Altered structure of dynamic 'Electroencephalogram oscillatory pattern' in major depression

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Abstract

Research on electroencephalogram (EEG) characteristics associated with major depression disorder (MDD) has accumulated diverse neurophysiological findings related to the content, topography, neurochemistry, and functions of EEG oscillations. Significant progress has been made since the first landmark EEG study on affective disorders by Davidson 35 years ago. A systematic account of these data is important and necessary for building a consistent neuropsychophysiologic model of MDD and other affective disorders. Given the extensive data on frequency-dependent functional significance of EEG oscillations, a frequency domain approach may reveal the types of brain functions involved and disturbed in MDD. In this review, we systematize and integrate diverse and often unconnected observations on the content, topography, neurochemistry, and functions of EEG oscillations involved in MDD within the general concept of an "EEG oscillatory pattern".

Key Words: electroencephalography (EEG), oscillatory patterns, major depression, anxiety, spectral power, brain connectivity, interhemisphere asymmetry, transcranial magnetic stimulation (TMS).

Introduction

The electroencephalography (EEG) still remains one of the principal methods for extracting information from the human brain noninvasively. Recent research shows that neuro-psychopathologies such as epilepsy, Alzheimer disease, schizophrenia, depression, obsessive-compulsive disorder, traumatic brain injury, attention-deficit/hyperactivity disorder, and some learning disabilities are associated with specific *oscillatory patterns* in spontaneous EEG and that these oscillatory patterns provide reliable markers of brain (dys)function (1-3). Given that depression is one of the most frequent mental disorder diagnoses in the general population (4) and its considerable economic burden to family members and society (5), the focus of this review is on EEG oscillatory pattern in major depression disorder (MDD).

Since Davidson's EEG study on affective disorders, research on EEG characteristics associated with MDD has yielded a great deal of data. This suggests the need to develop a general framework that would allow researchers to handle the enormous amount of diverse observations related to EEG characteristics in MDD. Therefore, the aim of this review is to organize systematically accumulated observations related to the EEG into a descriptive and comprehensive overview of the structure of the dynamic EEG oscillatory pattern in MDD.

Converging lines of evidence suggest that many EEG characteristics in MDD are altered (6-43). These results have been repeatedly demonstrated and replicated in large samples with 72–93% sensitivity and 75–88% specificity (2) for detection of MDD. How are these EEG characteristics expressed in MDD?

We suggest that a general concept of *EEG oscillatory pattern* can be useful to systematize diverse observations related to EEG characteristics in MDD. The *EEG oscillatory pattern* may be considered as a spatio-temporally organized superposition of multiple EEG oscillations in many frequency bands (44) where different oscillations are mixed in varying proportions, based on the vigilance level; perceptual, cognitive, and mental operations; or extent of pathologic process. *EEG oscillations* in their turn are rhythmic electrical events in the brain that emerge from the interaction of large populations of neurons and can be observed on several temporal scales (44-48). It is suggested that the oscillatory activity of neuronal pools, which is reflected in characteristic EEG rhythms, constitutes a mechanism by which the brain can regulate changes of a state in selected neuronal networks and cause qualitative transitions between modes of information processing (46).

Capitalizing on these observations, one could unite different EEG descriptors within EEG oscillatory pattern, which is characterized by (a) *frequency content*: composition of

delta (0.5-3Hz), theta (3-7Hz), alpha (7-13Hz), beta (13-30Hz) and gamma (30>Hz) EEG oscillations along with their percent ratio, and (b) *spatial heterogeneity* (expressed in spatially structured extracellular electric field): spatial complexity (amount of brain connectivity), inter-hemisphere asymmetry, and hubs (cortex areas with highest MDD effect or highest functional connectivity). In the following sections, we describe each attribute of the EEG oscillatory pattern for MDD.

Importance of resting-state condition

Studies of the closed-eyes resting state provide an important opportunity to examine EEG oscillatory patterns unbiased by any task. Indeed, the resting-state condition avoids the confounding effects of visual scenes, instructions, and task execution (i.e., capability to perform a task and strategies employed, motivation or lack of it, fatigue and anxiety associated with task performance). Additionally, resting state seems more self-relevant than standard cognitive tasks, which typically activate numerous cognitive processes and drive subjects to direct their attention away from their personal concerns (49). The resting-state condition thus permits assessment of "pure" self-relevant brain activity (50). This activity reflects spontaneous processing of an internal mental context (top-down processing) (51), such as random episodic memory (52) and related imagery (53), conceptual processing (54), stimulus-independent thought (55), self-reflection, internal "narrative," and "autobiographical" self (56-58). Therefore, the frequently expressed concern that unconstrained brain activity varies unpredictably does not apply to the passive resting-state condition of the human brain. Rather, it is intrinsically constrained by the default functionality of the resting-state condition (59). Moreover, all unstructured features of the resting mental state that do not systematically relate to MDD would cancel out when averaged between different subjects. Hence features of the resting-state condition associated with MDD would stand out because MDD is the only common feature among all subjects. Indeed, abnormalities of resting-state characteristics such as self-referential processing, increased self-focused thinking, and analytical self-focused rumination contribute to the manifestation of MDD (for the review see 60).

Based on this logic we consider abnormality in a closed-eyes resting-state EEG in a patient with MDD to be a core feature. In this context, alteration in the closed-eyes resting-state EEG oscillatory pattern in MDD may constitute a tonic component of EEG

microstructural organization that can serve as the field of action for abnormalities governed by multiple causalities.

