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Brain arousal regulation in SSRI-medicated patients with major depression

Christine Ulke[a,b,*,1], Dirk A. Wittekind[a,1], Janek Spada[b], Katharina Franik[a], Philippe Jawinski[b,c], Tilman Hensch[a], Ulrich Hegerl[a,b]

[a] Department of Psychiatry and Psychotherapy, University of Leipzig, Leipzig, Germany
[b] Research Centre of the German Depression Foundation, Leipzig, Germany
[c] Department of Psychology, Humboldt University Berlin, Berlin, Germany

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ABSTRACT

EEG measures of arousal have been suggested as diagnostic and predictive biomarkers for major depression. The aim of the present study was to examine whether self-rated depression severity in SSRI-medicated patients with major depression (MD) is associated with EEG measures of brain arousal. Based on previous studies, we expected that a higher level of brain arousal and a slower arousal decline during a 15-min EEG recording are associated with higher symptom severity as assessed with the Beck Depression Inventory (BDI) at the time of the EEG recording. EEGs of 78 MD patients and 46 healthy controls were analyzed. Brain arousal was assessed using the Vigilance Algorithm Leipzig (VIGALL 2.1). Based on automatically classified 1-s segments (EEG-vigilance Stages 0, A1, A2, A3, B1, B2/3 or C) we computed indices to assess the level (mean EEG-vigilance) and the decline of arousal (slope index) during the 15-min resting state EEG under eyes-closed condition. We found that a higher arousal level and a slower arousal decline corresponded to higher severity of depressive symptoms (rho = 0.238, p = .018; and rho = 0.236; p = .019). Self-rated non-remitters (BDI > 12) had a higher arousal level (mean EEG-vigilance: $t_{76} = -2.19$, p = .016) and slower arousal decline (slope index: Z = −2.08, p = .019) during the 15-min recording as compared to remitters. Similar results were obtained between non-remitters and healthy controls (mean EEG-vigilance: $t_{102} = -2.75$, p = .004; slope index: Z = −1.92, p = .028), but not between remitters and controls (p > .260). The findings support the model that brain arousal regulation plays an important role in the pathophysiology and treatment of MD.

1. Introduction

Arousal and regulatory systems constitute one of the five domains of a research framework—the NIMH Research Domain Criteria (RDoC)—for new approaches to investigate mental disorders (Insel et al., 2010). Concerning both affective disorders and ADHD, there is converging evidence from both clinical and preclinical studies that abnormalities in wakefulness and brain arousal regulation play an important role in the pathogenesis of these disorders (Hegerl et al., 2008; for review, see Hegerl and Hensch, 2014; Hegerl et al., 2016). Therein, the dimension of brain arousal is, on a behavioral level, understood as a continuum between cognitively active wakefulness and sleep, and evaluated using resting state electroencephalography (EEG). The term *arousal level* here refers to different functional global brain states, not a specific attentional function (Oken et al., 2006) or emotional arousal (Jaworska et al., 2012).

Using the Vigilance Algorithm Leipzig (VIGALL) for the objective assessment of brain arousal measures based on electroencephalographic recordings (EEG) at rest under eyes-closed condition, the Arousal Model of Affective Disorders and ADHD has been validated (Hegerl et al., 2012; Olbrich et al, 2012, 2016; Sander et al., 2010; Schmidt et al., 2016; Strauß et al., 2018; Ulke et al, 2017b, 2018; Wittekind et al., 2016). In addition, a recent genome-wide association analysis in healthy subjects with EEG-based arousal measures as phenotype identified TMEM159/Promethin as a novel candidate gene which may modulate the risk for psychiatric disorders through arousal mechanisms (Jawinski et al., 2018).

