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Alterations of neural network organisation during rapid eye movement sleep and slow-wave sleep in major depression: Implications for diagnosis, classification, and treatment

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ABSTRACT

The aim of this study was to empirically investigate the network organisation during rapid eye movement sleep (REMS) and slow-wave sleep (SWS) using the effective connectivity measured using the Granger causality to identify new potential biomarkers for the diagnosis, classification, and potential favourable response to treatment in major depression. Polysomnographic data were analysed from 24 healthy individuals and 16 major depressed individuals recruited prospectively. To obtain the 19×19 connectivity matrix of all possible pairwise combinations of electrodes by the Granger causality method from our electroencephalographic data, we used the Toolbox MVGC multivariate Granger causality. The computation of network measures was realised by importing these connectivity matrices into the EEGNET Toolbox. Major depressed individuals (versus healthy individuals) and those with endogenous depression (versus those with neurotic depression) present alterations of small-world network organisation during REMS, whereas major depressed individuals with potential favourable response to electroconvulsive therapy (versus those with potential unfavourable response) have a less efficient small-world network organisation during SWS. Thus, alterations in network organisation during REMS could be biomarkers for the diagnosis and classification of major depressive episodes, whereas alterations of network organisation during SWS could be a biomarker to predict potential favourable response to treatment by electroconvulsive therapy.

1. Introduction

In psychiatry, neuroscience is increasingly used to enable a better understanding of mental illnesses. Among the neuroscientific methods, the study of networks is particularly interesting because it allows mathematical representation of complex biological, social, and informatics systems through modelling in the form of a set of nodes (vertices) and links (edges) between pairs of nodes (Newman, 2003). For each network, it is possible to determine two fundamental parameters (the characteristic path length corresponding to the minimum number of edges needed to establish a connection between nodes and the clustering coefficient corresponding to a measure of the topological clustering of edges between nodes) (Milgram, 1967; Watts and Strogatz, 1998) whose combination enables the classification of networks into three categories according to their specific characteristics: ordered (characterised by a high clustering coefficient and long path length), random (characterised by a low clustering coefficient and short path length), and small-world (characterised by a high clustering coefficient and short path length) (Stam, 2010).

At the cerebral level, the emergence of complex behaviours and optimal cognitive functioning seems to be associated with the presence of a small-world network (SWN) organisation (Bassett and Bullmore, 2017; Woods and Kheirbek, 2017) that promotes a rapid transfer and synchronisation of information as well as a balance between local processing and global integration via minimal wiring costs (Stam and Reijneveld, 2007). Indeed, in the presence of an SWN organisation, cognitive functioning seems to be more efficient (Vecchio et al., 2016), whereas alterations of the SWN organisation are associated with the occurrence of cognitive dysfunction (Sanz-Arigita et al., 2010; He et al., 2012; Jhung et al., 2013). To highlight SWN organisation, there are

Abbreviations: 24-HAM-D, 24-item hamilton rating scale for depression; AASM, American academy of sleep medicine; DSM IV-TR, diagnostic and statistical manual of mental disorders, fourth edition, text revision; ECT, electroconvulsive therapy; MVAR, multivariable autoregressive; REMS, rapid eye movement sleep; SWN, small-world network; SWS, slow-wave sleep

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several methods based on different types of connectivity: anatomical (based on the physical or structural connections between the various brain structures), functional (measuring the statistical dependence between distant cerebral structures and highly time-dependent), and effective (measuring the direct or indirect causal influences between two brain regions) (Sporns et al., 2004; Rubinov and Sporns, 2010). Among the methods used to investigate effective connectivity, the Granger causality is a time series application based on the following prediction: "If the predicted error on the first time series is reduced by including measurements of the second in a linear regression model, then the second temporal series has a causal influence on the first" (Marinazzo et al., 2008; Bressler and Seth, 2011). Furthermore, the absence of a lag between recorded responses and their underlying causes as well as the ability to sample the data in a timely manner make it possible to apply the Granger causality to electrophysiological time series (EEG or MEG) (Friston et al., 2013). Thus, given its compatibility with both segregated/specialised and distributed/integrated information processing, the SWN organisation seems to provide an attractive model to explain the organisation of brain anatomical, functional, or effective networks (Bassett and Bullmore, 2006).

In major depression, although SWN organisation at the cerebral level seems to persist during wakefulness, it is apparently less efficient due to the presence of alterations affecting the global properties of the network architecture (Zhang et al., 2011). Moreover, since the majority of studies have investigated network organisation only during wakefulness (Li et al., 2015; Long et al., 2015), there are scant data on the effect of major depression on sleep network organisation (Leistedt et al., 2009). However, there is a special relationship between major depression and sleep. Indeed, the majority of major depressed individuals have insomnia complaints (Mendelson et al., 1977), whereas insomnia sufferers have a higher risk of developing depression (Baglioni et al., 2011). Furthermore, in major depressed individuals, the polysomnographic pattern is characterised by rapid eye movement sleep (REMS) alterations (REMS increased, REM latency shortened, and REM density increased) as well as a deficit in slow-wave sleep (SWS), which were considered potential biomarkers for diagnosing major depression, to classify subtypes of major depression (endogenous/neurotic) and predict the potential response to antidepressant treatments (medicated or non-medicated) (Pillai et al., 2011; Kudlow et al., 2013; Göder et al., 2016; Voegeli et al., 2017). However, it has been demonstrated that these polysomnographic alterations are not specific to major depression (Baglioni et al., 2016), further justifying the electrophysiological study of sleep by investigating network organisation during REMS and SWS to highlight more specific biomarkers for the diagnosis, classification, and potential favourable response to treatment in major depressed individuals.

Our first hypothesis was that compared with healthy individuals, major depressed individuals had altered network organisation during REMS and SWS. Our second hypothesis was that among major depressed individuals, network organisation during REMS and SWS differed according to the subtypes of major depression (endogenous/neurotic) and potential response to treatment using electroconvulsive therapy (ECT). To confirm these hypotheses, we empirically investigated network organisation during REMS and SWS as well as for all EEG bands during these sleep stages using effective connectivity measured by the Granger causality in healthy and major depressed individuals. The aim of this study was to ascertain new research perspectives for the identification of biomarkers related to sleep for the diagnosis, classification, and potential favourable response to treatment of major depression.