Frequency content of EEG oscillatory pattern in MDD

Composition of EEG oscillations

The EEG oscillatory patterns in both MDD and healthy condition are predominantly characterized by the same EEG oscillations in multiple frequency bands (delta, theta, and alpha), several of which are superimposed. However, only MDD is characterized by unique EEG oscillations in beta frequencies that are dominant in relation to delta, theta, and alpha (32). Although healthy subjects have beta oscillations, the oscillations are never dominant in relation to delta, theta, and alpha during resting-state condition. In contrast, an EEG from a patient with MDD is characterized by several episodes where coherent beta oscillations are dominant in relation to other oscillations (32).

Despite the fact that MDD and healthy condition are mostly characterized by the same dominant EEG oscillations, these conditions differ from one other by the percent ratio of these EEG oscillations.

Percent ratio of EEG oscillations

Comparative analysis demonstrated that patients with MDD had more (in amplitude/power) frontal theta, global alpha, and beta oscillations and fewer occipital-parietal theta and global delta oscillations than controls subjects without depression (1,6,8,10,11,13,18,19,22,23,29,31, 32,37,38,41,61-66). Some studies demonstrated an increase of delta power in MDD (8,37,67,68).

Advanced analysis of frequency content of EEG oscillatory patterns revealed that MDD differed from healthy condition not only by amplitude or power of oscillations but also by the probability for the occurrence of particular brain oscillations: some oscillations were more (alpha, beta, and frontal theta) or less (delta and occipital-parietal theta) probable for MDD than for healthy condition (32)[1]. These MDD effects were observed across the whole or major part of the cortex. In fact there was not a single EEG channel without a statistically

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[1] Although these results are based on one study (32) with relatively small samples, they are consistent with amplitude/power data obtained in other studies (1,6,8,10,11,13,18,19,22,23,29,31,37,38,41,61-66). Further study should be directed at replicating findings from this study (32) in larger samples.

significant difference in the relative presence of multiple EEG oscillations between patients with MDD and healthy subjects (32).

The importance of theta, alpha, and beta oscillations for MDD is supported by the facts that (a) widespread frontal-theta excess relates to nonresponsiveness to antidepressant treatments (69-71), whereas frontal-midline theta excess is associated with a favorable treatment outcome (72); (b) alpha excess is associated with a favorable response to antidepressant treatments (73) that decreases alpha power (74); and (c) beta oscillations correlate positively with relapsing depression (75) and number of depressive episodes (76) and have discriminative power to separate patients with MDD from healthy control subjects (77).

Considering that different EEG oscillations reflect functionally different components of information processing acting on various temporal scales (78-80), it is possible to map EEG oscillations onto mental or behavioral states (81). For the functional significance of the altered EEG oscillations in MDD see **Supplement-S1** in the end. It seems that manifestation of particular composition of EEG oscillations within multiple frequencies in MDD may reflect the involvement of particular brain functions in this psychopathological process (**Supplement-S1** in the end). Therefore discrepancies of findings from EEG-based measures may reflect different underlying mechanisms and functions and point to the existence of different subgroups within MDD that are not represented within diagnostic systems such as DSM-IV and ICD-10 (82)[2].

Because EEG-oscillations are homeostatically regulated and primarily generated by post-synaptic potentials, they are often sensitive to functioning of particular neural circuits and to alterations in neurotransmission secondary to brain dysfunction. Therefore, distinct aspects of pathophysiological mechanisms of MDD may be elucidated depending on which EEG oscillations or their combinations are altered in EEG oscillatory pattern during MDD. In this context, observed abnormal representativity of theta oscillations in MDD may relate to limbic-cortical pathways changes (83), atrophy in the hippocampus (84), norepinephrine and serotonin deficiency (85,86), and increased corticotropin-releasing hormone (87) that are often observed in MDD. Likewise, structural, neurochemical, and functional anterior cingulate cortex (ACC) abnormalities in MDD (88-90) have been related to altered theta oscillations (91). Indeed, the ACC is involved in conflict monitoring, error detection, and

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[2] Some methodologic aspects (most common is the choice of reference electrode) may also contribute to the diversity of findings. However, close inspection of this issue revealed that it is more a theoretical than practical possibility when it comes to 10-20 EEG montage (for a discussion see **Supplement-S2** in the end).

evaluation of the emotional significance of stimuli – functions that evoke theta activity (92). Hence, altered theta activity may reflect disrupted functional connectivity in frontal-cingulate pathways mediating emotive regulation in MDD (27). This supposition is strengthened further by fact that theta activity localized in the ACC is useful in predicting antidepressant treatment response (93).

Since theta and slow-alpha (7-10Hz) oscillations represent the activity in the thalamo-cortical network and fast-alpha (10-12Hz) oscillations reflect the activity in the cortico-cortical networks (47,94), the fact that MDD affects theta, slow-alpha, and fast-alpha oscillations suggests that MDD may alter the activity in both thalamo-cortical and cotico-cortical circuits. Indeed, it was demonstrated that the activity in thalamo-cortical circuits and thalamus is affected in MDD (95,96).

Thus, one can speculate that the observed departure from normal composition of oscillations in the ongoing EEG in MDD may reveal not only dysfunction of specific neural circuits but also an imbalance in monoamines and neuropeptides (74,97,98).

Taken all of the above-discussed information together, it is suggested that MDD affects brain activity in nearly the whole cortex and manifests through considerable reorganization of the composition of EEG oscillations and their percent ratio over a broad frequency range of 0.5-30Hz. These EEG oscillations are "mixed" or superimposed in proportions that depend on the specific monoamine/neuropeptide and neural circuit disturbance and on the presence of varied symptoms and affects.

