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CNS- and ANS-arousal predict response to antidepressant medication: Findings from the randomized iSPOT-D study

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ABSTRACT

Arousal systems are one of the recently announced NIMH Research Domain Criteria to inform future diagnostics and treatment prediction. In major depressive disorder (MDD), altered central nervous system (CNS) wakefulness regulation and an increased sympathetic autonomic nervous system (ANS) activity have been identified as biomarkers with possible discriminative value for prediction of antidepressant treatment response. Therefore, the hypothesis of a more pronounced decline of CNS and ANS-arousal being predictive for a positive treatment outcome to selective-serotonin-reuptake-inhibitor (SSRI) treatment was derived from a small, independent exploratory dataset (N = 25) and replicated using data from the randomized international Study to Predict Optimized Treatment Response in Depression (iSPOT-D). There, 1008 MDD participants were randomized to either a SSRI (escitalopram or sertraline) or a serotonin-norepinephrine-reuptake-inhibitor (SNRI-venlafaxine) arm. Treatment response was established after eight weeks using the 17-item Hamilton Rating Scale for Depression. CNS-arousal (i.e. electroencephalogram-vigilance), ANS-arousal (heart rate) and their change across time were assessed during rest. Responders and remitters to SSRI treatment were characterized by a faster decline of CNS-arousal during rest whereas SNRI responders showed a significant increase of ANS-arousal. Furthermore, SSRI responders/remitters showed an association between ANS- and CNS-arousal regulation in comparison to non-responders/non-remitters while this was not the case for SNRI treatment arm. Since positive treatment outcome to SSRI and SNRI was linked to distinct CNS and ANS-arousal profiles, these predictive markers probably are not disorder specific alterations but reflect the responsiveness of the nervous system to specific drugs.

1. Introduction

Recently, the United States National Institute of Mental Health (NIMH) has introduced the Research Domain Criteria (RDoC) project which is aimed to transform clinical syndrome-based diagnosis into an individualized framework of psychophysiology to support the diagnostic process of mental disorders (Insel et al., 2010). The major RDoC domains include the arousal/modulatory systems as separate criteria to inform transdiagnostic approaches and therapeutic/diagnostic decisions. In this study we will investigate how arousal/modulatory research domains are associated with antidepressant treatment outcome in major depressive disorder (MDD).

For all higher order organisms, the behavior and interaction with its environment are profoundly influenced by regulation of central nervous system (CNS) arousal (Hegerl and Hensch, 2012) and autonomic nervous system (ANS) arousal (Head, 1923). Maladaptive behavior as can be found in psychiatric disorders might

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hence reflect alterations in these global regulatory systems (Hegerl and Hensch, 2012). In MDD, the discussion about altered CNS-arousal and wakefulness-regulation as contributing factors for the disorder has been sparked by findings of disturbed sleep architecture (Arfken et al., 2014; Hoffmann et al., 2000; Lopez et al., 2010; Olbrich and Arns, 2013; Reynolds et al., 1985; Rotenberg et al., 2002) and the antidepressant effects of sleep-deprivation and chronobiological treatments (McClung, 2013). Facilitated by the clinical finding of disturbed sleep initiation in the majority of MDD patients, a conceptual framework has been proposed that links behavioral core dysfunction in MDD such as sleep disturbances and withdrawal from arousing environments to an increased cortical tonic arousal (Hegerl and Hensch, 2012). The symptoms of the disorder hence are interpreted as a counter-regulating mechanism to this elevated CNS-arousal.

Following this hypothesis, Hegerl et al. (Hegerl et al., 2011) demonstrated elevated CNS-arousal in patients suffering from MDD in comparison to healthy controls during resting electroencephalogram (EEG), a finding that was replicated by Olbrich et al. (Olbrich et al., 2012). Although several studies have reported greater resting state EEG-alpha power in responders to antidepressant medication than in non-responders (Bruder et al., 2001; Tenke et al., 2011; Ulrich, 1987), the predictive power of CNS-arousal regulation has not been addressed so far.

Further there is also a strong linkage between the activity of the ANS and mood symptoms (Brown et al., 2009). MDD is an independent risk factor for myocardial infarction and coronary heart disease (Nicholson et al., 2006) and patients with cardiovascular diseases show increased rates of MDD (Egede, 2007). Therefore the activity of the ANS, including a possible hyper activation of the sympathetic branch thereby seems to play a crucial role in the linkage of cardiovascular and mood symptomatology (Carney et al., 2005). In line with this, several studies report a shift toward an increased sympathetic and decreased parasympathetic activity in MDD (Brunoni et al., 2013; Kemp et al., 2010). Although some studies report of a predictive value of heart rate variability (HRV) in the treatment of MDD (Fraguas et al., 2007; Jain et al., 2014), no study to our knowledge exists that examined the predictive power of the heart rate (HR), which has been proven to be a reliable measure of ANS-function (Grassi et al., 1998).