While patients with (hypo)mania and ADHD show a more rapid decline of arousal levels during the EEG recording than healthy individuals (Hegerl et al, 2009, 2010; Strauß et al., 2018; Ulke et al., 2018a, an upregulated brain arousal (i.e. slow or no decline of arousal levels during the EEG recording) has been demonstrated in unmedicated patients with depression (Hegerl et al., 2012; Ulke et al., 2018b) and is supposed to play a relevant pathogenetic role in this

* Corresponding author. University of Leipzig, Department of Psychiatry and Psychotherapy, Semmelweisstr.10, 04103, Leipzig, Germany.
E-mail address: Christine.Ulke@medizin.uni-leipzig.de (C. Ulke).
[1] These authors have contributed equally to this work and are co-first authors.

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disorder (for review, see Hegerl and Hensch, 2014). Preclinical studies have consistently shown that selective serotonin reuptake inhibitors (SSRIs) and other antidepressant drugs decrease the neuronal firing rate of the locus coeruleus (West et al., 2009), a brainstem nucleus implicated in the control of brain arousal and wakefulness (Berridge et al., 2012). It is not unlikely that antidepressants act via counteracting the upregulated brain arousal in major depression (MD). Thus, the frequent side effect of drowsiness known for all common antidepressants might reflect the desired effect of arousal-reduction in treatment (Hensch et al., 2015). In line with this view, a higher level of brain arousal was demonstrated in unmedicated patients with MD who respond to antidepressants, using an observer-rated scale to assess treatment response (Schmidt et al., 2017).

The main aim of the present observational study was to examine whether the self-rated depression severity in SSRI-medicated MD patients is associated with EEG measures of brain arousal. We expected that a higher level of brain arousal and a slower arousal decline during a 15-min EEG recording would be associated with higher symptom severity and that such upregulation would be more pronounced in self-rated non-remitters (BDI > 12) compared to both, self-rated remitters and healthy controls.

2. Materials and methods

2.1. Study population

The study sample consisted of MD inpatients who underwent a 15-min resting EEG assessment during their inpatient treatment at the Leipzig University Hospital between 2008 and 2014. Main inclusion criteria were: current depressive episode (DSM-IV 296.21–23; 296.31–33), age between 18 and 60, and SSRI-medication for at least 48 h. At time of admission the diagnoses and the severity of the depressive episode were confirmed by a senior psychiatrist according to DSM-IV criteria. Main exclusion criteria: co-medication with tricyclic ADs, tranquilizers or hypnotics, substance abuse, pathological EEGs, and > 15% of artifacts in the 15-min EEG. From the 250 screened patient records, data of 78 MD patients were included in the analyses. Of those, four patients additionally received other psychotropic drugs as add-on medication. Four patients had comorbid anxiety. In some subjects, duration of AD treatment at time of the EEG recording could not be precisely ascertained, as patients who were on long-term AD treatment when admitted could not exactly remember how long medication had been taken. In these cases, we defined these patients as being in the category of four weeks of treatment or higher, as AD treatment is considered to be at a stable level after four weeks (American Psychiatric Association, 2010; N.I.C.E., 2009; Qaseem et al., 2008).

Healthy controls had been recruited for an EEG assessment between 2008 and 2012. Main inclusion criteria were age between 18 and 60 years, and no psychiatric diagnosis, as assessed with a structured clinical interview for DSM IV; main exclusion criteria were use of psychotropic medication, tranquilizer or hypnotics. Forty-six healthy controls were included in the final analysis. All subjects voluntarily gave written informed consent. The study protocol was approved by the Ethics Committee Leipzig University (#236–2007).

2.2. Questionnaires

At the time of the EEG recording the Beck Depression Inventory (BDI (Beck et al., 1961; Beck et al., 1997), was used to assess the severity of depressive symptomatology. Patients with a BDI (I or II, without divergent items 11, 14, 15, 19) sum-score > 12 were assigned to the self-rated non-remitters group, all others were assigned to the self-rated remitters group.

