampus and associated structures are organized in multiple loops and are part of all the allocortex, with reciprocal connections to the neocortex [Buzsáki, 2006]. Synchronous activity in the theta band over the frontal area increases strongly during tasks that are demanding for working memory [Stam et al., 2002]. Moreover, Tesche and Karhu succeeded in measuring, with MEG, theta activity in the hippocampus during performance of a working memory task. They showed that the working memory task stimuli induced brief bursts of theta band activity in the hippocampus [Tesche and Karhu, 2000]. These disturbances in the global mean synchronization of the theta band could probably be explained by seize and function modifications of the hippocampus, which is one of the "target structures" of depression.

Loss of the Small-World Networks Properties As "A Randomization Process"

There are indications that SWNs represent an optimal organization in terms of low "wiring costs," local independence, global integration, and resilience to error. Modeling studies have shown that neural networks with small-world configuration facilitate synchronization between distant neurons and efficient information processing [Masuda and Aihara, 2004]. In a study dealing with MEG recordings from healthy subjects, graph analysis of synchronization matrices revealed small-world patterns in both low- and high-frequency bands [Stam, 2004]. When C and L are expressed as ratios of C and L on random graphs, the results of the present study are quite compatible with those of several previous studies [Hilgetag et al., 2000; Stam, 2004]. Particularly, another study that extracted cerebral networks from these EEG data using a method described previously by Stam [2004], showed that networks demonstrated more small-world characteristics during all sleep stages as compared to the awake state, and that these features were even more pronounced during cyclic alternating pattern sleep phase A1 than B [Ferri et al., 2007].

The results of this study confirm that the functional connectivity of the sleep EEG activity has a tendency to show an organization similar to a SWN during sleep (with the values of C/C-s clearly higher than 1.5 and the values of L/L-s close to 1) [Ferri et al., 2007; Micheloyannis et al., 2006; Stam and Reijneveld, 2007]. The values found during sleep are clearly different from those characterizing random networks (both values around 1) and ordered networks (both values significantly higher than 1).

Our analyses showed that depressed patients still had a significantly shorter L in the theta and delta bands compared with controls, with no difference in C. These results reflect the fact that healthy controls exhibit neuronal networks closer to the ordered part of the rewiring scale. On the other hand, patients have brain networks closer to the random part of the scale.

These results are in line with those observed in another neuropsychiatric disease that has already been studied in several previous works: schizophrenia. The "disconnection hypothesis" proposed by Breakspear in 2003, has been confirmed by several studies, in which we also observed disturbed connectivity between different brain regions, especially the frontal area, and particularly in the left hemisphere [Breakspear et al., 2003; Micheloyannis et al., 2006; Rubinov et al., in press]. The general pattern that emerges from our study and those on Alzheimer's disease and schizophrenia is that networks of patients with disturbed cognition functions are more "random." As a consequence, it seems that this "disconnection hypothesis" of schizophrenia is not specific, but also founded during MDEs. This "randomization process" of the neuronal networks could be viewed as a general pattern of neuropsychiatric diseases.

Possible Functional and Clinical Consequences of Decreased Brain Functional Connectivity During MDE

Growing evidence indicates that sleep is important in learning and memory processing [Stickgold, 2005]. Over the last decade, a multitude of molecular, cellular, integrative systems and behavioral findings have demonstrated the need for sleep after learning to consolidate of memories [Walker and Stickgold, 2004, 2006]. Moreover, learning and memory depend on brain plasticity processes, and sleep-dependent learning and memory consolidation must be mediated by such processes [Walker and Stickgold, 2004, 2006]. Significant cognitive impairments are usually found in young and elderly people suffering from MDE [Castaneda et al., 2008]. Despite different study results, cognitive impairments during depression include executive dysfunctions, attention deficits, short-term and working memory impairments in both verbal and visual tasks, psychomotor skill deficits, verbal memory deficits, and learning functions impairments [Castaneda et al., 2008]. In relation to our results, authors argue, as a randomization process, that these modifications in the functional brain connectivity during sleep could have a part in these cognitive dysfunctions that are classically observed in acutely depressed patients.