In healthy subjects a tight interaction of ANS- and CNS arousal exists. During the resting state, high sympathetic activity is associated with a high CNS-arousal and high parasympathetic activity with low CNS-arousal (Olbrich et al., 2011). However, disturbances of the interaction between ANS-function and CNS-arousal in MDD have not been systematically investigated.

Following the above findings, the first goal of this study was to analyze whether successful antidepressant treatment (response or remission) with a selective-serotonin-reuptake-inhibitor (SSRI) in contrast to treatment failure (non-response or non-remission), is associated with differences in CNS-arousal (defined by EEG-vigilance) and ANS-arousal (defined by HR).

Further, different classes of antidepressant medications have been reported to evoke distinct changes in arousal function (Kemp et al., 2010; Licht et al., 2010). Thus a secondary goal was to investigate whether CNS- and ANS-arousal profiles differed for treatment outcome following treatment with SSRIs or with serotonin-norepinephrine-reuptake-inhibitors (SNRIs), pointing out a possible discriminative value for the choice of medication.

For generation of hypothesis about the direction of changes, a first small and independent dataset was analyzed by means of arousal function and SSRI treatment outcome. Then data from the multi-center, randomized, prospective open-label international Study to Predict Optimized Treatment Response in Depression (iSPOT-D) (see(Arns et al., 2015; Williams et al., 2011) for details) was used for confirmation of CNS- and ANS-arousal markers in the prediction of SSRI treatment outcome. Further, an exploratory analysis aimed at differences of CNS and ANS-arousal parameters in responder/remitters (non-responders/non-remitters respectively) during SSRI and SNRI treatment was carried out.

2. Materials and methods

2.1. Design, participants and treatment

2.1.1. Exploratory dataset

The exploratory first dataset consisted of 23 patients with MDD recruited at the university hospital Leipzig, Germany. All subjects were unmedicated at baseline and treated with a SSRI (escitalopram or sertraline). Re-evaluation of depressive symptoms was done after two weeks using the 17-item Hamilton Rating Scale for Depression ($HRSD_{17}$). Since a two-week interval is quite short to lead to a reduction of 50% in $HRSD_{17}$, response was defined as a reduction of only >33% in $HRSD_{17}$ in this exploratory dataset.

2.1.2. iSPOT-D dataset

In the second dataset from the international multi-center, randomized, prospective open-label trial (Phase-IV clinical trial), MDD participants were randomized in equal parts to escitalopram, sertraline or venlafaxine-extended release.

After screening 6693 patients for eligibility, 1008 were enrolled (Fig. 1 shows more detail of this trial see (Williams et al., 2011)). Diagnosis of non-psychotic MDD (allowing comorbid anxiety disorders) was confirmed before randomization at the baseline visit using the Mini-International Neuropsychiatric Interview (MINI-Plus) (Sheehan et al., 1998), according to DSM-IV criteria, and a score $\geq$16 on the $HRSD_{17}$. All participants were drug-naïve or underwent a sufficient washout period of at least five half-lives of the previously used medication. Remission was defined as a score of $\leq$7 and response as a >50% decrease in $HRSD_{17}$ score from baseline to week eight.

2.2. Ethics statement

The exploratory study and the iSPOT-study were approved by the institutional review boards at all of the participating sites and were conducted according to the principles of the Declaration of Helsinki 2008. After study procedures were fully explained, participants provided written informed consent. The iSPOT trial was registered with ClinicalTrials.gov. Registration Number: NCT00693849; URL: http://clinicaltrials.gov/ct2/show/NCT00693849.

2.3. Pre-treatment assessments

Electroencephalogram (EEG) and electrocardiogram (ECG) were recorded during 15 min (exploratory dataset) or 2 min (iSPOT-data) resting state with eyes closed. Details of the reliability and across-site consistency have been published elsewhere (Williams et al., 2005). Participants were seated in a sound and light attenuated room with temperature of 22 °C to avoid arousal changes due to uncomfortable light or temperature. EEG data were acquired from 26 channels (extended international 10–20 system, averaged mastoid reference, AFz ground, impedance<5kOhms, sampling rate >500 Hz) with additional ECG (sampling rate >500 Hz) and electrooculogram (EOG) channels (horizontal and vertical).