2.3. Acquisition of resting EEG

The resting EEG recordings began between 8 am and 2 pm in a sound- and light-attenuated room. Participants were instructed to close their eyes and to relax. During the 15-min recording participants lay comfortably on a lounge chair in semi-reclined position while the EEG was recorded from 31 monopolar referenced scalp electrodes placed according to the extended international 10–20 system with a QuickAmp amplifier (Brain Products GmbH, Gilching, Germany). Impedances were kept below 10 kΩ; the sample rate was 1 kHz. Bipolar referenced electro-oculogram (EOG) electrodes were placed at the canthus of each eye and above and below the right eye.

2.4. Assessment of brain arousal regulation

Data were analyzed using BrainVision Analyzer 2.0 software (Brain Products GmbH, Gilching, Germany). Prior to EEG-vigilance stage classification, the 15-min resting EEGs were processed according to a Standard Operating Procedure (SOP, described in the Vigilance Algorithm Leipzig [VIGALL] manual, download at http://www.uni-leipzig.de/vigall/). Preprocessing and artifact correction was executed as previously described (Wittekind et al, 2016). Consecutive 1-s EEG segments were classified into seven different EEG-vigilance stages: 0, A1, A2, A3, B1, B2/3, and C, using VIGALL 2.1 (http://www.uni-leipzig.de/vigall/). This EEG- and EOG-based algorithm incorporates information on the cortical distribution of the EEG activity using low-resolution electromagnetic tomography (LORETA (Pascual-Marqui and Michel, 1994); as well as the spectral composition of the EEG activity. It was validated in functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies (Guenther et al., 2011; Olbrich et al., 2009) against autonomic (Huang et al., 2018; Olbrich et al., 2011; Ulke et al., 2017a) and self-rated measures (Jawinski et al., 2017).

Each staged segment was assigned a score ranging from seven (highest score Stage 0: desynchronized non-alpha EEG in the absence of slow horizontal eye movements often found during an activated state [i.e. mental effort]) to one (lowest score Stage C: sleep onset), cf. Fig. 1.

The relative amount of segments was calculated for each vigilance stage. Scores of consecutive 1-s segments were averaged to obtain the

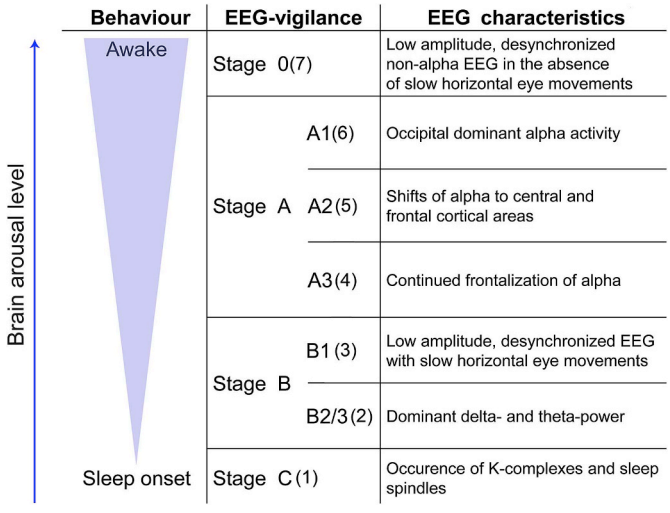

Fig. 1. EEG-vigilance stages, respective scores (in brackets) and EEG characteristics. EEG-vigilance stages can be automatically classified using the Vigilance Algorithm Leipzig (VIGALL). Figure from Hegerl U, Sander C, Ulke C et al. Vigilance Algorithm Leipzig (VIGALL) Version 2.1 Manual; https://research.uni-leipzig.de/vigall/. Accessed July 20, 2018.

mean EEG-vigilance for three consecutive 5-min blocks and for the 15-min EEG (mean EEG-vigilance). A slope index to assess the speed and extent of the arousal decline during the 15-min EEG (Huang et al., 2015) was calculated.