Spatial analysis revealed that different cortical areas are characterized by varying number of EEG oscillations with a statistically significant difference in their relative presence in EEG oscillatory pattern (32), thus suggesting *spatial heterogeneity* of EEG oscillatory pattern during MDD.

Spatial heterogeneity of EEG oscillatory pattern in MDD

Different cortex regions have different dominant EEG oscillations (99,100) that act as resonant communication networks through large populations of neurons (for reviews, see 79,101). That is, cortical oscillators communicate only with oscillators that have specific resonance frequencies (102). They do not communicate with oscillators that have non-resonant frequencies even though there might be synaptic connections between them. Thus, various assemblies of oscillators can process information without any cross-interference. Therefore, by changing the frequency content of bursts and subthreshold oscillations, the

brain determines communication at any particular moment (103). These oscillatory systems may provide a general communication framework parallel to the morphology of sensory networks (79).

It has been suggested that the disturbed synchrony in distributed EEG oscillations may reflect dysfunction within resting-state networks in MDD (31-33).

Spatial complexity (amount of brain connectivity)

Decreased complexity of EEG oscillatory pattern in MDD (104,105) is a proxy for increased functional interdependence of brain processes. Indeed, numerous highly significant connections across all frequency bands showed higher functional connectivity in MDD compared with healthy subjects (33,42,106). These differences were most notable in theta, alpha, and beta oscillations. For functional significance of these findings, see **Supplement-S3** in the end.

In summary, MDD can be conceptualized as a syndrome of thalamo-cortical dysrhythmia (25,66) with limbic hyperactivity and prefrontal hypoactivity (107) marked by persistent resonance of theta and alpha oscillations. This thalamo-cortical dysrhythmia is manifested in an inadequate relationship between multiple structures and functions of the brain. Also, in light of the above-mentioned findings, an overall increase in brain functional connectivity during rest suggests that patients with MDD tend to expend energy in a potentially excessive or inefficient neural processing manner. This view is consistent with the modern concept of brain and mind disorders, where the disease is considered to be a process with a change in the *balance* of autonomy (low functional connectivity) and connectedness (high functional connectivity) of different brain systems that sustains health (108,109). The alteration in brain functional connectivity therefore might serve as a contributing factor to the *disorganization syndrome* (110) (see **Supplement-S4** in the end).

Inter-hemisphere asymmetry

Findings suggest that resting EEG oscillatory pattern in MDD with relatively less left than right frontal activity (inferred by relatively more left than right alpha oscillations (111)) appears to characterize depressed individuals both when symptomatic (12,112) and during normothymic periods (112,113) as well as subclinically depressed individuals with high scores on the Beck Depression Inventory (BDI) (7), and likewise healthy men with high BDI scores (114). Additionally, adolescents with suicidal tendencies (115), children and adults with low sociability scores (116), infants of depressed mothers (117,118), shy individuals

(119), individuals with higher cortisol levels (120), and individuals with lower levels of natural killer cells activity (121) all have the same type of frontal asymmetry. Collectively, these findings reveal that frontal alpha asymmetry is not specific for MDD; however, individuals with relatively less left than right frontal activity have mental, cognitive, and immunophysiologic profiles that together represent a *vulnerability to negative affect* (withdrawal-related emotions (122)).

Often relatively more alpha oscillations in the right-posterior (parieto-temporal) region are reported in adolescents or adults with MDD and in close genetic relatives (children and grandchildren) of patients with MDD (20,24,123). According to Henriques and Davidson (113), this parietal asymmetry may correlate with poor orienting and social skills deficit. Heller *et al*. (124) hypothesized that parieto-temporal activity plays a key role in the *arousal dimension of emotion*. In this context, MDD not only involves frontal asymmetry (*valence dimension of emotion*) but also decreases right-parieto-temporal activity associated with low emotional arousal.

Anxious apprehension and anxious arousal, which are often comorbid symptoms of MDD, are reflected in EEG asymmetries as relatively greater left frontal and right parietal activity, respectively (124,125) (Fig. 1). Individuals with symptoms of both depression and anxiety are likely to show right-sided activation in both frontal and parietal scalp regions (20,126) (Fig. 1).
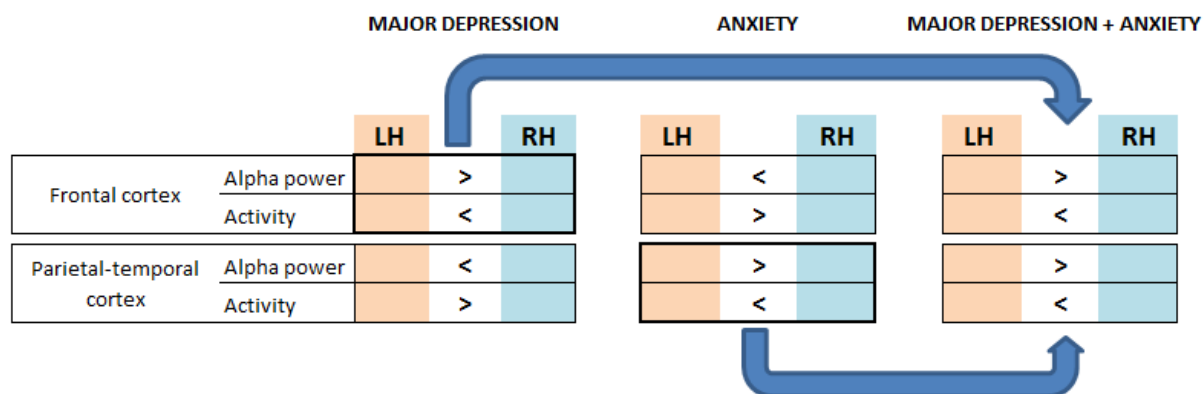

Figure 1. **Schematic representation of alpha interhemisphere asymmetry for major depression (MDD), anxiety and major depression with comorbid anxiety**. LH = left hemisphere, RH = right hemisphere.