2.4. Analysis

2.4.1. Data preprocessing

Notch filters of 50 or 60 Hz (depending on recording site) and high/low-pass filters (EEG: 0.5 Hz/70 Hz; EOG 0.05 Hz/70 Hz; ECG: 0.1 Hz/10 Hz) were applied to the data after EOG correction (details about EG processing are described in detail elsewhere: Arns et al. (2015)). Artifact epochs were marked using a maximum–minimum criterion of 100 μV in EEG-channels. A visual inspection of EEG-data by two experienced EEG-raters showed no sleep patterns. Data were resampled to 100 Hz. Horizontal slow eye movements (SEMs) as indicators of drowsiness were marked when the difference of left and right EOG-channels exceeded 150 μV within a moving time window of 6s.

2.4.2. CNS-arousal: EEG – vigilance analysis

CNS-arousal was assessed from EEG/EOG data by using the computer-based Vigilance Algorithm Leipzig (VIGALL 2.0 plug-in for Brain Vision Analyzer 2.0, Gilching, Germany). VIGALL classifies each 1-s segments of resting state EEG into different CNS-arousal levels. The resulting time series then consisted of ratings for every epoch ranging from 7 (highest CNS arousal) to 1 (lowest CNS arousal). For a more detailed description, please refer to the handbook (http://uni-leipzig.de/~vigall/), for validation studies of VIGALL see (Guenther et al., 2011; Olbrich et al., 2015, 2009). As a metric of CNS-arousal, the median (due to the ordinal-scale nature of the measure) of all one-second epochs (exploratory dataset: 900s; iSPOT-dataset: 120s) was calculated for each patient ("median vigilance"). To assess the change of CNS-arousal over time, the slope of the linear regression curve for median vigilance values of three consecutive blocks (exploratory dataset: 300s; iSPOT-dataset: 40s) was computed ("vigilance slope").

2.4.3. ANS-arousal: ECG pre-processing and heart rate analysis

A semiautomatic ECG R-peak detection was performed using Kubios software (University of Eastern Finland) (Tarvainen et al., 2014). Datasets were excluded when >5% of R-peaks could not be classified. As ANS-arousal metrics, the average heart rate ("heart rate") was calculated as beats per minute for the whole resting state period (exploratory dataset: 900s; iSPOT-data: 120s) as well as the slope of averaged HR for three consecutive blocks ("heart rate slope").

2.5. Statistics

SPSS 20 (IBM Corp. Released 2011. IBM SPSS Statistics, Version 20.0. Armonk, NY: IBM Corp.) was used for statistical analysis. Normal distribution of EEG/ECG measures was inspected and ANS/CNS parameters were log transformed before statistical analysis. Significance level was set to $p < 0.05$ for all analysis.

2.5.1. Exploratory dataset

ANS- and CNS arousal profile differences between responders and non-responders were tested using two-tailed t-test.

2.5.2. iSPOT-dataset

Differences in age, gender and education between groups were tested using One-Way analysis of variance (ANOVA) or non-parametric tests (chi^2 for gender) (see Table 1), parameters with significant differences were added as a covariate in further analysis.

For the confirmatory analysis of the findings from the exploratory dataset, a binary logistic regression with groups (responders vs non-responders; remitters vs non-remitters) as dependent variable and the ANS/CNS metrics as independent variables was used to test for differences of CNS and ANS-arousal parameters.

ANCOVA was applied with arousal parameters as dependent variables, medication (SSRI or SNRI) as factor and sociodemographic covariates to test for differences of arousal parameters of responders/remitters (non-responders/non-remitters respectively) between SSRI and SNRI treatment arms.

Repeated measures ANOVA with median vigilance or average heart rate during three consecutive 40s blocks as inter-subject factor ("vigilance time") and group (responders vs. non-responders; remitters vs. non-remitters) as between-subject factor were calculated while age was included as covariate. The three X 40s block design was chosen since Arns et al. (Arns et al., 2014) showed that the dynamic changes of EEG-parameters within two minutes have a predictive value in MDD treatment. Greenhouse-Geisser correction was applied to all tests for correction of degrees of freedom.

Further, a correlational analysis was performed for CNS and ANS-arousal parameters of responders/remitters and non-responders/non-remitters for the different treatment arms to investigate the interaction of CNS and ANS activity. Differences of correlation-coefficients were assessed using Fisher-z test. Also a correlation analysis on $HRSD_{17}$ changes and CNS and ANS-arousal parameters was performed.