2. Materials and methods

For a better understanding of this section, a glossary of terms more specific to neuroscience-related analyses is included in the Supplementary Data.

2.1. Population

This study included 24 healthy subjects and 16 major depressed individuals between January 2007 and January 2012. The healthy participants were recruited from the community by advertisements, and the major depressed individuals were recruited from the Mood Disorders Unit of Erasme Hospital's Department of Psychiatry.

On admission to the sleep laboratory at Erasme Hospital, the subjects were assessed during a systematic clinical interview by a unit psychiatrist and underwent from a complete somatic assessment (physical examination, chest X-ray, electrocardiography, electroencephalography, and laboratory tests, such as blood tests and urinalysis) by an internist for a systematic diagnosis of potential psychiatric, somatic, and sleep pathologies.

For the healthy participants, the specific inclusion criteria were the absence of an axis I or axis II disorder according to the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) (American Psychiatric Association, 2000), the presence of regular sleep-wake schedules, and the absence of current or past sleep disorders according to the diagnostic criteria of the American Academy of Sleep Medicine (AASM) (such as insomnia disorder, hypersomnia, parasomnia, sleep apnoea-hypopnea syndrome, or periodic limb movement disorder) (American Sleep Disorders Association, 2005). For the major depressed participants, the specific inclusion criteria were the presence of a major depressive episode without psychotic features according to the diagnostic criteria of the DSM-IV-TR (American Psychiatric Association, 2000), the absence of another axis I or axis II disorder according to the diagnostic criteria of the DSM-IV-TR (American Psychiatric Association, 2000), and the absence of current or past sleep disorders according to the diagnostic criteria of the AASM (except for insomnia disorder) (American Sleep Disorders Association, 2005).

The exclusion criteria for both healthy and major depressed participants were the presence of conditions or pathologies that may affect sleep (such as obesity, chronic liver disease, chronic pancreatic disease, chronic pulmonary disease, severe cardiovascular disease, severe renal disease, autoimmune disease, and pathologies with extreme changes of the activity of the hypothalamic-pituitary-adrenal axis such as Cushing's syndrome or Addison's disease), current or past use of somatic or psychotropic treatment that may influence sleep, and past or present substance abuse.

No drug weaning was necessary before the sleep examination since the healthy and major depressed participants were not undergoing treatment. The duration of the current episode of major depression was at least two weeks, meeting the diagnostic criteria of the DSM IV-TR (American Psychiatric Association, 2000).

2.2. Assessment of the severity and characteristics of the major depressive episode

The assessment of the severity and characteristics of the major depressive episode was conducted by a unit psychiatrist during a semi-structured interview based on the 24-item Hamilton Rating Scale for Depression (24-HAM-D) and the Newcastle Scale (Hamilton, 1960; Carney et al., 1965).

The 24-HAM-D assesses mood, somatic, and behavioural symptoms of major depression. It consists of items investigating frequent symptoms of major depression and items investigating particular clinical forms of major depression. Depending on the items, a higher score reflects either increased severity of the symptom investigated or the presence of a particular symptom. The higher the total 24-HAM-D score, the greater the severity of the major depressive episode (Hamilton, 1960).

The Newcastle Scale consists of a subscale investigating the subtypes of major depression (10 weighted items) and a subscale investigating the potential response to treatment by ECT (10 weighted items). For major depression subtypes, a score ≥6 indicates the presence of endogenous depression (induced by biochemical and/or genetic factors), whereas a score <6 indicates the presence of neurotic depression (induced by factors external to the individual). For potential response to treatment by ECT, a score ≥1 indicates a favourable response, whereas a score <1 indicates an unfavourable response (Carney et al., 1965).

2.3. EEG recordings and experimental conditions

All of the subjects included in this study underwent polysomnographic recordings within the sleep laboratory of Erasme Hospital during three consecutive nights. For our analysis, we used an "artefact-free night" from the last two nights recorded to avoid the "first night effect" on sleep parameters (Newell et al., 2012). However, in case of similar level of artefacts during these two nights, the night analysed was randomly selected. To enable the visual detection of these artefacts by our specialised technicians, we used Endymion software (Endymion 1993–2018, Sleep Laboratory, Erasme Hospital) developed at the sleep laboratory for data analysis (Hein et al., 2019a, b). The recording duration each night was a minimum of eight hours.

The healthy and major depressed subjects were instructed to respect their usual sleeping and waking hours, wake up spontaneously in the morning, turn off the lights during the hours spent in bed, refrain from consuming substances that may affect sleep (such as alcohol, coffee, or over-the-counter sleep aids), and avoid daytime naps during their stay at the sleep laboratory (Hein et al., 2017a).

The applied polysomnography montage (Alice 5 Respironics, Murrysville, PA, USA) was as follows: 19 electroencephalogram channels were placed according to the international 10–20 standard system with a contralateral reference to the A1 or A2 mastoid derivation, two electro-oculogram channels, one submental electromyogram channel, electrocardiogram, thermistors to detect the oro-nasal airflow (Infinity, Sleepmate Technologies, Midlothian, VA, USA), finger pulse-oximetry (Masimo MS-7, Irvine, CA, USA), a microphone to record breathing sounds and snoring, piezoelectric sensors to measure thoracic and abdominal breathing (Resp-EZ, Sleepmate Technologies), and ankle piezoelectric movement strain gauges to detect leg movements (Moving Images, Sleepmate Technologies). Specialised technicians visually scored the polysomnographic recordings to determine the different stages of sleep as classified by Rechtschaffen and Kales (1968).

All of the channels were sampled at 2,000 Hz-16 bits, whereas 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. Before downsampling, adequate analogue filters were applied to eliminate low-frequency artefacts, drifts, offsets, and aliasing. The data were exported to the EDF format using Alice Sleepware (Respironics). All of the subsequent analyses, such as stage determination and spectrum calculation, were carried out on the sampled data, avoiding synchronisation problems between the stages and the other calculations.