To summarize, MDD is associated with an inter-hemisphere imbalance where frontal right hemisphere (RH) and parieto-temporal left hemisphere (LH) are hyperactive (39) (Fig. 1). Considering the known predominant functions of the LH and RH (Fig. 2, see also 35,39), the observed inter-hemispheric imbalance in MDD is not surprising.

It seems that MDD *increases* inter-hemisphere brain asymmetry (32) and *changes it* from relatively left-sided dominance (which is species-specific for humans – healthy subjects demonstrate greater alpha activity in the right hemisphere than in the left hemisphere (115)) – to strong frontal right-sided dominance.
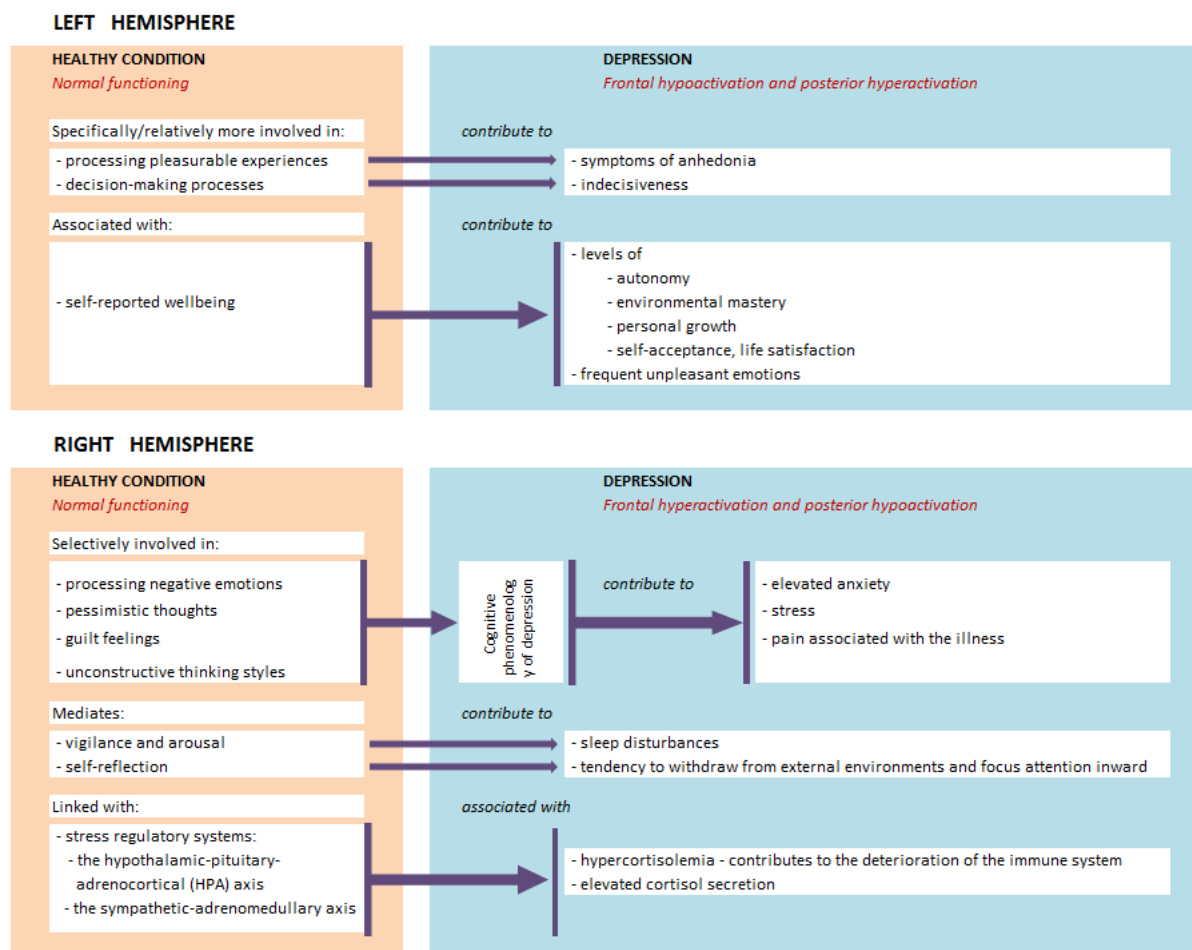

Figure 2. **Known predominant functional specialization of the brain hemispheres**. Functioning during normal condition and depression is illustrated. For detail description see (35,39).

Additionally, it was demonstrated that in MDD the number and strength of short functional connections were significantly larger for the LH than for the RH, whereas the opposite was true for long functional connections (33). These data may be interpreted within the *semantic context* model of MDD (33,127). Considering known functions of LH and RH within a semantic context framework (Fig. 3), in MDD neither hemisphere is able to deal with information in an appropriate manner (128), and as a result both hemispheres become informationally activated or overloaded (127). This situation may be interpreted as some level of functional insufficiency in both hemispheres during MDD (35). It was suggested that the unusual and significant increase in the number and strength of short-range functional