2.5. Statistical analyses

Statistical analyses were carried out with SPSS Statistics 24.0 (IBM corp.; Armonk, NY, USA).). Before testing the hypotheses, we checked for homogeneity of variances and normality. Group differences concerning age and gender and BDI scores were conducted with t-tests (age, BDI) and chi-squared tests (gender). For correlation analyses, Spearman rank correlation coefficients were computed. T-tests and Mann-Whitney U tests were conducted for between-group comparisons. In a sub-analysis, self-rated non-remitters and remitters were matched with the R-based SPSS extension bundle PS Matching 1.0 (Thoemmes, 2012). The significance level was set to $p \leq .05$ (one-tailed). Exploratory between-group comparisons of EEG-vigilance stages were conducted at $p \leq .05$ (two-tailed).

3. Results

3.1. Description of sample

The sample characteristics of all MD patients (N = 78) and healthy (N = 46) controls are described in Table 1. Of the 78 MD patients, 20 were assigned to the self-rated remitters group. Depressed patients did not differ significantly from healthy controls and from each other (self-rated remitters vs self-rated non-remitters) regarding age ($0.098 \leq p \leq .861$) or gender ($0.359 \leq p \leq .937$).

3.2. Descriptive analysis of EEG-Vigilance stages

The time of day of the EEG recording did not differ between groups ($0.107 \leq p \leq .894$).

The relative amount of each EEG-vigilance stage, calculated for the 15-min recording period, is presented in Table 2. In either group, EEG-vigilance Stage A was classified most frequently (healthy controls: 57.0%; non-remitters: 62.5%, remitters: 47.6%), with no significant difference between all groups ($0.059 \leq p \leq .297$). Group differences were obtained in Stage B1 (healthy controls: 25.8%, non-remitters: 16.1%, remitters: 29.0%), whereby non-remitters scored markedly lower on Stage B1 than healthy controls ($p = .005$) or remitters ($p = .010$).

Interestingly, MD patients had a higher relative amount of EEG-vigilance Stage 0 as compared to healthy controls ($p = .025$). Also, of note, remitters scored higher on Stage C (2.4%), in comparison to non-remitters ($p = .019$). Fig. 2 describes the relative amount of EEG-vigilance stages across the 15-min recording period in healthy controls and depressed patients, as well as in remitters and non-remitters.

3.3. Correlation analyses of self-rated depression score (BDI) and EEG-measures of arousal

We investigated the association between the self-rated depression scores and the EEG measures of arousal, *mean EEG-vigilance* (indicating arousal level) and *slope index* (indicating arousal decline) across all depressed subjects (N = 78). Spearman rank correlation analyses revealed low-positive and statistically significant relationships between EEG measures of arousal and severity of depressive symptoms (mean EEG-vigilance: rho = 0.238, $p = .018$; slope index: rho = 0.236; $p = .019$), wherein a higher level and a slower arousal decline during

Table 1
Sample characteristics of healthy controls and SSRI-medicated depressed patients.