3. Results

3.1. Exploratory dataset

Analysis of the exploratory dataset of 15 min of rest from 25 patients mean age 43 years, SD 16; 11 female; response in 17 out of 25 subjects (68%) revealed a significantly steeper decline in CNS arousal, i.e. a more negative CNS-arousal slope ($p < 0.03$; Cohen's $d = 0.84$) and a trend for a faster declining ANS-arousal, i.e. more negative ANS-arousal slope ($p < 0.06$; Cohen's $d = 0.94$) in responders compared to non-responders to SSRI treatment after 2 weeks.

When analyzing only the first two minutes (which was the length for the resting state in the following iSPOT dataset), results were not significant for CNS-arousal slope ($p = 0.57$; Cohen's $d = 0.34$) but were for ANS-arousal slope ($p < 0.04$; Cohen's $d = 0.86$).

Taken together, it was therefore hypothesized that in the iSPOT dataset, responders to SSRIs would reveal a faster declining CNS-arousal (more negative slope) and a faster declining ANS-arousal (more negative slope) as compared to non-responders. Since all patients in the exploratory dataset were treated with SSRIs, no hypothesis could be generated about different profiles of arousal parameters for treatment outcome following treatment with SSRIs or SNRIs.

3.2. iSPOT dataset

The duration of the resting state in the iSPOT dataset was limited to two minutes. Of the 1008 MDD participants enrolled in the study (intention to treat), 655 patients were reassessed at week eight and taking the medication they were randomized to (per protocol). The main reasons for drop-out after allocation were not starting the treatment, having less than six weeks of medication and having no assessment at week eight. After a further drop-out of 57 datasets due to unusable EEG or ECG data, 598 patients were included in the present study (for detailed consort diagram see Fig. 1). Remission and response rates were 46% and 64%, respectively. Medications randomized were as follows: SSRIs with N = 414 (escitalopram N = 198, sertraline N = 216) and SNRI with N = 184 (venlafaxine-XR). A detailed listing of the sociodemographic data, response and remission rates of the subgroups and CNS/ANS

Table 1
Sociodemographic parameters and values of the used CNS- and ANS-arousal measures for patients treated with SSRI or SNRI.

			Response SSRI		Remission SSRI		Response SNRI		Remission SNRI	
			No	Yes	No	Yes	No	Yes	No	Yes
Gender	FEMALE	n	88	144	122	110	35	74	57	52
		%	37.90%	62.10%	52.60%	47.40%	32.10%	67.90%	52.30%	47.70%
	MALE	n	63	119	97	85	30	45	45	30
		%	34.60%	65.40%	53.30%	46.70%	40.00%	60.00%	60.00%	40.00%
Education	Mean		14.66	14.59	14.64	14.58	14.34	14.33	14.25	14.44
	SD		3.02	2.85	2.96	2.87	3.1	2.69	2.9	2.76
Age	Mean		**40.88***	**37.02**	**40.48***	**36.13**	39.23	37.85	38.45	38.2
	SD		12.69	11.99	12.85	11.41	13.62	12.88	13.85	12.25
Median vigilance	Mean		4.19	4.13	4.11	4.19	4.25	4.24	4.22	4.27
	SD		1.38	1.42	1.37	1.44	1.58	1.49	1.57	1.44
Vigilance slope	Mean		**0***	**−0.15**	**−0.04***	**−0.16**	−0.15	−0.17	−0.15	−0.18
	SD		0.54	0.66	0.5	0.73	0.62	0.63	0.65	0.59
Heart rate bpm	Mean		69.77	69.32	69.35	69.63	70.3	69.83	70.32	69.6
	SD		10.75	10.82	10.78	10.82	10.02	10.09	9.9	10.26
Heart rate slope	Mean		0.61	0.61	0.61	0.62	**0.61***	**0.64**	0.63	0.64
	SD		0.13	0.1	0.12	0.1	0.1	0.12	0.11	0.12

*Significant ANOVA-differences are marked by an.
SD: Standard Derivation; SSRI: Selective-Serotonin-Reuptake-Inhibitor; SNRI: Serotonin-Norepinephrin-Reuptake-Inhibitor.

Fig. 1. Patient flow from recruitment over enrollment and allocation (per protocol) to final CNS- and ANS-arousal analysis.

metrics can be found in Table 1.

3.3. Sociodemographics

For the SSRI group, responders/remitters were younger (response: $F = 7.037$, $p = 0.008$; remission: $F = 13.087$, $p < 0.001$, see Table 1) in comparison to non-responders/non-remitters to SSRIs. No other significant sociodemographic differences were found (Table 1). Age was thus included as covariate in all subsequent analysis.