connections in the LH and the analogous increase in long-range functional connections in the RH are signs of *adaptive compensation* of the brain for functional insufficiency as the brain tries to achieve an adequate semantic context during MDD (33). As a result of such overcompensation, connections between neuronal representations of negative affects and semantic concepts are likely to be made. This hypothesis found indirect confirmation within a semantic network model (129) in which both semantic and affective features were represented as nodes in the network. It was found that people with depression experience strongly activated connections between negative affective nodes and multiple semantic concepts, creating feedback loops that maintain depressive affect and cognition (130). Increased functional connectivity in the brain may be a possible mechanism underlying this model. Patients with depression tend to see even positive information as negative because it becomes associated with personally relevant negative information (128). Indeed, an automatic, unintentional use of negative social constructs in self-perception was reported in patients with depression (131).
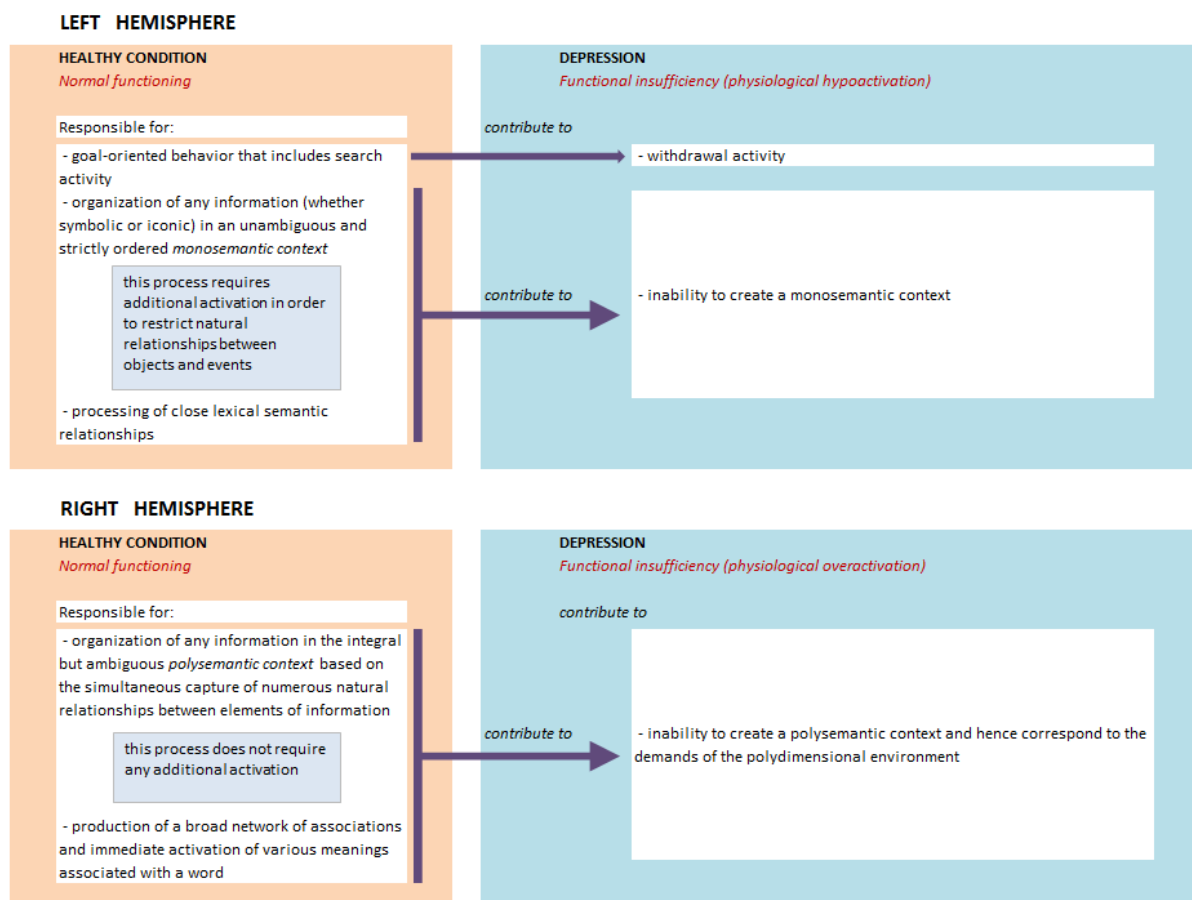

Figure 3. **Framework of major depression being based on semantic context model** (33,35,127). Functioning during normal condition and depression is illustrated.

Combining the above-mentioned observations suggests that either of the two hemispheres could be affected by MDD (32), but abnormal EEG sources can be found more frequently in the right hemisphere, with the maximal abnormal inverse solution at the alpha and theta bands in the frontal and parietal cortices (38). Thus, the observed inter-hemisphere asymmetry of EEG oscillatory pattern points at two MDD hubs (cortex areas with highest MDD effect or highest functional connectivity): (a) the *anterior region* – associated with *valance/motivation dimension* and (b) the *posterior region* – associated with *arousal dimension* (41).

Cortical hubs

Converging evidence suggests that MDD is characterized by two hubs: *anterior* and *posterior* (32,33,42). Indeed, the most representative and stable topologic combinations of functionally synchronized areas were located in the right frontal and left parietal-occipital cortex poles (33), which were hyperactivated in MDD (132).

Anterior hub. In MDD, higher theta and alpha coherence tended to be expressed in long-distance connections between frontopolar or dorsolateral-prefrontal cortical (DLPFC) regions and temporal or parietal-occipital regions, and higher beta coherence tended to be expressed in connections within and between DLPFC or temporal regions (42). Additionally, the frontal cortex had the largest number of short-range functional connections for alpha and theta oscillations that were related to MDD severity (33).