2.4. EEG signal analysis

In some of the study participants, it was impossible to obtain more than three 20-s epochs without artefacts (no eye blinks, slow eye movements, excess muscle activity, electrocardiogram artefacts, etc.) for REMS and/or SWS. In this context, we arbitrarily selected the first three 20-s epochs without artefacts for REMS and SWS in all of the subjects to investigate the network organisation of these sleep stages over an equal number of epochs. In addition, each selected 20-s epoch of REMS and SWS was divided into four 5-epochs (Hein et al., 2018). Moreover, this study not investigate network organisation during wakefulness given that it has already been documented in several reports on major depression (Zhang et al., 2011; Li et al., 2015; Long et al., 2015). Furthermore, since Leistedt et al. (2009) highlighted only alterations of the network organisation during REMS and SWS in their preliminary study, we focused on these sleep stages to facilitate a better understanding of the involvement of REMS and SWS in the pathophysiology of major depression.

2.5. The Granger causality

To obtain the 19×19 connectivity matrix of all possible pairwise combinations of electrodes via the Granger causality method from our EEG data, we used the Toolbox MVGC multivariate Granger causality developed for use under MATLAB (Barnett and Seth, 2014). This toolbox is based on a multivariable autoregressive (MVAR) data model. The mathematical developments used in the Toolbox MVGC multivariate Granger causality (model order estimation, MVAR model estimation, time domain analysis, and frequency domain analysis) are beyond the scope of this paper but are summarised in the Supplementary Data.

Since both the time and frequency domain causalities were obtained, we also calculated the time-domain causalities by integrating their spectral counterparts and ascertained that this frequency integrated value was not different from the time domain value. The frequency-based connectivity matrices were calculated for the following EEG bands: β (16–32 Hz), σ (12–16 Hz), α (8–12 Hz), θ (3–8 Hz), and δ (0.25–3 Hz) (Lanquart et al., 2018). These different analyses were performed separately for each subject included in our study. A comparison of our method based on the Granger causality with other methods in the literature is available in the Supplementary Data.

An example of the connectivity matrix obtained with the Toolbox MVGC multivariate Granger causality (Barnett and Seth, 2014) for the healthy and major depressed subjects in our sample is available (Supplementary Data, Figure 1).

2.6. Calculation of network characteristics

We imported the connectivity matrix obtained with the Toolbox MVGC multivariate Granger causality into the Toolbox EEGNET developed for use under MATLAB (Hassan et al., 2015) to determine the network organisation during REMS and SWS as well as for the different EEG bands during these sleep stages. Based on graph theory analysis, this software allows the computation of the small-world coefficient measuring the propensity of the network to have a small-world structure according to the method of Telesford et al. (2011) described in the Supplementary Data. Values of the small-world coefficient are restricted to the interval −1 to 1 regardless of the network size. Values close to zero, positive values, and negative values indicate a graph with more small-world, random, and regular characteristics, respectively.

2.7. Statistical analysis

Statistical analyses were performed using Stata version 14. The normal distribution of the data was verified using histograms, boxplots, and quantile-quantile plots. Since most of the data followed an asymmetric distribution, we used non-parametric tests for all of the variables, beginning with the Wilcoxon test to evaluate significant differences between the medians observed in different groups of individuals.

For comparisons between the healthy and major depressed groups, we adjusted our results to age because these variables did not match in our samples and because there are significant changes in sleep architecture and sleep network organisation depending on age (Ohayon et al., 2004; Hein et al., 2018). To enable this adjustment of our results to age, we used multivariate quantile regression models (based on the median). In these models, polysomnographic and network data were considered the dependent variables, whereas age was used as predictors to adjust the regression coefficient between the healthy and major depressed groups. Otherwise, no adjustment to age was made for comparisons between the subgroups of major depressed individuals because

Table 1
Comparison of demographic data and network characteristics during REMS and SWS between the different groups.

	Median (P25-P75) Healthy Group (N = 24)	Median (P25-P75) Depression Group (N = 16)	P-value	b_a(ES) Group "Depression" vs. "Healthy"	P-value adjusted for age
Demographic data					
Age (years)	29 (22—35.5)	43.5 (35–51)	< 0.001		
Hamilton scale	2 (1–3)	20.5 (18–27.5)	< 0.001		
Network characteristics					
REMS - Time domain					
SWC	0.049 (0.030–0.073)	0.090 (0.060–0.110)	0.006	0.057 (0.024)	0.020
SWS - Time domain					
SWC	0.005 (− 0.003–0.028)	0.007 (− 0.002–0.030)	0.912	0.002 (0.013)	0.904

	Median (P25-P75) Neurotic depression (N = 8)	Median (P25-P75) Endogenous depression (N = 8)	
Demographic data			
Age (years)	48 (39–53)	41 (35–47)	0.227
Hamilton scale	20 (18–27)	23.5 (16.5–28.5)	0.753
Network characteristics			
REMS - Time domain			
SWC	0.064 (0.048–0.088)	0.107 (0.090–0.130)	0.046
SWS - Time domain			
SWC	0.003 (− 0.002–0.011)	0.021 (− 0.006–0.038)	0.462

	Median (P25-P75) Potential unfavourable response to ECT (N = 10)	Median (P25-P75) Potential favourable response to ECT (N = 6)	
Demographic data			
Age (years)	42.5 (34–46)	50.5 (36–55)	0.175
Hamilton scale	20.5 (18–27)	23 (18–35)	0.664
Network characteristics			
REMS - Time domain			
SWC	0.092 (0.059–0.108)	0.085 (0.061–0.124)	0.828
SWS - Time domain			
SWC	0.0004 (− 0.011–0.012)	0.038 (0.010–0.059)	0.023

ba (ES): *quantile regression coefficient adjusted* (*standard error*). These coefficients are *the difference between* median adjusted for age *and gender* between "Depression" group and "*Healthy*" group.
ECT = Electroconvulsive therapy, SWS = Slow-wave sleep, REMS = Rapid eye movement sleep, SWC = small world coefficient.

there was no significant difference in the ages between these subgroups.

The results were considered significant when the p-value was < 0.05. Correlation analyses were performed using Spearman correlations.

3. Results

3.1. Comparison between healthy and depression groups

3.1.1. Demographic (Table 1) and polysomnographic data (Supplementary data, Table 1)

The major depressed participants in this study were older than the healthy subjects. Compared to the healthy individuals, major depressed participants had an increase in sleep latency and waking after sleep onset as well as a decrease in sleep efficiency, sleep period time, total sleep time, number of awakenings, stage 2, REMS, and SWS. There was no significant difference for stage 1 and REM latency. After adjusting for age, these results remained significant.

