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Heart rate variability and cordance in rapid eye movement sleep as biomarkers of depression and treatment response

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ABSTRACT

Objectives: The relevance of rapid eye movement (REM) sleep in affective disorders originates from its well-known abnormalities in depressed patients, who display disinhibition of REM sleep reflected by increased frequency of rapid eye movements (REM density). In this study we examined whether heart rate variability (HRV) and prefrontal theta cordance, both derived from REM sleep, could represent biomarkers of antidepressant treatment response.

Methods: In an open-label, case-control design, thirty-three in-patients (21 females) with a depressive episode were treated with various antidepressants for four weeks. Response to treatment was defined as a $\geq$50% reduction of HAM-D score at the end of the fourth week. Sleep EEG was recorded after the first and the fourth week of medication. HRV was derived from 3-min artifact-free electrocardiogram segments during REM sleep. Cordance was computed for prefrontal EEG channels in the theta frequency band during tonic REM sleep.

Results: HRV during REM sleep was decreased in depressed patients at week four as compared to controls (high effect size; Cohen's d > 1), and showed a negative correlation with REM density in both, healthy subjects and patients at week four. Further, the fourteen responders had significantly higher prefrontal theta cordance as compared to the nineteen non-responders after the first week of antidepressant medication; in contrast, HRV at week one did not discriminate between responders and non-responders.

Conclusions: Our data suggest that HRV in REM sleep categorizes healthy subjects and depressed patients, whereas REM sleep-derived prefrontal cordance may predict the response to antidepressant treatment in depressed patients.

1. Introduction

Clinical judgement after four weeks of treatment is the standard for evaluating the definite response to antidepressant (AD) therapy in major depressive disorder (MDD) (Gelenberg and Chesen, 2000; Souery et al., 2007). However, at that time, approximately 50% of patients will not have responded to initial treatment (Trivedi et al., 2006; Zajecka, 2003). Therefore, there is a need for biomarkers that allow prediction of treatment response earlier in order to optimise therapy outcome.

Depression is commonly associated with an imbalanced autonomic nervous system (ANS), which occurs due to a reduced parasympathetic and an increased sympathetic drive. This imbalance is reflected by changes of heart rate variability (HRV; Grippo and Johnson, 2009; Thayer et al., 2010), which refers to the variability of the beat-to-beat interval lengths (Task Force, 1996). Accordingly, HRV analysis may provide both, an indicator of ANS activity and a biomarker of MDD. Further, there is considerable

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neurobiological evidence supporting a linkage between HRV and depression: HRV is regulated by reflex loops as well as by the central autonomous network (CAN), consisting of medial prefrontal cortex (mPFC), insula and amygdala. In wake but even more in REM sleep HRV is regulated predominantly by the CAN (Chouchou and Desseilles, 2014). As the mPFC, exerting inhibitory control of the amygdala, is involved in self-regulating functions, emotion processing and cognitive functions, HRV has been proposed to be an indicator of self-regulatory capability in wake, as well as for emotional processing in REM-sleep, which is most relevant in MDD (Lane et al., 2009, 2013; Desseilles et al., 2006; Thayer and Lane, 2009; Thayer et al., 2012).

According to a meta-analysis on HRV and depression, MDD is indeed associated with blunted HRV (Kemp et al., 2010). However, HRV differences between patients and controls were of small to moderate effect sizes and none of those studies were performed under sleep conditions. Considering that HRV is subject to behavioural, emotional and cognitive influences, which are difficult to control during wake conditions (Task Force, 1996), we expected that association of HRV and depression would be stronger under off-line conditions of sleep. As HRV changes between sleep stages and correlates with brain activity during sleep (Spiegelhalder et al., 2011), we further proposed that REM sleep would be the ideal sleep stage to refer to HRV and depression: REM sleep is characterized by high activity of the mPFC, which influences the ANS and may amplify differences in HRV between depressed patients and controls (Desseilles et al., 2011). Moreover, as REM sleep is commonly disinhibited in depression (Steiger et al., 2015), we expected that REM sleep derived HRV would separate between patients and healthy controls distinctively.

Accordingly, we compared HRV in REM sleep with previously established REM sleep-derived biomarkers of depression, such as REM density and cordance. Elevated REM density (a measure of rapid eye movement frequency during REM sleep) is an endophenotype of depression (Lauer et al., 1995; Modell et al., 2005; Steiger et al., 2015), and indicates an increased risk of depression recurrence (Hatzinger et al., 2004). Further, in a sub-sample of this study population, we have previously shown that the quantitative electroencephalography (QEEG) biomarker cordance could predict antidepressant treatment response in MDD patients. When computed for the theta frequency band (4–8 Hz) during tonic REM sleep, cordance predicted the treatment outcome in patients with MDD already after the first week of novel medication (Adamczyk et al., 2015). Prefrontal theta cordance may reflect activity of prefrontal cortex and anterior cingulate cortex (ACC) (Asada et al., 1999), which both seem to be crucial in MDD (Drevets, 2000 and Drevets, 1999). During REM sleep, the ACC activity level is maximal, whereas the surrounding frontal cortex activity is minimal (Braun et al., 1997; Hobson and Pace-Schott, 2002). Furthermore, during REM sleep, ACC has prominent oscillatory activity in the theta frequency band (Nishida et al., 2004) marking an ideal frequency band to be detected by the prefrontal theta cordance, though simplifying a more complex interacting of a set of different brain regions during REM sleep (Kirov et al., 2012). Therefore, we expected to consolidate the previous results on cordance (Adamczyk et al., 2015) in this extended sample and further, we aimed to compare potential biomarker capabilities of HRV and cordance during REM sleep for the prediction of clinical response in depression.