Posterior hub. The parietal/occipital cortex areas were maximally affected by MDD – the number of EEG oscillations that demonstrated statistically significant difference in their relative presence in EEG oscillatory pattern reached up to 72% between patients with MDD and healthy subjects (32). Additionally, the posterior cortex had the largest number of short-range functional connections for alpha oscillations that were related to MDD severity (33). Involvement of the posterior hub indicates that patients with MDD may have increased arousal (133) expressed as increased activity in right posterior region (Fig. 1) and may reflect a prolonged stress and may serve as a background for development of psychopathology. This idea is supported by the fact that the posterior cortex was characterized by beta oscillations (among others) in MDD but not in healthy condition.

The fact that MDD hubs are located not only in the frontal region but also in other parts of the cortex suggests that the frontal areas do not mediate depression; rather, they moderate activity in other parts of the neurocircuit that control the primary emotional response owing to extensive anatomic connections (32,33). One may suppose that the

particular topography of functionally connected cortical areas reflects the convergence cortex zones that are simultaneously active and that together are likely to be responsible for MDD. The described hubs roughly correspond to cortices that are supposed to be responsible for modality specific sensory patterns, for implicit memories (autobiographical self), and for relationships between categories and abstract concepts (134). This distributed network for semantic and conceptual information seems to be significantly altered in MDD (33,135).

Specificity and causality of EEG oscillatory pattern in MDD

Differences between EEG oscillatory patterns in MDD and bipolar depression (Fig. 4) and some other mental disorders (1,2,136-142) suggest that certain characteristics of the EEG oscillatory pattern may be specific to MDD.

Characteristics of EEG oscillatory patterns	Typology	Major depression	Bipolar depression
Delta oscillations	global	⬇	⬆
Theta oscillations	global		⬆
	frontal	⬆	
	parietal-occipital	⬇	
Alpha oscillations	global	⬆	⬇
Beta oscillations	global	⬆	⬆
Synchronization	global	⬆	⬇
Interhemisphere asymmetry	frontal alpha	L > R	L < R

Figure 4. **Comparison of EEG oscillatory patterns for major depression and bipolar depression**. See references (32,33,136-142).

Indeed, some characteristics of the EEG oscillatory pattern in MDD demonstrated high *specificity* (33): the number and strength of short-range anterior and posterior functional connections were proportional to MDD severity. Short-range left functional connections were also related to MDD severity; this was observed for the alpha oscillations.

In contrast to the alpha oscillations, within theta oscillations, only the anterior short-range functional connections (number and strength) were associated with MDD severity (33). It is possible to interpret this finding in light of the fact that cortical frontal theta activity is mostly determined by activity of the limbic system and the ACC in particular (27). In this respect, increased functional connectivity within the theta frequency in the anterior cortex may be a sign of an adaptive, compensatory reaction to the decreased ACC activity and general insufficiency of the limbic-system typically reported in MDD (143).

Based on these findings, we may conclude that anterior short-range functional connections within theta oscillations as well as short-range anterior, posterior and short-range left functional connections within alpha oscillations seem to play an important role in the pathogenesis of MDD and its severity.

Nonlinear integration of MDD-specific EEG pattern parameters (amount and strength of alpha band functional connectivity) with EEG nonstationary features such as the overall topological pattern of the EEG quasi-stationary segment distribution, their power and duration (109) has enabled researchers to design an index (Factor-D) that correlates with MDD and its severity independent of subjective self-reports and impressions by patients and physicians. Such an index is especially important in cases in which patients are severely compromised and non-communicative, such as patients with advanced dementia, in vegetative or minimally conscious states, with locked-in syndrome, or during early recovery from serious brain injury (traumatic brain injury, stroke, anoxia, neurologic infection). The exact weightings used in the Factor-D index have been determined by correlating relevant EEG parameters with Hamilton Depression Scale (HAM-D), clinical impressions, and subjective patient reports.

Factor-D index has been tested in two independent patient populations of different nationality (drug-free (*n*=12) and medication-resistant (*n*=22) patient groups). The index scores remained stable despite variability in the patient groups, which proves the reliability of the index. Sensitivity of the Factor-D index was 82.35% (95% CI: 56.55-95.99), and specificity was 100% (95% CI: 47.95-100).

If the MDD-specific EEG oscillatory pattern does indeed constitute the neurophysiological mechanism for a depressed state, then forceful modification/normalization of this EEG oscillatory pattern by exogenous magnetic field stimulation should dramatically change the subjective experience of depression. By causally interfering with the brain electrical field, exogenous magnetic field stimulation allows researchers to determine the true functional significance of altered EEG oscillatory pattern in

MDD and causal inferences about its role in the pathogenesis of depression. The *causality* of the EEG oscillatory pattern in MDD can be demonstrated directly through repetitive transcranial magnetic stimulation (rTMS), which enables changes in ongoing cortex activity. It was demonstrated that MDD severity decreased clinically in patients with MDD after high-frequency rTMS over the left DLPFC and/or low-frequency rTMS over the right DLPFC (see reviews 144,145).

In the study, in which researchers applied the EEG-derived Factor-D index to measure severity of depression in medication-resistant patients (*n*=22) before and after rTMS[3], aiming to normalize the distorted structure of the EEG oscillatory pattern, it was shown that rTMS-induced significant normalization of EEG oscillatory pattern caused a significant normalization of subjectively experienced depression symptoms (>50% reduction in HAM-D scores in 60% of patients) to full remission (HAM-D scores <7 in 33% of patients) (146). The action of rTMS may be through entraining oscillations to the stimulation frequency, thus resetting cortical and thalamo-cortical oscillators and facilitating the re-emergence of normal, intrinsic oscillatory activity (147). Therefore, behavior may be affected through rTMS by biasing ongoing EEG and neural activity (owing to entrainment of EEG oscillations) related to specific cognitive processes (148).