Table 1

3.1.2. Network parameters-time domain (Table 1)

Compared to healthy individuals, major depressed individuals show an increase in small-world coefficient during REMS. After adjusting for age, this result remains significant. For SWS, there is no significant difference between healthy and major depressed individuals at the level of small-world coefficient.

3.1.3. Network parameters-frequency domain (Supplementary data, Table 1)

For all EEG bands during REMS, major depressed individuals have an increase in small-world coefficient compared to healthy individuals. After adjusting for age, these results remain significant except for EEG bands α and θ. For all EEG bands during SWS, there is no significant difference between healthy and major depressed individuals at the level of small-world coefficient.

Table 2
Correlations between depression severity/endogenous characteristic of depression/potential favourable response to electroconvulsive therapy and network parameters during REMS and SWS.

(N = 40)	Depression severity	(N = 16)	Endogenous characteristic of depression	(N = 16)	Potential favourable response to ECT
REMS - Time domain					
SWC	0.418[a]		0.515[a]		0.056
SWS - Time domain					
SWC	0.129		0.190		0.588[a]
					[a]**p < 0.05**

ECT = Electroconvulsive therapy, SWS = Slow-wave sleep, REMS = Rapid eye movement sleep, SWC = small world coefficient.

3.2. Comparison between endogenous and neurotic depression groups

3.2.1. Demographic (Table 1) and polysomnographic data (Supplementary data, Table 2)

There is no significant difference between endogenous and neurotic depression groups for demographic and polysomnographic data.

3.2.2. Network parameters-time domain (Table 1)

Compared to those with neurotic depression, the participants with endogenous depression showed an increase in the small-world coefficient during REMS. For SWS, there was no significant difference between the endogenous and neurotic depression groups at the level of the small-world coefficient.

3.2.3. Network parameters-frequency domain (Supplementary data, Table 2)

Only for EEG band δ during REMS, the participants with endogenous depression had an increase in the small-world coefficient compared to those with neurotic depression. For all of the EEG bands during SWS, there was no significant difference between the endogenous and neurotic depression groups at the level of the small-world coefficient.

3.3. Comparison between potential favourable and unfavourable response to ECT groups

3.3.1. Demographic (Table 1) and polysomnographic data (Supplementary data, Table 3)

Compared to those with potential unfavourable response to ECT, the major depressed individuals with potential favourable response to ECT had an increase in stage 1 as well as a decrease in REM latency. There was no significant difference between the endogenous and neurotic depression groups for other polysomnographic data and demographic parameters.

3.3.2. Network parameters-time domain (Table 1)

Compared to those with potential unfavourable response to ECT, the major depressed participants with potential favourable response to ECT showed an increase in the small-world coefficient during SWS. For REMS, there was no significant difference between potential favourable and unfavourable response to ECT groups at the level of the small-world coefficient.

3.3.3. Network parameters-frequency domain (Supplementary data, Table 3)

For all of the EEG bands during SWS, the major depressed participants with potential favourable response to ECT had an increase in the small-world coefficient compared to those with potential unfavourable response to ECT. For all of the EEG bands during REMS, there was no significant difference between potential favourable and unfavourable response to ECT groups at the level of the small-world coefficient.

3.4. Correlation analyses (Table 2)

Depression severity and endogenous characteristics of depression positively correlated with the small-world coefficient only for REMS, whereas potential favourable response to ECT positively correlated with the small-world coefficient only for SWS. The results for all of the EEG bands during REMS and SWS are available in the Supplementary Data, Table 4.

4. Discussion

This study demonstrated that compared to the healthy participants, the major depressed individuals presented alterations of network organisation during REMS, which correlate with the severity of the depression. Moreover, in the major depressed individuals, the endogenous subtype of major depression was associated with alterations in network organisation during REMS and the potential favourable response to ECT was associated with alterations of network organisation during SWS. Our results therefore seem to suggest that alterations of network organisation during REMS could be biomarkers for the diagnosis and classification of major depressive episodes, whereas alterations of network organisation during SWS could be biomarkers to predict a potential favourable response to treatment by ECT.

In major depression, there are alterations in neurotransmission characterised by hypoactivity of the monoaminergic system and hyperactivity of the cholinergic system (Palagini et al., 2013) which are more important in the most severe forms of major depression (Chiuccariello et al., 2014) and in some subtypes of major depression (such as endogenous depression) (Adrien, 2002). In the endogenous subtype of major depression, this imbalance between monoaminergic and cholinergic systems may be induced primarily by genetic factors in the absence of external factors (Gillin et al., 1991; Paykel, 2008; Malki et al., 2014). Furthermore, these alterations of neurotransmission may be associated with a deregulation of REMS (REMS increased, REM latency shortened, and REM density increased) in major depression and more particularly in the endogenous subtype (Hubain et al., 1995; Wang et al., 2015). However, these alterations of REMS are not specific for major depression and its endogenous subtype since they may occur in other psychiatric pathologies (such as schizophrenia) as well as in other subtypes of major depression (such as psychotic depression) where they may reflect other pathophysiological mechanisms (Stefos et al., 1998; Gottesmann and Gottesman, 2007; Chan et al., 2017). Moreover, in major depressed individuals, the presence of this altered neurotransmission is associated with changes in both the processing and transmission pathways of information (Jesulola et al., 2018), which may affect sleep network organisation. However, our study highlighted that major depressed individuals (compared to healthy subjects) and those with endogenous depression (compared to those with neurotic depression) presented only alterations of SWN organisation during REMS, which seems to confirm that in major depression and its endogenous subtype, there is a less efficient network organisation during REMS reflecting failures in both processing and transmission of information secondary to alterations of neurotransmission in this sleep stage. Thus, these various elements seem to indicate that in major depression and its endogenous subtype, the alterations of SWN organisation during REMS could more specifically reflect the altered neurotransmission of information during this sleep stage than conventional markers related to REMS (REMS increased, REM latency shortened, and REM density increased) and be biomarkers more specific for the diagnosis and classification of major depression.