2. Methods

2.1. Study participants

The study population was an extended sample of the study on cordance in REM sleep as response predictor previously published by Adamczyk et al., 2015. For the current study we screened n = 42 and enrolled n = 33 adult inpatients from the hospital of the Max Planck Institute of Psychiatry. All patients met DSM-IV criteria for major depression or bipolar I or II disorder (depressive episode), as diagnosed by 2 senior psychiatrists, and had HAM-D scores ≥14 on the 21-item scale at inclusion. All patients underwent antidepressant treatment according to doctor's choice within a few days after admission. Subjects were excluded in case of pregnancy, history of drug/alcohol dependance, history of head trauma, serious risk of suicide, personality disorder and severe somatic diseases as well as long-acting medication including fluoxetine and depot neuroleptics. Patients did not experience therapeutic sleep deprivation, electroconvulsive therapy, shift work or transmeridian travel within 3 months prior to investigation. Benzodiazepine or non-benzodiazepine anxiolytics were allowed in low unchanged dosages.

While n = 9 patients were excluded because of the aforementioned criteria, n = 33 subjects (12 males, age mean (SD): 46 (16) years) were included. They had the following diagnoses: n = 9 subjects with a First Depressive Episode (ICD-10 F 32.1 (n = 4), F 32.2 (n = 5)), n = 3 subjects with a Severe Depressive Episode within a Bipolar Affective Disorder (ICD-10 F 31.4) and n = 21 subjects with a Recurrent Depressive Disorder (ICD-10 F33.1 (n = 3), F33.2 (n = 16), F33.3 (n = 2)). Thirty-three healthy volunteers have been examined by routine blood and urine diagnostics including testing for drug abuse, have been examined physically and especially neurologically, have been interviewed extensively regarding current or past psychiatric disorders, noticeable affective disorders in family history, any medication including thyroid hormones, any nicotine intake and sleep disorders as well as shift working. In case of complete inconspicuousness, subjects have been matched for age (±2 y.) and gender. During our study, patients were treated with various antidepressants depicted in Table 1. One patient received an atypical antipsychotic drug in addition to the antidepressant medication and one other patient had low unchanged dosages of an anxiolytic medication (Lorazepam 1.0 mg/d). Plasma concentration of antidepressant medication was monitored weekly to ensure clinically efficient drug levels.

The Ethics Committee of the Ludwig Maximilian University of Munich approved the study. Written informed consent was obtained after experimental procedures were explained to subjects.

2.2. Procedures

The length of the open-label, case-control study was four weeks (see Fig. 1). Patients spent two consecutive nights (from 23:00 till 07:00) in our sleep laboratory each after the first and the fourth week of antidepressant treatment (Fig. 1), whereas controls spent two consecutive nights in the sleep laboratory once. The first night served for adaptation and exclusion of sleep disorders.

2.3. Assessments

2.3.1. EEG recording and analysis

Polysomnographic recordings were acquired with a Comlab 32 Digital Sleep Lab amplifier (Schwarzer GmbH, Munich, Germany) using Ag/AgCl electrodes. Nineteen EEG electrodes (FP1, FP2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, O2) were placed according to the international 10–20 system as described by Leuchter et al. (1994) and referenced to the electrode situated between electrodes Cz and Pz in the midline (CPz).

We monitored electrocardiogram (ECG), electromyogram, horizontal and vertical electrooculogram (EOG, two electrodes for each direction) referenced to the left mastoid electrode. The sampling

Table 1
Types of medicine administered to depressed patients during the measurement time.

	Number of Depressed Patients[a]
Antidepressant medication:	
Serotonin-noradrenaline reuptake inhibitor	12 (36%)
Selective serotonin reuptake inhibitor	4 (12%)
Tricyclic antidepressant	11 (33%)
Noradrenaline-dopamine reuptake inhibitor	4 (12%)
Noradrenergic and specific serotonergic antidepressant	2 (6%)
Noradrenaline reuptake inhibitor	1 (3%)
Cardiac/antihypertensive medication:	
Beta-blocker	2 (6%)
ACE-inhibitor	2 (6%)
AT1-receptor-antagonist	1 (3%)
ACE-inhibitor and beta -blocker	1 (3%)

Medication was not changed between week 1 and week 4. Healthy controls (N = 33) did not receive any antidepressant or cardiac/antihypertensive medication.
[a] Percentage of treated patients from the total patients group.

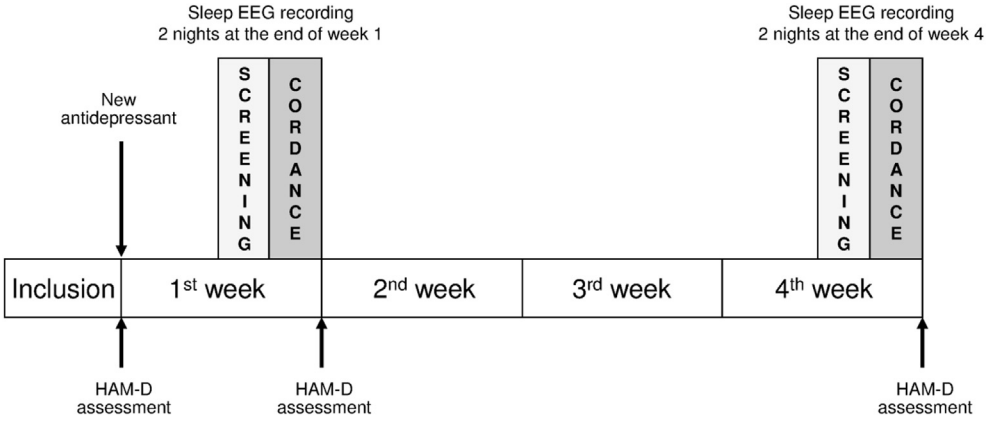

Fig. 1. Study design.

rate for EEG channels was 250 Hz. Signal was high-pass filtered at 0.53 Hz (3 dB/octave) and low-pass filtered at 70 Hz (12 dB/octave). Electrode impedances were below 5 kOhm. ECG and EOG channels were recorded at 250 Hz and band-pass-filtered (EOG: 0.095–30 Hz; ECG: 0.26–30 Hz). Experts visually scored sleep stages according to standard guidelines (Rechtschaffen and Kales, 1968).