3.4. Binary logistic regression

For confirmation of the findings from the exploratory dataset,

we tested for arousal-parameter predictors of treatment outcome to SSRIs, using the binary logistic regression model. It showed a significant difference between groups (response: $chi^2 = 17.917$, DF 5, $p = 0.003$; remission: $chi^2 = 20.716$, DF 5, $p = 0.001$) with a significant contribution of CNS-arousal slope (Cohens' d for vigilance slope for responders vs non-responders: 0.25; remitters vs. non-remitters was 0.20) and age (Cohen's d = 0.31 and 0.36 respectively) (Fig. 2). CNS-arousal slope thereby was lower for responders in comparison to non-responders and responders were younger than non-responders (see Table 1). No difference was found for the ANS-arousal parameters.

In an exploratory analysis a binary logistic regression was performed stepwise for the independent variables of the SNRI group. Responders there were separated from non-responders ($chi^2 = 3.859$, DF 1, $p = 0.049$) only by heart rate slope (Cohens'd = −0.27).

3.5. Repeated measure ANOVA

The repeated measures ANOVA analysis with CNS-arousal as within-subject factor ("vigilance"), outcome as between-subject factor and age as covariate showed a significant interaction for "vigilance * response" ($F = 3.128$, DF 1.873, $p = 0.048$, Fig. 2) with a significant contribution of age ($F = 4.383$, $DF = 1$, $p = 0.040$) but not for "vigilance * remission" ($F = 2.012$ DF 1.872, $p = 0.137$, Fig. 2). No significant interactions were found when treatment (SSRI or SNRI) was added as between subject factors.

Performing separate analysis for treatment groups (SSRI group and SNRI group) revealed a significant interaction "vigilance * response" ($F = 3.928$, DF 1.877, $p = 0.022$, Fig. 2) with a significant contribution of age ($F = 5.451$, DF = 1, $p = 0.02$) and a trend

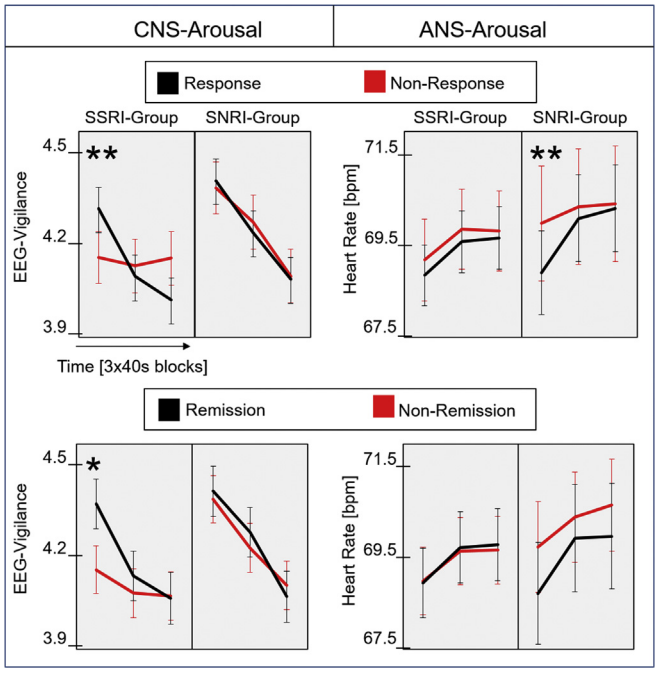

Fig. 2. Comparison of two-minute time series of CNS-arousal (EEG-vigilance, left panels) and ANS-arousal (heart rate, right panels) for response/non-response (upper panels) and remission/non-remission (lower panels). In the SSRI group, responders and remitters show a significantly faster declining CNS-arousal, i.e. a more negative slope than non-responders/non-remitters (significant repeated measures ANOVA results are marked by **; a trend by *). Responders to SNRI treatment reveal a more increasing ANS-arousal than non-responders. Error bars are standard error of the mean.

"vigilance * remission" ($F = 2.539$, DF 1.874, $p = 0.083$, Fig. 2; age with $F = 4.894$, $DF = 1$, $p = 0.028$) only for the SSRI group but not for the patients treated with SNRI ("vigilance*response": $F = 0.060$, DF 1.807, $p = 0.942$, Fig. 2; "vigilance*remission": $F = 0.177$, $DF = 1.807$, $p = 0.817$, Fig. 2).

The same repeated measures ANOVA model with ANS arousal as within-subject factor ("heartrate") resulted in no significant interactions "heartrate*response" or "heartrate*remission" for the whole patient group (response: $F = 0.734$, DF 1.620, $p = 0.454$, Fig. 2; remission: $F = 0.194$, DF 1.620, $p = 0.777$, Fig. 2).