Clinically, since unaltered SWN organisation is associated with better cognitive performance and efficient segregation/integration of information at low cost and energy costs (Douw et al., 2011; Liao et al., 2017), the presence of altered SWN organisation during REMS could explain the dysfunction of some cognitive functions related to REMS (memory consolidation, emotional adaptation, and mood regulation) and the occurrence of some characteristic symptoms (such as the particular quality of mood) in major depression and its endogenous subtype (Austin et al., 1992; Hasler et al., 2004; Kyung Lee and Douglass, 2010). Moreover, the presence of these alterations of SWN organisation during REMS also faciltates a better understanding of the beneficial effects of antidepressant treatments rebalancing monoaminergic and cholinergic systems on these cognitive dysfunction and clinical symptoms related to REMS in major depressed individuals (especially those with endogenous depression) (Raskin et al., 1970; Goldstein and Walker, 2014) because they probably allow a restoration of SWN organisation during REMS through superior neurotransmission of information. Furthermore, the classification of major depressive episodes according to their endogenous or neurotic features is no longer used in routine clinical practise given the absence of reliable biomarkers to definitively validate the presence of these subtypes of major depression (Carroll et al., 1980; Berger et al., 1983; O'Leary, 1996). However, in our study, the highlighting of potential biomarkers more specifically characterised by alterations of SWN organisation during REMS in those with endogenous depression (compared to those with neurotic depression) could allow a renaissance of this particular classification in the clinical management of major depressed individuals.

On the other hand, this study demonstrated that major depressed individuals (compared to healthy subjects) and those with endogenous depression (compared to those with neurotic depression) have no alterations of SWN organisation during SWS, which could be explained by the fact that even if major depression and its endogenous subtype induce a deficit in SWS (Kerkhofs et al., 1988; Hein et al., b, c, d), the residual SWS is always composed of highly synchronised delta waves (Riemann et al., 2001) characterised by more efficient cortical communication and more synchronised cortical EEG activity (Schwartz and Kilduff, 2015) favouring the persistence of a network organisation with small-world characteristics. However, in some major depressed individuals, this slow-wave activity may be characterised by intrusions of fast-frequency activity (Cheng et al., 2015) associated with a state of hyperarousal of the central nervous system (Hein et al., 2016) that may make cortical communication less efficient (Brown et al., 2012) and generate a dysfunction of some cognitive functions (mood regulation and memorisation) (Nishida et al., 2016; Goldschmied et al., 2018). However, our study found that the presence of less efficient SWN organisation during SWS in some major depressed individuals was associated with a potentially favourable response to ECT. This may be explained by the fact that ECT probably does not have only a quantitative action on slow-wave activity (Göder et al., 2016) but also a qualitative action via a modulation of neurotransmission associated with adenosine (Van Calker and Berger, 1993; Korkutata et al., 2018). These elements may also facilitate the understanding of why there are cognitive and clinical improvements in major depressed individuals with a favourable response to ECT (Semkovska and McLoughlin, 2010). Indeed, ECT probably allows in major depressed individuals responding to this type of treatment an upgrade of SWN organisation during SWS through more efficient cortical communication induced by the modulation of neurotransmission associated with adenosine promoting better slow-wave activity (Huang et al., 2014). Thus, it would seem that the alterations of SWN organisation during SWS could be biomarkers more specific than previously studied markers related to sleep (Grunhaus et al., 1996, 1997) to predict a potential response favourable to treatment by ECT.

Finally, our results must be replicated on larger samples to eventually highlight reliable cut-offs at the level of the small-world coefficient:

- During REMS to facilitate better diagnosis and classification of major depressive episodes
- During SWS to enable better prediction of the favourable response to treatment by ECT

Thus, our study should be seen as a first step toward facilitating original research perspectives for the identification of novel biomarkers related to sleep in major depression through new methods inspired by neuroscience.

4.1. Limitations

This study measured the effective connectivity determined by the Granger causality only at the level of the scalp, which may limit the interpretations of our results. In addition, we only analysed data from a relatively small group of healthy and major depressed individuals, which means that new studies need to be conducted on larger samples to confirm our results. Moreover, in our study, there was only a partial overlap in the age distribution between the healthy and major depressed participants. This absence of perfect matching for age between these groups may have ultimately limited the interpretations of our results even though we adjusted for age in our analyses. Currently, there are several methods based on the effective connectivity measured by the Granger causality (each with advantages and disadvantages) developed by different research teams, which leads to many expert debates on the preferential method (Stokes and Purdon, 2017). Another possible limitation of our study was the use of the Newcastle Scale to evaluate the subtypes of major depression and the potential response to ECT. Indeed, despite some satisfactory empirical results, the validity of this scale has often been contested given that the assumptions underlying this scale have not been completely confirmed (Pélissolo, 2009). However, its use may be justified by the fact that the Newcastle Scale has acceptable psychometric properties and a good construct validity with other definitions of endogeneity available in the literature (Zimmerman et al., 1985; Hubain et al., 1995).

4.2. Conclusion

This study highlighted that alterations of network organisation during REMS could be biomarkers for the diagnosis and classification of major depressive episodes, whereas alterations of network organisation during SWS could be biomarkers predicting a potential favourable response to treatment by ECT. Our results demonstrate new research perspectives for the identification of potential biomarkers related to sleep in major depression.

Declarations

Ethics approval and consent to participate

This research protocol was approved by the Hospital and Medical School Ethics Committee of Erasme Hospital (Brussels University Clinics) (Erasme Reference: P2007/229). All of the participants in this study provided their consent for the use of their data as part of the scientific research.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

CRediT authorship contribution statement

Matthieu Hein: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing - original draft, Writing - review & editing. **Jean-Pol Lanquart:** Data curation, Formal analysis, Investigation, Methodology, Software, Writing - original draft, Writing - review & editing. **Gwenolé Loas:** Supervision, Writing - original draft, Writing - review & editing. **Philippe Hubain:** Supervision, Writing - original draft, Writing - review & editing. **Paul Linkowski:** Conceptualization, Supervision, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors have no conflicts of interest with the work carried out in this study.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2019.08.003.