2.3.2. Rapid eye movements detection

Rapid eye movements (REMs) were detected automatically using both horizontal and vertical pairs of EOG channels. Detection thresholds were based on estimated signal background noise. Duration of most REMs have been described to range from 1 Hz to 5 Hz (Boukadoum and Ktonas, 1986). On the other hand, frequencies above 20 Hz may be influenced by muscle artifacts. For these reasons, to estimate the background noise, EOG signals were band-pass filtered (pass-band: 7–16 Hz). Each filtered EOG signal was used to calculate the median of standard deviations (medStd) computed on a 1-sec sliding window with a 1-sec shift. The background noise for a pair of investigated EOG signals was estimated as a mean of their respective medStd's. The noise threshold (NT) used during the detection was equal to the estimated background noise. REM was detected, if there was a synchronized (within 70 msec) change in EOG potentials of opposite polarity for a time period of a minimum of 40 msec. In at least one EOG derivation, the potential change had to exceed the 70xNT/sec, whereas in the second EOG derivation the potential change had to exceed the 46xNT/sec. These values were optimized using sixty polysomnographic recordings (development set) from sixty healthy subjects which were scored by one expert. For the development set, mean epoch-wise correlation for REM density scoring between the expert and algorithm with optimized thresholds was 0.94.

Then, the automatic algorithm was validated in twelve polysomnographic recordings from seven healthy subjects which were scored by two experts. Mean epoch-wise correlation for REM density scoring between the experts was 0.91, whereas comparison of automatic scoring with each of the scorers revealed mean correlations of 0.93 (the same expert who scored the validation set) and 0.91. The mean REM density index was defined as the average ratio of 3-sec mini epochs of REM sleep, including REMs, to the total amount of 3-sec mini epochs of REM sleep (Lauer et al., 1995). According to this definition, absolute values of REM density ranged between 0 and 10 for each 30-sec epoch of REM sleep.

2.3.3. HRV analysis

HRV analysis was performed using Kubios HRV (Tarvainen et al., 2014) software (version 2.2). We analyzed 3-min segments of artifact-free REM sleep selected always from the second third of the night. Confounders of HRV, like specific sleep disorders (e.g. restless legs syndrome, obstructive sleep apnea syndrome) or severe medical illness were excluded. Cardiac/antihypertensive concurrent medication was administered to six of the n = 33 (18.2%) patients (Table 1). Post-hoc analyses showed that excluding this cardiac/antihypertensive medication did not influence the results significantly; therefore we resigned from excluding these patients from the analysis. We computed heart rate and the following HRV

measures: the time domain measures SDNN (standard deviation of all RR intervals) and RMSSD (square root of the mean of the squares of differences between adjacent NN intervals); the frequency domain measures: low frequency power (LF: 0.04–0.15 Hz), high frequency power (HF: 0.15–0.4 Hz), and the LF/HF ratio. Since distributions of HRV measures were not normal, we performed natural logarithm transformation prior to statistical analysis.

2.3.4. Cordance computation

We computed cordance from all artifact-free tonic REM sleep epochs. To eliminate phasic REM sleep, we excluded all REM periods that preceded and followed REMs within 10 sec. Fragments with artifacts in any EEG channel were excluded from the analysis. Artifact-free signal was submitted to spectral analysis. The duration of EEG signal used for cordance computation differed according to the amount of tonic REM sleep available. In responder group, we used on average [mean (SD)] 15.5 (12.0) minutes in week 1 and 17.0 (14.9) minutes in week 4. In non-responder group, we used on average 11.7 (9.0) minutes in week 1 and 12.7 (11.1) minutes in week 4. In healthy subjects group matched with responders, we used on average 30.4 (11.0) minutes and in controls group matched with non-responders we used on average 27.9 (16.7) minutes. Significantly longer (T test, two-tailed, unpaired, $p < 0.05$) signal was used for cordance computation in healthy controls when compared to both, responders and non-responders. The reason for uneven amounts of tonic REM was the fact that healthy subjects had both longer REM sleep and less rapid eye movements (see results section).

The algorithm to compute cordance was described and explained in detail elsewhere (Leuchter et al., 1999). In brief, the absolute power is computed for each bipolar pair of neighbouring electrodes. The absolute power is then reattributed to each electrode by averaging the power from all bipolar pairs including that electrode. Subsequently, the relative and absolute power for the theta band (4–8 Hz) is calculated. The relative power is obtained by dividing the absolute theta power by the absolute total power in 0.5–20 Hz and absolute theta power is square-root transformed to minimize skewness and curtosis. Next, the absolute and relative power for each electrode site (s) is spatially normalized using z-scores. The spatially normalized absolute ($A_{norm(s)}$) and relative ($R_{norm(s)}$) theta powers are then used to compute cordance (Z_s) at each electrode site:

$$Z_s = A_{norm(s)} + R_{norm(s)}$$

We computed theta cordance using nineteen electrodes placed according to description provided by Leuchter et al. (1994). Previous studies on prefrontal theta cordance investigated average cordance values from three electrodes: either Fp1, Fp2 and Fz (Bares et al., 2007, 2008) or Fp1, Fp2 and Fpz (Cook et al., 2002). Due to the discrepancy regarding inclusion of either Fz or Fpz electrode, we focused only on Fp1 and Fp2. Mean cordance values from two prefrontal electrodes (Fp1, Fp2) were subjected to statistical analysis.

2.4. Statistical analysis

Categorical data were compared using Fisher's exact test, whereas continuous variables were compared using t-tests. To evaluate potential confounding factors, we applied analysis of covariance (ANCOVA) with cordance as the dependent variable, response as grouping factor, and age, sex and number of previous depressive episodes as the covariates. Response to treatment was defined as a ≥50% reduction of HAM-D score at the end of four weeks of active medication. The relationship between improvement in HAM-D score during four weeks of treatment and cordance after the first week of treatment was examined using Pearson's correlation coefficient. All tests were two-tailed with the adopted significance level of 0.05. Analyses were performed using SPSS version 18. In order to evaluate the predictive value of cordance, we established a classification threshold using the receiver operating characteristics (ROC).