To summarize, rTMS entrains and resets thalamo-cortical oscillators, which facilitates the re-emergence of intrinsic cortical rhythms and normalizes their composition, percent ratio, and temporal and spatial interrelations (147,148). Through this mechanism, normal brain activity and mental functions are restored, supporting the *causal role* of the EEG oscillatory pattern in MDD.

Conclusions

In the context of this review, MDD might be considered to be a disorder of distributed large-scale cortical (and subcortical) systems that are functionally connected in the frontal, temporal, parietal and occipital lobes (16,149) with the signal transmission in multiple resonant-frequency channels – EEG oscillations (44). These multiple regions form an

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[3] 1500 pulses of low-frequency (1Hz) rTMS were applied over the sites discovered to be optimal for every patient within cortical hub-A, followed by 3000 pulses of high-frequency (10Hz) rTMS over the sites discovered to be individually optimal within cortical hub-B with intensity 120% of motor stimulation threshold. During all 10 sessions, each patient received of 15,000 pulses of low-frequency rTMS and 30,000 pulses of high-frequency rTMS.

interconnected and self-sustaining distributed neural network that displays pathologic patterns of neurotransmission and altered EEG oscillations across 0.5-30Hz.

The symptoms and severity of MDD hinge on the imbalance of monoamines and neuropeptides, the type and input (external or internal) of affect, and additional physiologic and cognitive demands that are expressed in an altered EEG oscillatory pattern. In this sense, MDD is characterized by a certain altered distributed EEG oscillatory pattern that presents a *new stable state* of altered brain activity (80) that according to Olbrich and Arns (82), "might reflect a rigid and less flexible CNS [central nervous system] that leads to impaired behavioral adaption of the whole organism to the requirements of its environment in MDD" (see also 150).

In this context, a constellation of different EEG characteristics united within EEG oscillatory pattern should be considered more appropriate for diagnostic and medication-response purposes. However, before *EEG oscillatory pattern* can be implemented in clinical practice, more blinded, prospective multicentre trials examining reliability, sensitivity, and specificity are needed.

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Supplemental Information

S1. Functional Significances of the Altered Electroencephalographic Oscillations in Major Depressive Disorder

Based on known functional significance of different electroencephalographic (EEG) oscillations (1-3) and known alterations of EEG oscillations in major depressive disorder (MDD) (see present review) it is possible to anticipate which types of brain functions are involved and disturbed in MDD (4). Below we present functional significance of the altered EEG oscillations in MDD.

Information processing and memory

Theta activity may serve as a gating function on information processing flow in limbic regions (5), as well as a reflection of the encoding and retrieval from memory (6). At the same time, delta oscillation is related to signal detection (7). All these suggest that decreased delta and parietal-occipital-theta oscillations in MDD (8) may be signs of impaired information processing and decreased working-memory load (9), decreased quantity of engrams decoded from the memory (10), altered encoding with reduced retrieval (11), and decreased cerebral metabolism in the areas which are expected to be regulated by the limbic system (12). The stimulus-independent thoughts taking place during eyes-closed wakeful rest are characterized by a large degree of functional integrity over time, in the sense that information at various stages is linked throughout and that requires memory (13).

This view is supported by the following converging observations: (a) The results from 726 patients with MDD and 795 healthy controls revealed that MDD had the largest effect on encoding and retrieval from memory (14). (b) Dopamine deficiency also contributes to altered encoding, since dopamine has been shown to be important in information encoding with respect to prediction, evaluation, and occurrence of reward (15). (c) Williams *et al.* (16) proposed that depression is characterized by a bias in memory for negative information (17). Furthermore it was demonstrated that depressed individuals remember negative information better than positive information (18,19).

Additionally, increased alpha oscillations during MDD (8) support the deactivation of cognitive and perceptual processes, and altering of stimulus encoding, which was shown for alpha synchronization by Klimesch (6).

Attention

In humans, frontal-theta oscillations have been linked to alert states characterized by focused attention (7,20,21). Thus, the increase of frontal-theta oscillations in MDD (8) may reflect the involvement of focused attention in depression. This view is in line with the research showing that depressed individuals selectively attend to negative information over positive information (22,23). Such attentional bias has been shown consistently for patients with MDD (24).

Alertness and anxiety

A decrease in posterior-theta oscillations has been associated with increased alertness (20). Thus, more posteriorly distributed decrease of theta oscillations during MDD (8) may reflect

increased alertness. Such alertness may contribute to comorbid anxiety that feeds into an attentional bias towards threat-relevant stimuli (16). The involvement of anxiety symptoms to MDD may be supported by the increase of beta (25,26) and alpha (27,28) oscillations. Additionally, the increase of beta and fast-alpha oscillations during MDD may be indicative of increased alertness and increased excitatory activity (29,30). Support for this supposition can be found in (31-34) who demonstrated that patients with MDD exhibited an increased tonic vigilance level quantified via increased beta activity.

Generalized blunted affect and anhedonia

Bilateral prefrontal increase of alpha oscillations reflects decreased activation in both the left and right prefrontal regions and is predicted to be associated with deficits in both the approach and withdrawal system, respectively, and as such, is likely to be associated with symptoms such as generalized blunted affect and anhedonia (35,36). Additionally anhedonia is associated with increased delta oscillations in rostral anterior cingulate cortex (37) and prefrontal cortex (38). It is possible that in those studies where an increase of delta power in MDD (39,40-42) was demonstrated, patients had anhedonia symptoms among others.