References

Adrien, J., 2002. Neurobiological bases for the relation between sleep and depression. Sleep Med. Rev. 6 (5), 341–351.
American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. text rev. American Psychiatric Publishing, Arlington, VA.
American Sleep Disorders Association, Diagnostic Classification Steering Committee, 2005. International Classification of Sleep Disorders: Diagnostic and Coding Manual. ICSD-R. American Academy of Sleep Medicine, Westchester, IL.
Austin, M.P., Ross, M., Murray, C., O'Carroll, R.E., Ebmeier, K.P., Goodwin, G.M., 1992. Cognitive function in major depression. J. Affect. Disord. 25 (1), 21–29.
Baglioni, C., Battagliese, G., Feige, B., Spiegelhalder, K., Nissen, C., Voderholzer, U., Lombardo, C., Riemann, D., 2011. Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. J. Affect. Disord. 135 (1–3), 10–19.
Baglioni, C., Nanovska, S., Regen, W., Spiegelhalder, K., Feige, B., Nissen, C., Reynolds, C.F., Riemann, D., 2016. Sleep and mental disorders: a meta-analysis of polysomnographic research. Psychol. Bull. 142 (9), 969–990.
Barnett, L., Seth, A.K., 2014. The MVGC multivariate Granger causality toolbox: a new approach to Granger-causal inference. J. Neurosci. Methods 223, 50–68.
Bassett, D.S., Bullmore, E.T., 2006. Small-World Brain Networks. Neuroscientist 12 (6), 512–523.
Bassett, D.S., Bullmore, E.T., 2017. Small-World Brain Networks Revisited. Neuroscientist 23 (5), 499–516.
Berger, M., Lund, R., Bronisch, T., von Zerssen, D., 1983. REM latency in neurotic and endogenous depression and the cholinergic REM induction test. Psychiatry Res 10 (2), 113–123.
Bressler, S.L., Seth, A.K., 2011. Wiener-Granger causality: a well-established methodology. Neuroimage 58 (2), 323–329.
Brown, R.E., Basheer, R., McKenna, J.T., Strecker, R.E., McCarley, R.W., 2012. Control of sleep and wakefulness. Physiol. Rev. 92 (3), 1087–1187.
Carney, M.W., Roth, M., Garside, R.F., 1965. The diagnosis of depressive syndromes and the prediction of ECT response. Br. J. Psychiatry 111, 659–674.
Carroll, B.J., Feinberg, M., Greden, J.F., Haskett, R.F., James, N.M., Steiner, M., Tarika, J., 1980. Diagnosis of endogenous depression. Comparison of clinical, research and neuroendocrine criteria. J. Affect. Disord. 2 (3), 177–194.
Chan, M.S., Chung, K.F., Yung, K.P., Yeung, W.F., 2017. Sleep in schizophrenia: a systematic review and meta-analysis of polysomnographic findings in case-control studies. Sleep Med. Rev. 32, 69–84.
Cheng, P., Goldschmied, J., Deldin, P., Hoffmann, R., Armitage, R., 2015. The role of fast and slow EEG activity during sleep in males and females with major depressive disorder. Psychophysiology 52 (10), 1375–1381.
Chiuccariello, L., Houle, S., Miler, L., Cooke, R.G., Rusjan, P.M., Rajkowska, G., Levitan, R.D., Kish, S.J., Kolla, N.J., Ou, X., Wilson, A.A., Meyer, J.H., 2014. Elevated monoamine oxidase a binding during major depressive episodes is associated with greater severity and reversed neurovegetative symptoms. Neuropsychopharmacology 39 (4), 973–980.
Douw, L., Schoonheim, M.M., Landi, D., van der Meer, M.L., Geurts, J.J., Reijneveld, J.C., Klein, M., Stam, C.J., 2011. Cognition is related to resting-state small-world network topology: an magnetoencephalographic study. Neuroscience 175, 169–177.
Friston, K., Moran, R., Seth, A.K., 2013. Analysing connectivity with Granger causality and dynamic causal modelling. Curr. Opin. Neurobiol. 23 (2), 172–178.
Gillin, J.C., Sutton, L., Ruiz, C., Kelsoe, J., Dupont, R.M., Darko, D., Risch, S.C., Golshan, S., Janowsky, D., 1991. The cholinergic rapid eye movement induction test with arecoline in depression. Arch. Gen. Psychiatry 48 (3), 264–270.
Göder, R., Hinrichsen, I., Seeck-Hirschner, M., Pfeiffer, R., Weinhold, S.L., Baier, P.C., Hanss, R., Schulz-DuBois, C., 2016. Sleep at baseline and after electroconvulsive therapy in patients with major depression. Psychiatry Res. 246, 683–687.
Goldschmied, J.R., Cheng, P., Hoffmann, R., Boland, E.M., Deldin, P.J., Armitage, R., 2018. Effects of slow-wave activity on mood disturbance in major depressive disorder. Psychol. Med. https://doi.org/10.1017/S0033291718001332.
Goldstein, A.N., Walker, M.P., 2014. The role of sleep in emotional brain function. Annu. Rev. Clin. Psychol. 10, 679–708.
Gottesmann, C., Gottesman, I., 2007. The neurobiological characteristics of rapid eye movement (REM) sleep are candidate endophenotypes of depression, schizophrenia, mental retardation and dementia. Prog. Neurobiol. 81 (4), 237–250.
Grunhaus, L., Shipley, J.E., Eiser, A., Pande, A.C., Tandon, R., Remen, A., Greden, J.F., 1996. Polysomnographic studies in patients referred for ECT: pre-ECT studies. Convuls. Ther. 12 (4), 224–231.
Grunhaus, L., Shipley, J.E., Eiser, A., Pande, A.C., Tandon, R., Krahn, D.D., Demitrack, M.A., Remen, A., Hirschmann, S., Greden, J.F., 1997. Sleep-onset rapid eye movement after electroconvulsive therapy is more frequent in patients who respond less well to electroconvulsive therapy. Biol. Psychiatry 42 (3), 191–200.
Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23, 56–62.
Hasler, G., Drevets, W.C., Manji, H.K., Charney, D.S., 2004. Discovering endophenotypes for major depression. Neuropsychopharmacology 29 (10), 1765–1781.