When applied to the treatment arms separately, no significant interaction was found for the SSRI arm. Patients treated with a SNRI showed significant interactions "heartrate * response" ($F = 4.957$, DF 1.571, $p = 0.013$, Fig. 2, no significant contribution of covariate age) but not for remission ($F = 1.757$, DF 1.554, $p = 0.182$, Fig. 2).

4. Ancova

To exploratory analyze whether arousal parameters differed between subjects with a positive (or negative) treatment outcome following medication with a SSRI or a SNRI, an ANCOVA was performed including age as a covariate. Non-responders and non-remitters to SSRI treatment showed a significantly slower decline of CNS-arousal level during the two-minute resting recording in comparison to SNRI non-responders ($F = 4.18$; $DF = 1$; $p = 0.04$; Cohens' d = 0.29) and non-remitters ($F = 4.22$; $DF = 1$; $p = 0.04$; Cohens' d = 0.24). Covariate age had no significant influence on the dependent variable. Further, non-responders to SNRI treatment showed a smaller ANS-arousal slope (slower increasing heart rate) than non-responders to SSRI treatment ($F = 3.93$; $DF = 1$; $p = 0.05$; Cohens' d = 0.40), again with no significant contribution of covariate age.

No significant effects were found when comparing SSRI responders or remitters to SNRI responders or remitters.

4.1. Correlation analysis

When correlating $HRSD_{17}$ and CNS- and ANS-arousal parameters, a weak significant correlation was found only for the association between CNS-arousal slope and $HRSD_{17}$ ($r = 0.082$, $p < 0.05$). For separate correlations of the treatment arms (SSRI or SNRI), this correlation was only found significant for the SSRI group with $r = 0.104$, $p < 0.05$. In the SNRI group, the strongest correlation was found for $HRSD_{17}$ and ANS-arousal slope with $r = -0.095$, remaining not significant.

In patients with positive outcome following SSRI treatment, CNS-arousal slope and ANS-arousal level (but not CNS-arousal slope and ANS-arousal slope) were significantly correlated (responders $r = 0.217$, $p < 0.001$; remitters $r = 0.272$, $p < 0.001$, Fig. 3, left top panel) while this was not the case for SSRI non-responders ($r = 0.043$, $p = 0.604$) or SSRI non-remitters ($r = 0.038$, $p = 0.574$, Fig. 3, left bottom panel). No other meaningful correlations between ANS- and CNS arousal parameters were found. Comparison of correlations between successful or failed treatment showed a significant difference between remitters and non-remitters ($z = 2.39$; $p = 0.017$) and a trend between responders and non-responders ($z = 1.78$; $p = 0.08$). No such difference was found for the SNRI treatment arm (Fig. 3, right panels).

Further, there was a significant difference between the correlations of CNS-arousal slope and ANS-arousal level in SSRI responders and SSRI remitters in comparison to SNRI responders and SNRI remitters ($z = 2.45$; $p = 0.014$ and $z = 2.37$; $p = 0.018$). No other meaningful correlations between ANS- and CNS arousal parameters were found.

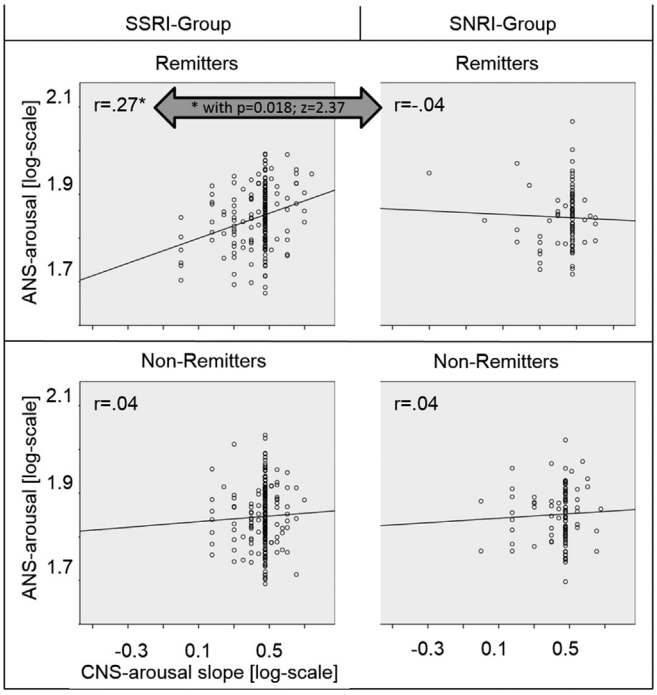

Fig. 3. Correlation between ANS-arousal level and CNS-arousal slope. Only remitters to SSRI treatment show a significant correlation (upper left panel). Further, the correlations for the SSRI and SNRI group differed significantly for remitters with SSRI remitters showing a concordant ANS-CNS patters.