3. Results

3.1. Clinical measures

After four weeks, n = 14 out of n = 33 patients responded to antidepressant treatment (42%). Responders, as compared to non-responders, showed significantly lower final HAM-D score after four weeks of treatment ($p < 0.001$), but not after one week ($p = 0.88$). There were no significant differences between the groups regarding other clinical parameters (Table 2). Use of medication with (e.g. escitalopram) (Gursky and Krahn, 2000) and without (trimipramine, mirtazapine and bupropione) (Nofzinger et al., 1995; Schmid et al., 2006; Sonntag et al., 1996) REM sleep-suppressing effects was balanced between responders and non-responders ($p = 0.86$).

3.2. Sleep architecture and spectral analysis

After the first week of treatment responders and non-responders did not display any significant differences in sleep EEG variables. Compared to controls, responders had significantly longer REM latency ($p = 0.01$) and higher amounts of stage 1 sleep ($p = 0.02$). Non-responders exhibited significantly longer REM latency ($p < 0.001$) and sleep onset latency ($p = 0.036$), shorter duration of total REM sleep ($p = 0.005$) and lower relative prefrontal power in the theta frequency band ($p = 0.017$). Other conventional sleep parameters did not exhibit significant differences between groups (Table 2).

3.3. HRV in REM sleep

After the first week of antidepressant medication, RMSSD, LF-power and HF-power were significantly lower in patients compared to controls (Table 3). After four weeks, heart rate was significantly higher whereas SDNN, RMSSD, LF-power and HF-power were significantly lower in patients compared to controls. Differences between controls and patients were larger after four weeks compared to after one week (Cohen's d = 0.98 to 1.36 for SDNN, RMSSD, LF-power and HF-power). LF/HF-ratio did not differ between patients and controls.

As tricyclic antidepressants (TCA) significantly decrease HRV (Kemp et al., 2010), we excluded patients with TCA treatment (n = 11, 33.3%) in post-hoc analysis. After TCA exclusion, all HRV parameters in patients at week four were still decreased compared to controls (Cohen's d = 0.79 to 1.03).

HRV variables did not separate between responders and non-responders, neither at week one nor at week 4 (Table 4). HRV (RMSSD, LF- and HF-power) were decreased in both, responders and non-responders, at week 1 and week 4, though at week 4 difference between NR and Controls was larger than between R and Controls (Fig. 2 for LF-power). After four weeks of medication, LF-power correlated with the HAM-D score ($r = -0.32$; $p < 0.1$).

3.4. REM density

REM sleep density was higher in patients than in controls (Table 3) and these differences were more pronounced after four

Table 2
Demographic, clinical, conventional and quantitative EEG sleep parameters of responders, non-responders and healthy controls after one week of antidepressant medication.

	Responders (N = 14)	Non-Responders (N = 19)	Comparison Subjects for Responders (N = 14)	Comparison Subjects for Non-Responders (N = 19)	Analysis		
	Ratio	Ratio	Ratio	Ratio	p[a]		
Gender (Female: Male)	10: 4	11: 8	10: 4	11: 8	ns		
Diagnose (Recurrent Affective Disorder: First Episode)	9: 5	15: 4			ns		
Antidepressant medication (REM-suppressing: REM-not-suppressing)	10: 4	13: 6			ns		
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	p[b]		
Age (years)	45 (20)	47 (14)	44 (20)	47 (13)	ns		
Previous depressive episodes	2.2 (2.9)	3 (3)	0 (0)	0 (0)	ns		
HAM-D at inclusion	24.9 (5.6)	24 (7)			ns		
HAM-D at week 1	18.8 (7.5)	21.7 (6.2)			ns		
HAM-D at week 4	7.9 (5)	18.8 (5.9)			<0.001		
Sleep continuity					p[b]	p[c]	p[d]
Total sleep time (min)	421.6 (30.5)	418.8 (39.2)	431.4 (43.2)	424.2 (34.3)	ns	ns	ns
Sleep efficiency[e]	87.7 (6.4)	87 (8.1)	90 (9.1)	88 (7.2)	ns	ns	ns
Sleep architecture (minutes)							
REM latency	175.4 (128.3)	191.4 (101.1)	76.1 (39.7)	76.3 (36.2)	ns	**0.01**	**<0.001**
REM duration	64.9 (44.1)	52.6 (29.6)	88.5 (21.3)	79.4 (24.9)	ns	ns	**0.005**
Sleep onset latency	21.1 (15.4)	19.9 (14.9)	12 (16.3)	11.8 (6.2)	ns	ns	**0.036**
S1 duration	59.3 (19.8)	65.9 (36.6)	43.5 (14.1)	48.4 (18.9)	ns	**0.02**	ns
S2 duration	226.5 (49.3)	224.3 (60.6)	221.5 (42.3)	227 (28.6)	ns	ns	ns
Slow wave sleep latency	12.8 (6.1)	19.8 (20.3)	11 (6.3)	22.2 (33.5)	ns	ns	ns
Slow wave sleep duration	62.5 (44)	74.6 (56.4)	76.6 (37.2)	68.3 (37.6)	ns	ns	ns
Relative prefrontal power in theta (4–8 Hz) band[f,g]	23.7 (4.8)	22.8 (6.6)	23 (4.6)	27.4 (4.6)	ns	ns	**0.017**

Responders fulfilled criterion of decreased HAM-D score of at least 50%.
HAM-D: Hamilton Depression Rating Scale; REM: rapid eye movement sleep, S1: Non REM sleep stage1; S2: Non REM sleep stage 2; ns: not significant, i.e. $p \geq 0.05$.
[a] Fisher Exact test, two-tailed, between responders and non-responders.
[b] T test, two-tailed, unpaired, between responders and non-responders.
[c] T test, two-tailed, unpaired, between responders and matched healthy controls.
[d] T test, two-tailed, unpaired, between non-responders and matched healthy controls.
[e] Sleep efficiency is the ratio of sleep to time spent in bed showed as percentage.
[f] The mean value from 2 prefrontal electrodes (Fp1, Fp2) in theta frequency band.
[g] Percentage of total power in 0.5–20 Hz frequency range.