Hassan, M., Shamas, M., Khalil, M., El Falou, W., Wendling, F., 2015. EEGNET: an OpenSourceTool for Analyzing and Visualizing M/EEG Connectome. PLoS One 10 (9), e0138297.
He, H., Sui, J., Yu, Q., Turner, J.A., Ho, B.C., Sponheim, S.R., Manoach, D.S., Clark, V.P., Calhoun, V.D., 2012. Altered small-world brain networks in schizophrenia patients during working memory performance. PLoS One 7 (6), e38195.
Hein, M., Hubain, P., Linkowski, P., Loas, G., 2016. Support for insomnia: recommendations for practice in general medicine. Rev. Med. Brux 37 (4), 235–241.
Hein, M., Lanquart, J.P., Loas, G., Hubain, P., Linkowski, P., 2017a. Prevalence and risk factors of moderate to severe obstructive sleep apnea syndrome in insomnia sufferers: a study on 1311 subjects. Respir. Res. 18 (1), 135.
Hein, M., Senterre, C., Lanquart, J.P., Montana, X., Loas, G., Linkowski, P., Hubain, P., 2017b. Hyperarousal during sleep in untreated, major depressed subjects with prodromal insomnia: a polysomnographic study. Psychiatry Res. 258, 387–395.
Hein, M., Senterre, C., Lanquart, J.P., Montana, X., Loas, G., Linkowski, P., Hubain, P., 2017c. Hyperarousal during sleep in untreated primary insomnia sufferers: a polysomnographic study. Psychiatry Res. 253, 71–78.
Hein, M., Lanquart, J.P., Loas, G., Hubain, P., Linkowski, P., 2017d. Similar polysomnographic pattern in primary insomnia and major depression with objective insomnia: a sign of common pathophysiology? BMC Psychiatry 17 (1), 273.
Hein, M., Lanquart, J.P., Loas, G., Hubain, P., Linkowski, P., 2018. The sleep network organization during slow-wave sleep is more stable with age and has small-world characteristics more marked than during REM sleep in healthy men. Neurosci. Res. https://doi.org/10.1016/j.neures.2018.08.001.
Hein, M., Lanquart, J.P., Loas, G., Hubain, P., Linkowski, P., 2019a. Prevalence and risk factors of excessive daytime sleepiness in major depression: a study with 703 individuals referred for polysomnography. J. Affect. Disord. 243, 23–32.
Hein, M., Lanquart, J.P., Loas, G., Hubain, P., Linkowski, P., 2019b. Objective sleep alterations and long-term use of short or intermediate half-life benzodiazepine receptor agonists are risk factors for high blood pressure in individuals with insomnia: a study in 1272 individuals referred for sleep examinations. Sleep Med. 53, 115–123.
Huang, Z.L., Zhang, Z., Qu, W.M., 2014. Roles of adenosine and its receptors in sleep-wake regulation. Int. Rev. Neurobiol. 119, 349–371.
Hubain, P.P., Souery, D., Jönck, L., Staner, L., Van Veeren, C., Kerkhofs, M., Mendlewicz, J., Linkowski, P., 1995. Relationship between the Newcastle scale and sleep polysomnographic variables in major depression: a controlled study. Eur. Neuropsychopharmacol. 5 (2), 129–134.
Jesulola, E., Micalos, P., Baguley, I.J., 2018. Understanding the pathophysiology of depression: from monoamines to the neurogenesis hypothesis model - are we there yet? Behav. Brain Res. 341, 79–90.
Jhung, K., Cho, S.H., Jang, J.H., Park, J.Y., Shin, D., Kim, K.R., Lee, E., Cho, K.H., An, S.K., 2013. Small-world networks in individuals at ultra-high risk for psychosis and first-episode schizophrenia during a working memory task. Neurosci. Lett. 535, 35–39.
Kerkhofs, M., Kempenaers, C., Linkowski, P., de Maertelaer, V., Mendlewicz, J., 1988. Multivariate study of sleep EEG in depression. Acta Psychiatr. Scand. 77 (4), 463–468.
Korkutata, M., Saitoh, T., Cherasse, Y., Ioka, S., Duo, F., Qin, R., Murakoshi, N., Fujii, S., Zhou, X., Sugiyama, F., Chen, J.F., Kumagai, H., Nagase, H., Lazarus, M., 2018. Enhancing endogenous adenosine A_{2A} receptor signaling induces slow-wave sleep without affecting body temperature and cardiovascular function. Neuropharmacology. https://doi.org/10.1016/j.neuropharm.2018.10.022.
Kudlow, P.A., Cha, D.S., Lam, R.W., McIntyre, R.S., 2013. Sleep architecture variation: a mediator of metabolic disturbance in individuals with major depressive disorder. Sleep Med. 14 (10), 943–949.
Kyung Lee, E., Douglass, A.B., 2010. Sleep in psychiatric disorders: where are we now? Can. J. Psychiatry 55 (7), 403–412.
Lanquart, J.P., Nardone, P., Hubain, P., Loas, G., Linkowski, P., 2018. The dichotomy between low frequency and delta waves in human sleep: a reappraisal. J. Neurosci. Methods 293, 234–246.
Leistedt, S.J., Coumans, N., Dumont, M., Lanquart, J.P., Stam, C.J., Linkowski, P., 2009. Altered sleep brain functional connectivity in acutely depressed patients. Hum. Brain Mapp. 30 (7), 2207–2219.
Li, W., Douglas Ward, B., Liu, X., Chen, G., Jones, J.L., Antuono, P.G., Li, S.J., Goveas, J.S., 2015. Disrupted small world topology and modular organisation of functional networks in late-life depression with and without amnestic mild cognitive impairment. J. Neurol. Neurosurg. Psychiatry 86 (10), 1097–1105.
Liao, X., Vasilakos, A.V., He, Y., 2017. Small-world human brain networks: perspectives and challenges. Neurosci. Biobehav. Rev. 77, 286–300.
Long, Z., Duan, X., Wang, Y., Liu, F., Zeng, L., Zhao, J.P., Chen, H., 2015. Disrupted structural connectivity network in treatment-naive depression. Prog Neuropsychopharmacol. Biol. Psychiatry 56, 18–26.
Malki, K., Keers, R., Tosto, M.G., Lourdusamy, A., Carboni, L., Domenici, E., Uher, R., McGuffin, P., Schalkwyk, L.C., 2014. The endogenous and reactive depression