5. Discussion

The main finding of this study is the replication of the hypothesis derived from an exploratory dataset, that MDD patients with response or remission after SSRI treatment showed significant differences in CNS-arousal slope over time as compared to non-responders or non-remitters at baseline. In detail, a faster decline of CNS-arousal predicted positive outcome following SSRI treatment while this was not the case in the SNRI group. There, a larger increase of ANS-arousal predicted response. Further, especially non-responders and non-remitters of the SSRI and SNRI treatment arms could be differentiated from each other using the ANS- and CNS arousal slopes.

Additionally, in the SSRI treatment arm, responders and remitters showed significantly higher correlations, suggestive of concordant ANS-arousal level and CNS-arousal slope over time, compared to non-responders and non-remitters, while this was not the case in subjects treated with an SNRI. Although effect sizes were small, the results point out toward possible arousal related biomarkers that might help to individualize treatment of MDD.

MDD has been associated with alterations of wakefulness regulation (Arfken et al., 2014; Lopez et al., 2010; Lovato and Gradisar, 2014; Olbrich and Arns, 2013), Accordingly, EEG-studies have consistently reported increased CNS arousal levels (Hegerl et al., 2011; Olbrich et al., 2012) and increased EEG-alpha activity (Tenke et al., 2011) in MDD. However, not the absolute level but the change of CNS-arousal was predictive for treatment outcome in this study. The fact, that this effect was found only for patients treated with SSRI but not with SNRI might be explained by different modes of action: While SSRIs have been found to decrease the firing rate of norepinephrine neurons in the locus coeruleus (LC) in rats (Grant and Weiss, 2001; West et al., 2009), for SNRI compounds electrophysiological effects on NE neurons seem to be more dose dependent (Béïque et al., 2000). A diminished activity of NE neurons of the LC is thought to decrease wakefulness through widespread projections to cortical areas (Aston-Jones, 2005). In conclusion, a faster decline of CNS-arousal during rest in responders and remitters might indicate a sensitivity to medication that has direct influence on LC neurons.

The recently proposed “EEG-vigilance” framework (Hegerl and Hensch, 2012) suggests an increased CNS-arousal in MDD that can be assessed by EEG-vigilance stages and their time course over time. In their framework, Hegerl and Hensch (2012) describe some core symptoms of MDD such as sleep problems and sensation avoidance as a behavioral counter-mechanism to decrease electrophysiologically assessable vigilance. In this light, the findings of the presented study further point out an important role of EEG-vigilance regulation and MDD.

Concerning autonomic arousal, patients that responded to SNRIs showed more pronounced increases of heart rate, suggesting an increased activity of the sympathetic branch of the ANS (Grassi et al., 1998). As has be shown by Licht et al. (Licht et al., 2012), SNRI treatment but not SSRI treatment leads to increased sympathetic control. The heart rate increase in SNRI responders that was not found for the SSRI arm might be a sign of a higher reactivity of the ANS in those subjects that profit from SNRI medication. This is in line with studies that have demonstrated that parameters of ANS function are trait markers in MDD patients (Brunoni et al., 2013) and have a predictive value for treatment (Jain et al., 2014). Within our study we were able to extend these findings and showed that the regulation of heart rate is, in particular, predictive for SNRI treatment outcome. However, the ANS is influenced by two separate branches (i.e. the sympathetic and the parasympathetic system). Since the heart rate is a measure of the resulting interaction of both systems, by means of heart rate alone one cannot differentiate between e.g. a decreasing sympathetic activity or an increasing parasympathetic activity that both could be responsible for a declining heart rate over time. Also in the light of a possible association of decreased parasympathetic and lower sympathetic tone in MDD (Kemp et al., 2010), which may also be involved in treatment response (Thorell and d’Elia, 1988), an interpretation of the ANS-findings of this study is limited. More sophisticated analysis of heart rate variability measures in the context of treatment response is warranted.

The fact that the slope of CNS arousal was positively associated to the overall arousal level of the ANS only in responders and remitters to SSRI treatment but not in subjects treated with an SNRI, suggests a predictive value for a concordant ANS- CNS arousal regulation especially when using SSRIs. This is further underlined by the significant positive correlation of CNS-arousal slope and change in HDRS only in the SSRI group but not in the SNRI treatment arm. Again these findings supports the fact that the effects are linked to different modes of action of SSRIs and SNRIs and to the individual responsiveness to them and do not reflect a MDD-specific alteration.