Table 3
Cordance, HRV parameters and REM-variables of patients after the first and fourth week of antidepressant medication and healthy controls.

	Patients W1 (n = 33)	Patients W4 (n = 30) [a]	Controls (N = 33)	Analysis [b]		
	Mean (SD)	Mean (SD)	Mean (SD)	W1 v W4	W1 v C	W4 v C
Prefrontal theta cordance	−2.58 (0.68)	−2.69 (0.72)	−2.48 (0.95)	0.599	0.628	0.340
Heart rate, (min^{-1})	66.15 (9.64)	69.97 (10.94)	62.42 (7.86)	0.145 [S]	0.090 [S]	0.002 [M]
HRV Parameters						
SDNN, ln	3.82 (0.60)	3.50 (0.12)	4.07 (0.58)	0.049 [M]	0.084 [S]	0.001 [L]
RMSSD, ln	3.17 (0.82)	2.81 (0.84)	3.62 (0.82)	0.092 [S]	0.027 [M]	<0.001 [L]
LF power, ln	5.64 (1.69)	4.89 (1.69)	6.75 (1.29)	0.087 [S]	0.004 [M]	<0.001 [L]
HF power, ln	4.79 (1.84)	4.16 (1.61)	5.84 (1.73)	0.157 [S]	0.019 [M]	<0.001 [L]
LF/HF ratio, ln	1.36 (0.82)	1.31 (0.77)	1.36 (0.83)	0.803	0.990	0.815
REM-Variables						
REM density	2.43 (1.67)	2.82 (1.56)	1.78 (0.81)	0.333 [S]	0.050 [M]	0.002 [L]
REM latency	184.55 (111.84)	169.17 (98.64)	76.23 (37.09)	0.559	<0.001 [L]	<0.001 [L]
REM duration	57.79 (36.36)	65.70 (36.45)	83.27 (23.54)	0.381 [S]	0.001 [L]	0.024 [M]

SD: standard deviation; HRV: heart rate variability; SDNN: standard deviation of all NN intervals; RMSSD: square root of the mean of the squares of differences between adjacent NN intervals; LF power: low frequency power (0.04–0.15 Hz); HF power: high frequency power (0.15–0.4 Hz); REM: rapid eye movement sleep; HAMD-D: Hamilton Depression rating scale; Cohen's d: [S]: small effect size, $0.20 \leq d \leq 0.49$; [M]: moderate effect size, $0.50 \leq d \leq 0.79$; [L]: large effect size, $d \geq 0.80$.
[a] Due to the absence of 3min continuous REM sleep at week 4 (W4) three responders had to be excluded.
[b] T test, two-tailed, unpaired, between patients after one week treatment (W1), four weeks (W4) or healthy matched controls (C).

Table 4
Cordance, REM-density and HRV parameters of responders and non-responders and matched controls after the first and fourth week of antidepressant medication.

		Responders (R) (n = 14)	Non-Responders (NR) (n = 19)	Controls for R (C-R) (n = 14)	Controls for NR (C-NR) (n = 19)	R vs NR	Analysis[b] R vs. C-R	NR vs. C-NR
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	P	p	p
Prefrontal theta cordance	W1:	−2.15 (0.78)	−2.90 (0.37)	−2.77 (0.51)	−2.27 (1.15)	<0.001 [L]	0.020 [L]	0.029 [M]
	W4:	−2.30 (0.94)[a]	−2.95 (0.36)			0.011 [L]	0.118	0.020 [M]
REM-density	W1:	2.15 (1.53)	2.63 (1.78)	1.73 (0.74)	1.81 (0.87)	0.420	0.368	0.083 [M]
	W4:	2.98 (1.64)	2.71 (1.53)			0.832	0.023[L]	0.034 [M]
Heart rate, min	W1:	67.4 (11.2)	65.3 (8.5)	61.8 (7.9)	62.9 (8.0)	0.561	0.144	0.377
	W4:	70.4 (11.7)	69.7 (10.8)			0.858	0.036 [L]	0.035 [M]
HRV Parameters								
SDNN, ln	W1:	3.80 (0.63)	3.83 (0.60)	4.17 (0.73)	4.00 (0.44)	0.872	0.157	0.338
	W4:	3.69 (0.79)	3.37 (0.55)			0.198	0.118	<0.001[L]
RMSSD, ln	W1:	3.29 (0.73)	3.07 (0.89)	3.88 (0.94)	3.43 (0.68)	0.460	0.077 [M]	0.171
	W4:	3.06 (1.00)	2.63 (0.68)			0.173	0.043 [L]	0.001 [L]
LF power, ln	W1:	5.74 (1.80)	5.56 (1.66)	6.72 (1.49)	6.77 (1.16)	0.763	0.130	0.013 [L]
	W4:	5.53 (1.78)	4.47 (1.53)			0.094	0.075 [M]	<0.001[L]
HF power, ln	W1:	4.89 (1.84)	4.72 (1.89)	6.34 (1.91)	5.49 (1.54)	0.797	0.050 [M]	0.180
	W4:	4.63 (1.91)	3.85 (1.35)			0.201	0.032 [L]	0.002 [L]
LF/HF ratio, ln	W1:	1.39 (0.95)	1.34 (0.74)	0.98 (0.54)	1.64 (0.91)	0.868	0.175	0.276
	W4:	1.35 (0.72)	1.29 (0.83)			0.832	0.148	0.228

Note: Responders fulfilled criterion of depressed HAMD-D score of at least 50%.
[a] Due to the absence of REM sleep in EEG recording after 4 weeks of treatment one responder had to be excluded from 4th week cordance comparison.
[b] T-Tests, two-tailed, unpaired between responders (R), non-responders (NR) or matched controls (C-R and C-NR, resp.).