	Depressed patients (N = 78)	Self-rated non-remitters (NR; n = 58)	Self-rated remitters (R; n = 20)	*test value*	*p value*	Healthy controls (HC; N = 46)	*test value*	*p value*
Demographics								
Age [mean ± SD (range)]	37.8 ± 11.5 (18–60)	38.6 ± 11.5 (18–59)	35.4 ± 11.2 (19–60)	$t_{76} = -1.10$	.280	35.0 ± 11.3 (20–60)	NR: $t_{102} = -1.67$ R: $t_{64} = -0.18$	NR: .098 R: .861
Gender [f/m ratio]	52/26	37/21	15/5	$\chi^2 = 0.84$	.421	42/27	NR: $\chi^2 = 0.01$ R: $\chi^2 = 0.84$	NR: .937 R: .359
BDI score[a] [mean ± SD]	18.7 ± 9.0	22.4 ± 7.1	7.9 ± 3.7	$t_{63} = -11.62$	$2.6\,E^{-17}$	3.7 ± 4.5	NR: Z = −8.55 R: Z = −3.33	NR: $1.3\,E^{-17}$ R: .001
Severity of episode[b]				$\chi^2 = 1.28$	.528	–		
mild [n]	2	2	–					
moderate [n]	56	40	16					
severe [n]	20	16	4					
Suicidal ideation[c]	0.6 ± 0.5	0.7 ± 0.6	0.3 ± 0.5	Z = −2.59	.010	–		
Duration of illness [yrs, mean ± SD]	4.0 ± 5.8	4.2 ± 5.8	3.5 ± 5.9	Z = −0.86	.390	–		
Number of episodes [mean ± SD, (range)]	1.3 ± 0.7 (1–4)	1.4 ± 0.7 (1–4)	1.0 ± 0.2 (1–2)	Z = −2.56	.011	–		
AD medication				$\chi^2 = 1.70$	.637	–		
citalopram	35	29	6					
escitalopram	34	23	11					
fluoxetine	3	2	1					
sertraline	6	4	2					
Duration of AD medication[d]				$\chi^2 = 2.78$	.428	–		
≤1 week [n]	31	26	5					
> 1 ≤ 2 weeks [n]	8	6	2					
> 2 < 4 weeks [n]	8	5	3					
≥4 weeks [n]	31	21	10					

Annotations: AD = antidepressant; BDI = Beck Depression Inventory; NR = self-rated non-remitter; SD = standard deviation; R = self-rated remitter.
[a] BDI (I or II) sum-scores didn't include divergent items 11, 14, 15, and 19; BDI was assessed at the time of the EEG recording.
[b] At the time of admission.
[c] Assessed with BDI item 9 (range 0–3; 0 = no suicidal thoughts, 3 = would do it if there was a chance) at the time of the EEG recording.
[d] At the time of the EEG recording; median score NR = 2.0; R = 3.5 (range 1–4; 1 = ≤1 week, 4 = ≥4 weeks).

Table 2
EEG-based measures in healthy controls and SSRI-medicated depressed patients.

	Depressed patients (N = 78)	Self-rated non-remitters (NR; n = 58)	Self-rated remitters (R; n = 20)	*test value Z (NR vs R)*	*p value* [d]	Healthy controls (HC; N = 46)	test value Z (NR vs HC)[f]	*p value (NR vs HC)*[d]
	Mean ± SD	Mean ± SD	Mean ± SD			Mean ± SD		
Vigilance stages[a] [%]								
Stage 0	14.7 ± 17.9	14.8 ± 18.4	14.5 ± 17.0	−0.41	.684	8.0 ± 13.40	−2.23	.025
Stage A	58.7 ± 28.7	62.5 ± 28.3	47.6 ± 27.5	−1.89	.059	57.0 ± 27.3	−1.04	.297
A1	49.1 ± 30.5	52.6 ± 30.5	39.3 ± 28.7	−1.67	.091	46.5 ± 26.4	−1.02	.306
A2	7.9 ± 12.2	8.3 ± 12.6	6.5 ± 11.0	−0.18	.859	8.0 ± 14.0	−0.22	.826
A3	1.7 ± 3.8	1.6 ± 3.5	1.8 ± 4.4	−0.33	.742	2.3 ± 4.8	−0.37	.737
Stage B	26.0 ± 23.7	22.7 ± 23.3	35.6 ± 22.8	−2.32	.020	34.0 ± 24.3	−2.63	.008
B1	19.4 ± 19.2	16.1 ± 17.8	29.0 ± 20.3	−2.53	.011	25.8 ± 21.4	−2.79	.005
B2/3	6.6 ± 12.0	6.6 ± 12.6	6.6 ± 10.5	−1.23	.218	8.1 ± 11.5	−1.31	.192
Stage C	0.6 ± 3.4	0.0 ± 0.0	2.4 ± 6.5	−2.35	.019	1.3 ± 6.4	−1.68	.093
				test value	*p value*[e]		*test value*	*p value*[e]
Mean vigilance score[b]	5.2 ± 0.9	5.3 ± 0.8	4.8 ± 1.0	**t_{76} = -2.19**	**.016**	4.8 ± 0.9	NR: **t_{102} = -2.75** R: **t_{64} = 0.12**	NR: **.004** R: **.453**
Slope Index[c]	−1.4 ± 0.8	−1.3 ± 0.7	−1.7 ± 0.8	**Z = -2.08**	**.019**	−1.6 ± 0.8	NR: **Z = -1.92** R: **Z = -0.66**	NR: **.028** R: **.260**