Thus, the manifestation of particular composition of EEG oscillations within multiple frequencies in MDD may reflect the involvement of particular brain functions in this psychopathological process.

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S2. Methodological Aspects of EEG-Based Measures

Regarding spectral measurements

A previous study (1) where spectral analysis was performed for the data collected from parallel and simultaneous registration of EEG (reference dependent) and magnetoencephalography (reference independent and with minimal influence of the volume conduction) revealed no difference neither in spectra, nor in spectra classes, nor in proportions between spectra classes (1). This suggests that results of spectral analysis were not influenced significantly by the reference electrode. This is due to the fact that reference choice influences magnitude of power spectra but not their shape (2,3). Moreover, it was shown that there is little effect of volume conduction on the shape of the spectrum below about 25 Hz and spatial filtering is significant only for frequencies above the major rhythms (4). Majority of MDD effects were shown below 25 Hz (see the main text).

Regarding connectivity measurements

Topographic measures are reference-independent. The shape of the electric field at the scalp will not change even if one chooses another reference (cf. Fig. 3 in (5)). Indeed the effect of a reference on the shape of a temporal EEG potential map is to add or subtract a constant value at all locations, like raising or lowering the water level in a landscape, without changing the overall shape (6). These two points suggest that the effect of reference on spatial aspect is not a crucial consideration. While there is some evidence that several different source configurations can generate the same distribution of potentials and electromagnetic fields on the scalp (for a review see (7)), the converse is also valid: different scalp topographies of electromagnetic fields must have been generated by different configurations of brain sources (5). Furthermore, although it is often claimed that volume conduction is the main obstacle in interpreting EEG data in terms of brain connectivity, the accuracy of topographic EEG mapping for determining local (immediately under the recording electrode) brain activity was experimentally shown with radioactive marker (8; for further argumentation see (9-11)). Further, experimental findings demonstrated that the probabilities of firing of neurons observed singly and in small groups simultaneously are in close statistical relationship to the EEG recorded in the near vicinity (12,13). Therefore the EEG can provide an experimental basis for estimating the local mean field of contributory neurons (14) located in cortical regions near the recording electrodes (15). Lachaux *et al.* (16) demonstrated that volume-conduction-induced spurious synchrony extended no further than 2 cm in normal brain tissue. In another study Nunez *et al.* (17) found that the effects of volume conduction on coherence between scalp electrodes had virtually no spurious coherence for separations of 4 cm or more between scalp electrodes. Convergence between the results of the several analyses is a good indication that the synchronization observed is not spurious, especially for electrodes separated by 4 cm or more (18). Additionally it has been shown previously through modeling experiments that in contrast to many other measures of functional synchrony, brain connectivity measure based on temporal coincidences of quasi-stationary EEG segments and used in (19) is sensitive to the morpho-functional organization of the cortex rather than to the volume conduction and/or reference electrode (for relevant details, see (20, 21)).

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S3. Functional Significance of the Increased Functional Connectivity Within Theta and Alpha EEG Oscillations in MDD

It has been suggested that the increased functional connectivity in mood regulating networks might be associated with impaired cognitive processing in MDD (1,2).

The fact that the most significant increases in functional connectivity were found for alpha oscillations could be interpreted as failure of the top-down control exerted by rhythmic alpha activity (3). This idea is supported by the facts that alpha rhythm is generated by the cortex under the influence of cortico-thalamic neuronal loops (4) and that at rest thalamic functional connectivity with the default mode network is significantly increased in MDD (2). Additionally, the modulation of brain connectivity in alpha oscillations has been linked with shifts in attention focus, working memory and executive demands (5,6), whereas beta oscillation modulation is related to response preparation and cognitive control (7). In this context a "pathological" increase in brain connectivity in alpha and beta oscillations may be associated with deterioration in cognitive flexibility and control, with MDD subjects more prone to attending internal thoughts.

Theta oscillations play a significant role in memory function (8) and processing emotional information (9). Therefore excessive brain connectivity in theta oscillations may reflect alteration in these functions. Indeed, negative mood typically co-occurs with poor memory and learning (10). Additionally, it was demonstrated that anxious rumination was associated with increases in brain connectivity in theta and alpha oscillations (11). It is likely that networks overloaded with emotional information processing have limited capacity to modulate synchronization in response to other processing demands (3).

In summary, MDD can be conceptualized as a syndrome of thalamo-cortical dysrhythmia (12,13) with limbic hyperactivity and prefrontal hypoactivity (14) marked by persistent resonance of theta and alpha oscillations.

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S4. "Disorganization Syndrome" and Alteration in Functional Connectivity in MDD

It has been suggested that the operational elements of behavioral and mental activity in norm are originated in the periods of short-term spatio-temporal patterns (metastable states) in the activity of the whole brain and its individual subsystems (see review (1)). In this metastable regime, the brain operates in a state that allows both integration and segregation of function (2,3): individual neuronal networks are dynamically balanced in their tendency to function autonomously and their tendency for coordinated activity (4). Together, these processes reflect the temporal and spatial organization of the brain.

The disruption in brain metastability and temporal dynamic is suggested as a contributing factor to the "disorganization syndrome" (which has long been deemed to be a

condition of impaired cognitive association) in many psychiatric and brain diseases (5,6). From this perspective, then, disorganization is viewed as a disorder of the metastable balance between large-scale integration and independent processing in the cortex, in favor of either independent (uncorrelated randomness expressed as low or no functional connectivity) or hyper-ordered (high functional connectivity) processing (4). In this context an overall increase in brain connectivity in patients with MDD during rest (7-9) suggests that these patients have a disorganization syndrome.

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