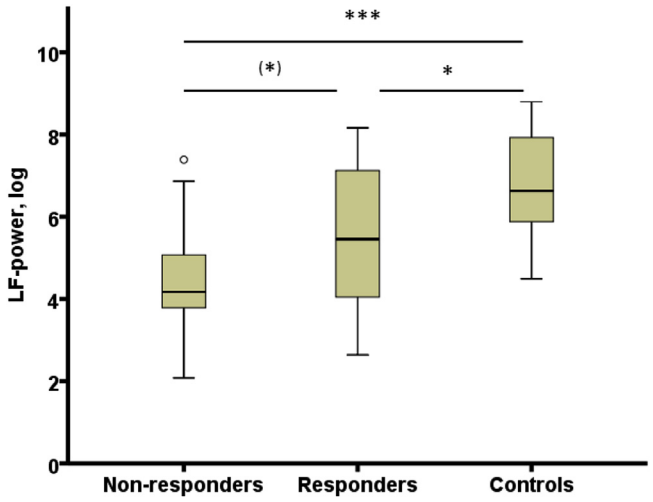

Fig. 2. HRV (LF-power, log) in non-responders and responders at week 4 and controls. HRV: heart rate variability; LF-power, log: power in low frequency range (0.04–0.15 Hz) transformed with natural logarithm; $^{(*)}p < 0.10$; $^{*}p < 0.05$; $^{***}p < 0.001$.

weeks than after the first week (week 1: d = 0.50; week 4: d = 0.84). Comparing responders (N = 14) and non-responders (N = 19), both sub-samples showed higher REM density than matched controls, not significantly at week 1 (R: d = 0.37; NR: d = 0.56) but at week 4 ($p < 0.05$; R: d = 0.99; NR: d = 0.73) (Table 4). Moreover, REM density did not differ between responders and non-responders, neither at week 1 nor at week 4 ($p > 0.40$).

3.5. Prefrontal cordance

After the first week of antidepressant treatment, cordance was significantly higher ($p < 0.001$) in responders compared to non-responders with large effect size (Cohen's d = 1.3, Table 4, Fig. 3), irrespective of covariates (patient's age, sex and number of previous depressive episodes; ANCOVA, $F_{1,28} = 6.012$, $p < 0.001$). After four weeks of treatment, cordance was still significantly higher in responders than in non-responders ($p = 0.011$). However, including covariates masked these differences (ANCOVA, $F_{1,28} = 2.067$, $p = 0.113$). Significant changes in cordance between the first and fourth week did not occur neither in responders ($p = 0.647$) nor in non-responders ($p = 0.709$).

As compared to controls, we observed significant differences in cordance in both responders ($p = 0.020$) and non-responders ($p = 0.029$) after the first week of medication. In addition, after the fourth week of medication, non-responders still differed significantly from controls ($p = 0.020$), while responders reached similar cordance values as controls.

After the first week cordance correlated positively with the improvement in the HAM-D score when all patients (N = 33) were considered (Pearson's correlation, $r = 0.48$; $p = 0.005$); the higher the cordance after the first week, the larger the improvement in HAM-D between inclusion and the fourth week. We did not observe significant correlations between cordance at week 1 and HAM-D at week 1 ($r = 0.23$; $p = 0.202$), as well as cordance at week 4 and HAM-D at week 4 ($r = 0.32$; $p = 0.076$).

3.6. Outcome prediction

The Receiver Operating Characteristics (ROC) analysis, applied to prefrontal theta cordance computed from all the tonic REM sleep epochs after the first week of treatment, yielded an area under the curve of 0.90 ($p < 0.001$). Based upon ROC analysis, a prefrontal cordance threshold value of −2.52 was selected to classify responders and non-responders: patients with cordance above this threshold were predicted as responders and those below were predicted as non-responders. The prefrontal cordance predicted the treatment response with an overall accuracy of 88% (79% sensitivity, 95% specificity, 92% positive predictive value, 86% negative predictive value).

3.7. The interplay between HRV, REM density and cordance

There was a significant negative correlation between HRV and REM-density not influenced by severity of depression or treatment response in controls (HF-power: $r = -0.35$, $p < 0.05$) and in patients

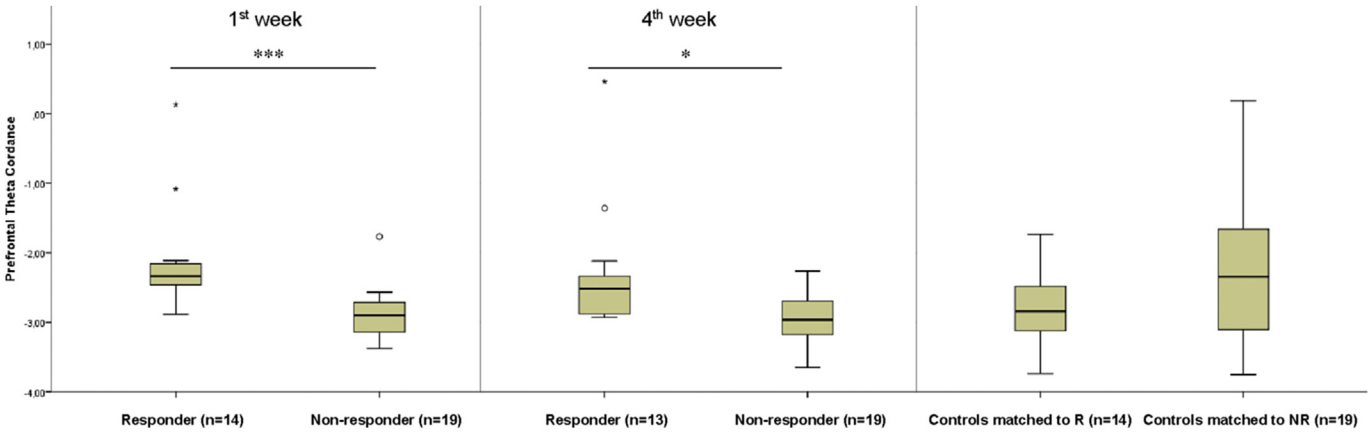

Fig. 3. Cordance in responders, non-responders and healthy controls after the first and fourth week of antidepressant medication.
After first week of antidepressant medication responders showed higher prefrontal theta cordance than non-responders ($p < 0.001$), still significant in ANCOVA with age, sex and number of previous depressive episodes beforehand ($F_{1,14} = 6.012$, $p < 0.001$) as covariates. At fourth week responders differed from non-responders ($p = 0.011$), but without significance in ANCOVA anymore. Healthy matched to responders or non-responders are displayed on the right side. $^{*}p < 0.05$; $^{***}p < 0.001$.