[a] To obtain the relative amount of EEG-vigilance stages, consecutive 1-s segments were classified into seven different EEG-vigilance stages: 0, A1, A2, A3, B1, B2/3, and C and their percentage (amount * 100/total number of non-artifactual segments) was calculated for the 15-min EEG.
[b] To obtain the mean EEG-vigilance for the 15-min EEG, each staged segment was assigned a score ranging from 7 (highest score Stage 0: desynchronized non-alpha EEG in the absence of slow horizontal eye movements) to 1 (lowest score Stage C: sleep onset); scores of consecutive 1-s segments were averaged.
[c] Quantifies the decline of arousal during the 15-min EEG (cf. Huang et al., 2015); low score corresponds to fast arousal decline.
[d] Two-sided.
[e] one-sided.
[f] o note: Exploratory analyses of the relative amount of EEG-vigilance stages between self-rated remitters and controls yielded no significant differences (.176 ≤ p ≤ .938).

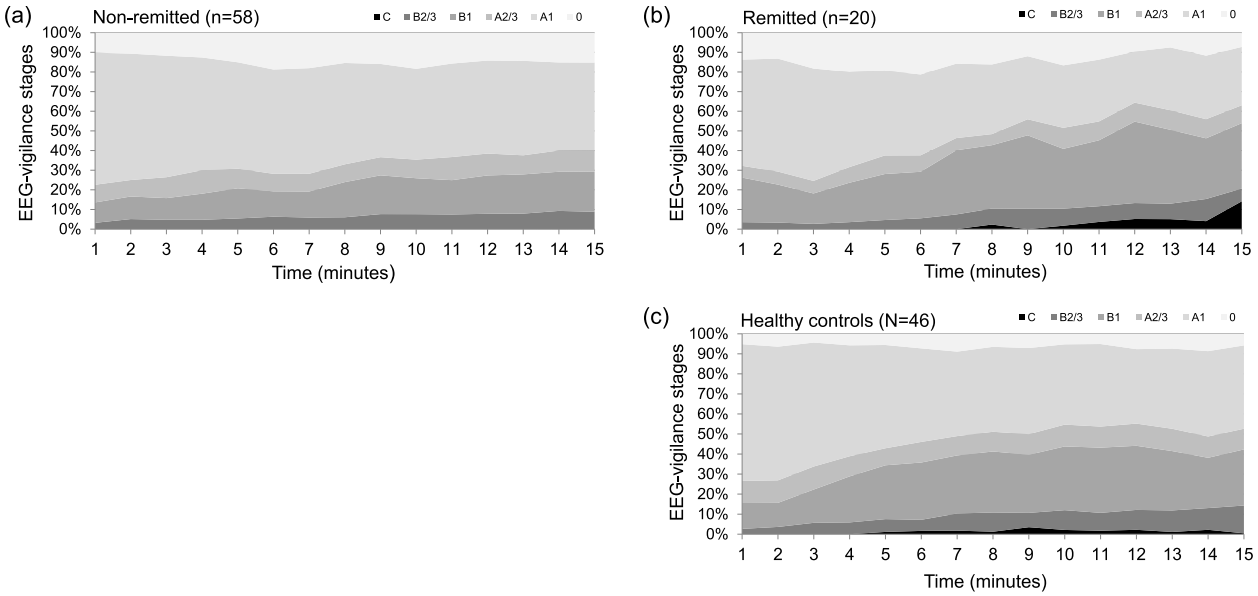

Fig. 2. Relative amount of EEG-vigilance stages across the 15-min recording period in (a) self-rated non-remitters (BDI > 12; n = 20), (b) self-rated remitters (BDI ≤ 12; n = 58) and healthy controls (N = 46). Consecutive 1-s segments were classified into seven different EEG-vigilance stages: 0, A1, A2, A3, B1, B2/3, and C. The percentage (amount * 100/total number of non-artifactual segments) of EEG-vigilance stages were calculated for each 1-min block. BDI = Beck Depression Inventory; BDI was assessed at the time of the EEG recording.

the 15-min recording corresponded to higher self-rated symptom severity. To ensure that these findings are consistent if only patients with at least 21 days of medication (n = 32) are included in the correlation analysis, we conducted post-hoc analyses, demonstrating similar relationships between EEG measures of arousal and depressive symptom severity (mean EEG-vigilance: rho = 0.309, p = .043; slope index: rho = 0.309; p = .043), wherein a higher level and slower arousal decline during the 15-min recording corresponded to higher self-rated symptom severity at the time of recording.