Neuronal Networks and the Depressive Disease: Implications of the Network Hypothesis of Depression

The view of mood disorders as a problem of neuronal networks and information processing in the brain has several important implications [Castrén, 2005]. Neuronal networks develop through interactions with the environment, and neurotransmission in these networks are constantly being refined through activity-dependent synaptic plasticity to optimal process and store relevant information [Katz and Shatz, 1996]. Like other brain diseases, depression may represent disturbances in the activity-dependent information processing of the brain rather than the chemical balance of signaling molecules [Castrén, 2005; Fingelkurts et al., 2007]. Perhaps, the most important evidence for this hypothesis is the recent observation that antidepressants increase the production of new neurons in the rodent hippocampus [Malberg et al., 2000]. Newly generated neurons differentiate over time and are only mature enough to participate in information processing several weeks after birth [van Praag et al., 2002]. The fact that this time course correlates with the delayed onset of the clinical effects of antidepressants has created a lot of excitement among neuropharmacologists [Castrén, 2005]. Antidepressants may facilitate optimization of cerebral connectivity by (i) increasing the choice of neurons available for selection through activity-dependent mechanisms [Castrén, 2005], (ii) stimulating the turnover of axonal branches and synaptic contact (thereby providing more material for activity-dependent selection), and (iii) activating the neurotrophin signaling as a brain-derived neurotrophic factor [Castrén, 2004]. Analogously, psychological therapies (psychotherapy, cognitive behavioral therapy, etc.), electroconvulsive shock treatment could also have therapeutic effects on mood disorders through use-dependent neuronal plasticity [Castrén, 2005]. In this scenario, a combination of drug treatment and psychological rehabilitation would be expected to be more beneficial than either treatment alone [TADS, 2004]. As the network hypothesis emphasizes the importance of environmental information in the process of activity-dependent selection of neurons and synapses, it predicts that full recovery would not even be possible with drug treatment alone, but that external stimuli, such as social communication, would be required to provide environmental input for the selection of the appropriate network connections [Castrén, 2005].

Through the different data that are summarized above, it is clear that there is some evidence that antidepressants activate plasticity processes, which are thought to gradually improve information processing in the neural networks that are involved in different brain functions such as sleep and mood regulation.

Through functional brain network models, our study argues for considering MDE as a problem of neuronal networks and a problem of information processing as well.

CONCLUDING REMARKS AND PERSPECTIVES

Limitations of this study are primarily related to methodology. First, major depression is a heterogeneous syndrome, and other sources of variance may exist within patients (e.g., severity, atypicality, seasonality, number of previous episode, etc.). Second, by excluding patients with more serious forms of psychiatric comorbidity, our conclusions should be interpreted with care. Third, the sample size and the psychopathological assessment of the subjects did not allow for stratifying the patient sample by depres-

sive subtypes. Replicating our study in a larger group is clearly required in order to further examine the neurophysiological aspects that were revealed in this study. Finally, confirming our findings will have to await a more complete understanding of the neural network dynamics in healthy subjects and patients suffering from several neuropsychiatric diseases.

In summary, this study provides further support for the presence of small-world features in functional networks in the brain during sleep stages. Patients suffering from acute depression have significantly shorter path lengths in their EEG graphs, even after correcting for differences in the mean level of synchronization. This suggests a disruption in effective interactions between and across cortical regions, and provides further support for the concept of depression as a disconnection disease.

Recent reports show that many (but not all) functional abnormalities found during a depressive episode recover after pharmacological or psychotherapeutic treatment [Austin et al., 2001; Castrén, 2005]. Future studies should establish whether the functional connectivity of the sleep EEG increases with recovery after a depressive episode or whether impaired functional brain connectivity represents trait abnormalities.

Finally, understanding how more complicated neuronal network topologies influence both human behaviors and also mental disorders represents one particularly important challenge that needs to be tackled as the mathematical study of neuronal networks advances.

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