Taken together, the clinical psychopathology might be a good guide for chosing the right treatment along with the underlying biomarker pattern of an organsim, independent from symptomatology. When the means of ANS- and CNS arousal parameters were used as cut-off values to assign subjects to SSRI or SNRI treatment retrospectively, response rates for SSRI treatment increased from 63.5% to 73.3%, remission rate from 47.1% to 58.4%. For treatment with the SNRI, response rates increased from 64.7% to 72.3%, remission rates from 43.2% to 46.5%. These findings underline the importance of the Research Domain Criteria announced by the NIH (Insel et al., 2010) and validate CNS and ANS arousal systems as potential biomarkers to guide treatment in MDD. Future studies should analyze whether subjects with a pattern for non-response to both, SSRI and SNRI treatment could further benefit from

drugs with a distinct mode of action e.g. via dopaminergic pathways or from early treatment augmentation.

Limitations of the study include the rather short recording time of two minutes in the iSPOT dataset. It can be assumed that a longer recording of e.g. 15 min in the replication dataset would probably have led to increased effect sizes and a higher discriminative power, most specifically for the CNS arousal (vigilance) as this was the case in the exploratory dataset (effect sizes in the 15 min dataset 0.84–0.94; in the two minutes dataset 0.20–0.27). Further, a two minute recording does only allow for a limited analysis of HRV. Also the calculation of sensitivity and specificity of the CNS-arousal slope for SSRI treatment (with the group average as cut-off value for response) with 0.73 and 0.40 seems rather small. Still falsely declared non-responders do not receive the wrong treatment (or no treatment), they would have been treated with a SNRI with a similar response rate as compared to a non-selected sample. Sensitivity of 0.73 on the other hand means a response rate of 73% which is a remarkable improvement in comparison to the non-selected sample.

Although effect sizes were rather small, findings were consistent for response and remission markers. Further, the correlations of HRDS change and arousal markers pointed into the same direction. Hence, CNS and ANS arousal seem to be possible biomarkers for the improvement of treatment outcome in MDD, informing the decision between different drug-classes. Arousal systems are indeed a viable research domain criterium in MDD, bearing also a relations with differential treatment outcome. Importantly, the averaged CNS- or ANS-measures did not show the strongest effects but their change across time and the interrelation between ANS and CNS arousal (i.e. a concordance between these is reflective of response to SSRIs). To neglect these dynamics and look at the mere average values is an often repeated mistake. Therefore the different temporal CNS- and ANS-profiles for positive outcome to SSRI or SNRI treatment might be used to create neurophysiological-based criteria for the decision for one of the two medication classes and to reduce the rate of non-responders and non-remitters as has been shown in a first simulation. To increase the power of these markers, studies with longer recording periods of resting state data, e.g. 15 min or longer, are needed and these results require replication in an independent and possibly prospective study.

Contributors

All authors have materially participated in the research and/or article preparation. S.O. worked on the initial hypothesis, did data processing, statistical analysis and wrote large parts of the manuscript. A.T.and G.S. worked on the hypothesis and on the manuscript, R.G. and E.G. were involved in the study enrollment, data assessment and contributed to the manuscript, U.H. contributed to the manuscript and M.A. was involved in all steps from data assessment, preprocessing, analysis to the writing of the manuscript. All authors have approved the final version of the article.

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Conflict of interest

EG is founder and receives income as Chief Executive Officer and Chairman for Brain Resource Ltd. He has stock options in Brain Resource Ltd. MA reports research grants and options from Brain Resource Ltd. (Sydney, Australia), acted as a paid consultant for the United BioSource Corporation (UBC), Bracket, Mindmedia and Vivatech and is a co-inventor on 3 patent applications (A61B5/0402; US2007/0299323, A1; WO2010/139361 A1) related to EEG, neuromodulation and psychophysiology, but does not own these nor receives any proceeds related to these patents. SO, AT, GS, RG, JR and UH report no conflict of interest.

Disclosures

EG is founder and receives income as Chief Executive Officer and Chairman for Brain Resource Ltd. He has stock options in Brain Resource Ltd. MA reports research grants and options from Brain Resource Ltd. (Sydney, Australia), acted as a paid consultant for the United BioSource Corporation (UBC), Bracket, Mindmedia and Vivatech and is a co-inventor on 3 patent applications (A61B5/0402; US2007/0299323, A1; WO2010/139361 A1) related to EEG, neuromodulation and psychophysiology, but does not own these nor receives any proceeds related to these patents. SO, AT, GS, RG, JR and UH report no financial conflict of interest.

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