3.4. Group comparisons of EEG-based measures of brain arousal

Next, we conducted group comparisons between self-rated non-remitters and self-rated remitters, and between both patient groups and

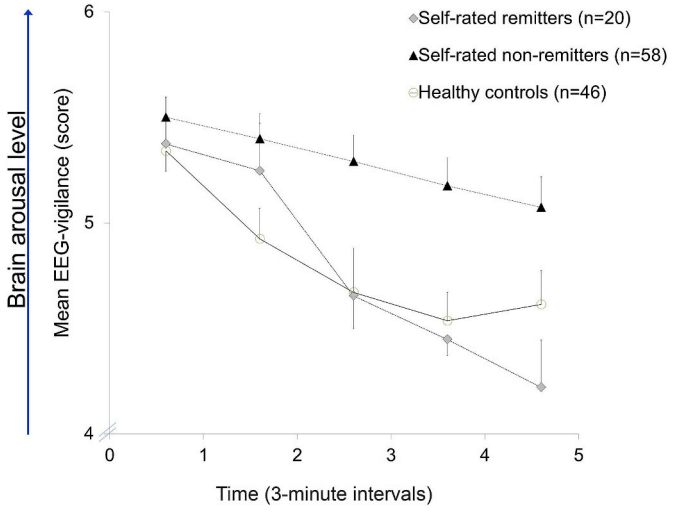

Fig. 3. Time course of mean EEG-vigilance over five consecutive 3-min intervals in SSRI-medicated patients with major depression (N = 78; self-rated non-remitters: BDI > 12; n = 58, self-rated remitters: BDI ≤ 12; n = 20) and healthy controls (N = 46). Error bars represent ± 1 standard error. To assess the level of arousal, consecutive 1-s EEG segments were classified into seven different EEG-vigilance stages: 0, A1, A2, A3, B1, B2/3, and C (based on frequency bands and source localization with LORETA) using VIGALL 2.1. Each EEG-vigilance staged segment was assigned a score ranging from 7 (highest stage 0, cognitively active wakefulness) to 1 (lowest stage C, sleep onset). Scores of consecutive 1-s segments of each 3-min interval were averaged to obtain the mean EEG-vigilance for the five blocks. BDI = Beck Depression Inventory; BDI was assessed at the time of the EEG recording.

controls. Compared to remitters, non-remitters had a higher arousal level (mean EEG-vigilance: $t_{76} = -2.19$, $p = .016$) and slower arousal decline (slope index: $Z = -2.08$, $p = .019$). Results remained consistent, when groups were matched for *duration of medication* using propensity score matching (cf. supplementary material). Similar results were obtained between non-remitters and healthy controls (mean EEG-vigilance: $t_{102} = -2.75$, $p = .004$; slope index: $Z = -1.92$, $p = .028$), but not between remitters and controls ($p > .260$). Fig. 3 shows the mean EEG-vigilance over five consecutive 3-min intervals in all groups.