Table 5
Bivariate Pearson's correlations r and partial correlations (controlled for HAM-D-score) between REM density and different HRV variables in controls, patients at week 1 and patients at week 4.

	Correlation	SDNN	RMSSD	LFpower	HFpower	ratio LF/HF
Controls (N = 33)	Pearson	r = -0.25	r = -0.29	r = -0.29$^{(*)}$	r = -0.35*	r = 0.22
Patients W1 (N = 33)	Pearson	r = -0.12	r = -0.23	r = -0.16	r = -0.13	r = -0.02
	Partial	r = -0.13	r = -0.23	r = -0.17	r = -0.13	r = -0.03
Patients W4 (N = 30)	Pearson	r = -0.39*	r = -0.22	r = -0.39*	r = -0.23	r = -0.21
	Partial	r = -0.39*	r = -0.22	r = -0.41*	r = -0.23	r = -0.22

Correlations between REM density and different HRV variables. Partial correlations are corrected with HAM-D as covariate.
HAM-D: Hamilton Depression rating scale; REM: rapid eye movement sleep; W1: week 1; W4: week 4; SDNN: standard deviation of all NN intervals; RMSSD: square root of the mean of the sum of the squares of differences between adjacent NN intervals; LFpower: Power in low frequency range 0.04–0.15 Hz; HFpower: Power in high frequency range 0.15–0.4 Hz; $^{(*)}$ $p < 0.10$; $^{*}p < 0.05$.

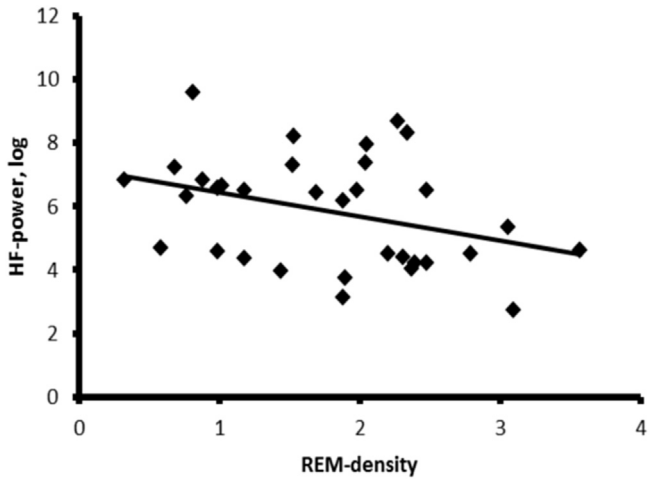

Fig. 4. Correlation between REM density and the HRV parameter HF power (log-transformed) in controls. (Pearson's Correlation r = -0.35, $p < 0.05$).
Relationship between HRV and REM density shows a negative correlation in healthy controls (HF-power: r = -0.35, $p < 0.05$). HRV: heart rate variability; REM: rapid eye movement sleep; HF power, log: power in high frequency range (0.15–0.4 Hz), transformed with natural logarithm.

at week 4 (LF-power: $r = -0.39$, $p = 0.03$; Table 5 and Fig. 4).

There were no significant correlations between any of the assessed HRV variables and cordance neither in control subjects nor in patients at any time point (Pearson's correlations always $p > 0.20$). We also did not find significant correlations between cordance and REM density (always $p > 0.4$).

4. Discussion

This study shows that REM sleep-derived HRV distinguishes between depressed patients and healthy subjects both, at the end of the first and the fourth week of antidepressant treatment. In addition REM sleep-derived HRV correlated negatively with REM density, which was evident in healthy subjects and in patients after four weeks of treatment. Although, HRV during REM sleep did not separate between responders and non-responders, these results indicate that REM sleep derived HRV may be used as a biomarker of depression though not treatment response.

To the best of our knowledge, this study is the first to evaluate HRV during REM sleep as marker of depression and antidepressant treatment outcome. Our results confirm studies of HRV during wakefulness, by showing that HRV is consistently decreased in depression (Kemp et al., 2010). Moreover, REM sleep derived HRV seems to indicate depression with more accuracy than HRV during waking state (considering effect sizes of Cohen's d = 0.8 to 1.4 in this study; compared to 0.3 to 0.6 in the meta-analysis of Kemp et al. (2010)). Therefore, HRV analysis during REM sleep appears more conclusive than during wakefulness when examining depressed patients.

Our results confirm previous findings showing that despite an improvement of depression, HRV measures were not restored (Glassman et al., 2007; Kemp et al., 2010). Although responders presented with descriptively higher HRV measures than non-responders, this difference was not caused by the increase of HRV in responders but by a further decrease in non-responders. There are only few studies that found differences of HRV between responders and non-responders. Khaykin et al. (1998) did also observe a further decrease of HRV in non-responders but only a mild increase in responders. Others did not find any pre-post treatment difference of HRV related to clinical outcome (Kemp et al., 2010). The persistent HRV reduction in patients despite improvement of depression cannot be attributed to mere side effects of antidepressants: First of all, this observation is very consistent in studies with different antidepressants (Kemp et al., 2010; Udupa et al., 2011). Second, our results did not change significantly when excluding cases with TCA-treatment from analysis (the class of antidepressants with the putatively largest blunting effect on HRV (Udupa et al., 2011)). And finally, even in studies, which applied treatment strategies with no or minimal effect on HRV (e.g. cognitive behavioural therapy, transcranial direct current stimulation or SSRI), HRV did not resolve (Agelink et al., 2001; Brunoni et al., 2013; Carney et al., 2000; Glassman et al., 2007; Kemp et al., 2010; Udupa et al., 2011; Van Zyl et al., 2008). Therefore, we suggest that the persistent reduction of HRV may be a trait marker of MDD beyond improvement of the actual depressive episode.