subtypes revisited: integrative animal and human studies implicate multiple distinct molecular mechanisms underlying major depressive disorder. BMC Med. 12, 73.
Marinazzo, D., Pellicoro, M., Stramaglia, S., 2008. Kernel-Granger causality and the analysis of dynamical networks. Phys. Rev. E Stat Nonlin. Soft Matter Phys 77 (5 Pt 2), 056215.
Mendelson, W.B., Gillin, J.C., Wyatt, R.D., 1977. Human Sleep and Its Disorders. Plenum Press, NY.
Milgram, S., 1967. The small world problem. Psychol. Today 2, 60–67.
Newell, J., Mairesse, O., Verbanck, P., Neu, D., 2012. Is a one-night stay in the lab really enough to conclude? First-night effect and night-to-night variability in polysomnographic recordings among different clinical population samples. See comment in. PubMed Commons below Psychiatry Res. 200 (2–3), 795–801.
Newman, M.E., 2003. The structure and function of complex networks. SIAM Rev. 45, 167–256.
Nishida, M., Nakashima, Y., Nishikawa, T., 2016. Slow sleep spindle and procedural memory consolidation in patients with major depressive disorder. Nat. Sci. Sleep 8, 63–72.
O'Leary, D., 1996. The endogenous subtype and naturalistic course in depression. J. Affect. Disord. 41 (2), 117–123.
Ohayon, M.M., Carskadon, M.A., Guilleminault, C., Vitiello, M.V., 2004. Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. Sleep 27 (7), 1255–1273.
Palagini, L., Baglioni, C., Ciapparelli, A., Gemignani, A., Riemann, D., 2013. REM sleep dysregulation in depression: state of the art. Sleep Med. Rev. 17 (5), 377–390.
Paykel, E.S., 2008. Basic concepts of depression. Dialogues Clin. Neurosci. 10 (3), 279–289.
Pélissolo, A., 2009. Severe depression : which concept? which criteria? Encephale 35 (Suppl 7), S243–S249.
Pillai, V., Kalmbach, D.A., Ciesla, J.A., 2011. A meta-analysis of electroencephalographic sleep in depression: evidence for genetic biomarkers. Biol. Psychiatry 70 (10), 912–919.
Raskin, A., Schulterbrandt, J.G., Reatig, N., McKeon, J.J., 1970. Differential response to chlorpromazine, imipramine, and placebo. A study of subgroups of hospitalized depressed patients. Arch. Gen. Psychiatry. 23 (2), 164–173.
Rechtschaffen, A., Kales, A., 1968. A Manual of Standardized Terminology. Techniques and Scoring System For Sleep Stages of Human Subjects. U.S. Dept. of Health, Education and Welfare, Washington, DC.
Riemann, D., Berger, M., Voderholzer, U., 2001. Sleep and depression–results from psychobiological studies: an overview. Biol. Psychol. 57 (1–3), 67–103.
Rubinov, M., Sporns, O., 2010. Complex network measures of brain connectivity: uses and interpretations. Neuroimage 52 (3), 1059–1069.
Sanz-Arigita, E.J., Schoonheim, M.M., Damoiseaux, J.S., Rombouts, S.A., Maris, E., Barkhof, F., Scheltens, P., Stam, C.J., 2010. Loss of 'small-world' networks in Alzheimer's disease: graph analysis of FMRI resting-state functional connectivity. PLoS One 5 (11), e13788.
Schwartz, M.D., Kilduff, T.S., 2015. The Neurobiology of Sleep and Wakefulness. Psychiatr. Clin. North Am. 38 (4), 615–644.
Semkovska, M., McLoughlin, D.M., 2010. Objective cognitive performance associated with electroconvulsive therapy for depression: a systematic review and meta-analysis. Biol. Psychiatry 68 (6), 568–577.
Sporns, O., Chialvo, D.R., Kaiser, M., Hilgetag, C.C., 2004. Organization, development and function of complex brain networks. Trends Cogn. Sci. 8 (9), 418–425.
Stam, C.J., Reijneveld, J.C., 2007. Graph theoretical analysis of complex networks in the brain. Nonlinear Biomed. Phys. 1 (1), 3.
Stam, C.J., 2010. Characterization of anatomical and functional connectivity in the brain: a complex networks perspective. Int. J. Psychophysiol. 77 (3), 186–194.
Stefos, G., Staner, L., Kerkhofs, M., Hubain, P., Mendlewicz, J., Linkowski, P., 1998. Shortened REM latency as a psychobiological marker for psychotic depression? An age-, gender-, and polarity-controlled study. Biol. Psychiatry 44 (12), 1314–1320.
Stokes, P.A., Purdon, P.L., 2017. A study of problems encountered in Granger causality analysis from a neuroscience perspective. Proc. Natl. Acad. Sci. USA 114 (34), E7063–E7072.
Telesford, Q.K., Joyce, K.E., Hayasaka, S., Burdette, J.H., Laurienti, P.J., 2011. The ubiquity of small-world networks. Brain Connect 1 (5), 367–375.
Van Calker, D., Berger, M., 1993. Possible role of adenosine receptors in psychiatric diseases. Drug Dev. Res. 28, 354–358.
Vecchio, F., Miraglia, F., Quaranta, D., Granata, G., Romanello, R., Marra, C., Bramanti, P., Rossini, P.M., 2016. Cortical connectivity and memory performance in cognitive decline: a study via graph theory from EEG data. Neuroscience 316, 143–150.
Voegeli, G., Cléry-Melin, M.L., Ramoz, N., Gorwood, P., 2017. Progress in Elucidating Biomarkers of Antidepressant Pharmacological Treatment Response: a Systematic Review and Meta-analysis of the Last 15 Years. Drugs 77 (18), 1967–1986.
Wang, Y.Q., Li, R., Zhang, M.Q., Zhang, Z., Qu, W.M., Huang, Z.L., 2015. The neurobiological mechanisms and treatments of REM sleep disturbances in depression. Curr. Neuropharmacol. 13 (4), 543–553.
Watts, D.J., Strogatz, S.H., 1998. Collective dynamics of “small-world” networks. Nature 393 (6684), 440–442.
Woods, N.I., Kheirbek, M.A., 2017. The Small World of a Fear Memory. Neuron 94 (2), 226–227.
Zimmerman, M., Coryell, W., Pfohl, B., Stangl, D., 1985. Four definitions of endogenous depression and the dexamethasone suppression test. J. Affect. Disord. 8 (1), 37–45.
Zhang, J., Wang, J., Wu, Q., Kuang, W., Huang, X., He, Y., Gong, Q., 2011. Disrupted brain connectivity networks in drug-naive, first-episode major depressive disorder. Biol. Psychiatry 70 (4), 334–342.