Actually, biomarker properties of HRV in REM sleep did resemble REM density. The latter is considered a trait marker of MDD, with high values indicating increased risk of depression (review: Steiger et al., 2015). In our study, both, HRV and REM density separated between patients (total group at week 1 and 4; responders and non-responders at week 4) and matched controls but they did not predict response. Moreover, deviation of HRV and REM densitiy persisted despite clinical improvement in responders at week 4. This similarities are further supported by a correlation between decreased HRV measures in REM-sleep and an increased REM-density in both, healthy controls and patients at week 4. To conclude, HRV in REM-sleep has similar trait marker properties as REM density.

This is in line with the common neural correlates of HRV and REM sleep regulation: During REM sleep there is an enhanced activity in CAN which is involved in cardiovascular regulation and influences the HRV (Desseilles et al., 2006). In addition, CAN influences the activity of REM sleep-generating brain areas (Chouchou and Desseilles, 2014). Thereby, changes in the top-down-control of CAN may lead to predominance of sympathetic activity and may indirectly converge with the disinhibition of REM sleep, which would be reflected by increased REM density.

In contrast to HRV, cordance does not serve to distinguish between depressed patients and control subjects, but rather predicts treatment outcome in depression. This study corroborates preliminary data performed on 20 patients (Adamczyk et al., 2015), which showed that prefrontal theta cordance measured during REM sleep in MDD patients predicted antidepressant treatment response already after one week of treatment. Responders displayed a significantly higher absolute cordance compared to non-responders based on a total night tonic REM sleep analysis. Compared to healthy subjects cordance tended to be higher in responders but lower in non-responders. In our previous report (Adamczyk et al., 2015) the overall accuracy was 79% (sensitivity 62%, positive predictive value 83%) and improved to 88% (sensitivity 79%, positive predictive value 92%) in the current study. Taking all patients together, we observed a positive correlation between cordance after the first week of treatment and improvement in HAM-D score after the fourth week. Based on the high positive predictive value of 92% in this study, compared to the positive predictive value of cordance obtained during wakefulness, which ranged between 69% and 75% (Bares et al., 2007, 2008; Cook et al., 2002), we conclude that, similar to HRV, REM sleep is superior to waking state in providing cordance with highly accurate predictive value. The distinct utility of REM sleep is due to the fact that in contrast to wakefulness tonic REM sleep is very homogenous and well defined (American Academy of Sleep Medicine, 2009).

Finally, prefrontal theta cordance and HRV during REM sleep seem to be uncorrelated variables. From a clinical point of view, cordance relates to the capacity of response to antidepressant treatment, whereas HRV, similar to REM density, represents a trait marker of depression. Even though our data do not provide a direct answer to the neurophysiological background of this difference, we may speculate that as prefrontal theta cordance is positively correlated with cerebral perfusion in the PFC and the ACC, it may index the capability of these structures to therapeutical interventions (Leuchter et al., 1999; Nishida et al., 2004). In contrast, HRV in REM sleep may index the activity of the CAN consisting of PFC, ACC, insula and amygdala resulting in regulation of medullary cardo-acceleratory circuits (Aron et al., 2014; Chikazoe et al., 2007; Chouchou and Desseilles, 2014; Thayer and Lane, 2009; Thayer et al., 2012).

5. Limitations

There are several limitations of this study. The lack of base-line sleep assessments before start of treatment was due to the fact, that some patients were treated with ADs before, and in common clinical practice, ineffective ADs are switched without wash-out and drug free period. Therefore, we timed the first assessment after one week of treatment with the new AD, when all patients had achieved standard dosage. In order to search for robust and feasible biomarkers for natural clinical settings this procedure seemed appropriate to us. In addition, our patients were treated with various antidepressants. It is noteworthy that previous cordance studies in wakefulness reported consistent changes in prefrontal brain activity under various antidepressants, also in treatment-resistant patients without a wash-out period between treatment regimens (Cook et al., 2005), showing a promising robustness of cordance as a biomarker for applied medication. Regarding the detected optimal cut-off used for prediction (to differentiate between responders and non-responders) it is necessary to point out that it is valid only for our study sample and cannot be used generally.

Further, as HRV measurements before onset of treatment were lacking, we could not examine the influence of antidepressant medication on HRV directly. According to studies of HRV in wakefulness, some antidepressants, especially TCAs, may have a small attenuating effect on HRV (Bär et al., 2004; Kemp et al., 2010; Licht et al., 2010, 2015), an effect possibly accumulating with the HRV blunting effect of untreated depression, however, post hoc analyses without the TCA treated patients did not change the pattern of results significantly. Further, long-term follow-up data are required extending to the time of complete remission and final washout from antidepressants. This would allow us to address whether HRV in REM sleep has properties of a trait marker, representing a biological “scar”, indicating an increased risk of recurrent depression.

6. Conclusion

Our results confirm preliminary data that prefrontal theta cordance measured during REM sleep has the potential to become a promising biomarker for antidepressant treatment response. It

offers a better predictive value than cordance measured during wakefulness. Further studies will test prefrontal theta cordance during REM sleep in prospective clinical trials. In contrast to cordance, HRV during REM sleep does not predict response to treatment. However, it distinguishes depressed patients from healthy subjects and correlates with REM density. The negative correlation, in the healthy subjects without confounding factors, confirms physiological expectations, that an unfavourable low HRV goes along with an unfavourable high REM density – both biomarkers being most likely trait markers within a top-down regulation.

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