4. Discussion

The present study examined whether self-rated depression severity in SSRI-medicated MD patients is associated with objectively assessed EEG measures of brain arousal (using VIGALL 2.1) during a 15-min EEG at rest with eyes closed and whether a high level of brain arousal and a slow arousal decline during the 15-min EEG is more pronounced in self-rated non-remitters compared to self-rated remitters and healthy controls. As hypothesized, we found a positive correlation between the severity of depressive symptoms across all patients, as assessed with the BDI, and EEG measures of brain arousal. Therein, a higher level and a slower decline of brain arousal during the 15-min EEG were associated with a higher BDI score ($p \leq .019$). Self-rated non-remitters had a significantly higher arousal level and slower arousal decline relative to remitters and controls ($0.004 \leq p \leq .028$). In contrast, no significant differences were found when comparing remitters and healthy controls.

The finding of the correlation between self-rated severity of depressive symptoms and EEG measures of arousal in medicated patients are in line with the analyses of Schmidt et al. (2017) who found that (previously unmedicated) SSRIs-responders differed in the overall distribution of EEG-vigilance stages after 14 days of treatment—despite the fact that Schmidt et al. used a clinician-administered depression assessment scale. Moreover, in the current study we could demonstrate that SSRI-medicated self-rated non-remitters had greater stability of arousal during the 15-min resting EEG as compared to healthy controls. This result replicates the finding of arousal upregulation in depression, as reported previously (Hegerl et al., 2012; Olbrich et al., 2012b; Schmidt et al., 2016; Ulke et al., 2017b, Ulke et al., 2018b)—though here for the first time in self-rated non-remitted MD patients on a SSRI medication.

SSRI-medicated remitters had less stable arousal regulation than non-remitters. This was mostly due to more frequent occurrence of Stages B1 and C during the 15-min EEG relative to non-remitted patients. These findings are in line with the exploratory analyses of Schmidt et al. (2017) who found that SSRIs responders had a higher amount of low EEG-vigilance stages after 14 days of treatment. In addition, remitters did not differ concerning the EEG measures of arousal from healthy controls. These results may suggest state rather than trait characteristics of the EEG measures applied in the current study. However, due to the cross-sectional design, such conclusions cannot be drawn. Conversely, a previous study examining the value of EEG-alpha power as SSRI-response predictor (based on four 2-min periods, half with eyes open, half with eyes closed) alpha power did not change after treatment in SSRI treatment responders and test-retest correlations pre- and post-treatment were high (Bruder et al., 2008) suggesting state-independent characteristics of EEG-alpha power. This may indicate that EEG measures of brain arousal based on 15-min resting state recordings could be valuable additional markers to monitor treatment response in SSRI-medicated patients which needs to be addressed in a future study.

In contrast to previous studies in unmedicated depressed patients, SSRI-medicated patients did not score higher on EEG-vigilance Stage A or A1 in comparison to healthy controls. For example, in a study by Hegerl et al. (2012), 70% of the 1-s EEG-segments of a 15-min recording in the depressed group (vs. 60% in healthy controls) were classified as Stage A, as compared to 59% in the depressed group (respectively 57% in controls) in the current study. Moreover, in self-rated remitters, frequency of Stage A was even less frequent (< 48%). While the cross-sectional study design precludes the interpretation of causality, our findings suggest that SSRIs contribute to a reduced amount of Stage A in the 15-min resting EEG. This view is also supported by the results of the aforementioned recent longitudinal study, in which SSRI-responders had reduced frequency of Stage A segments after 14 days of treatment as compared to baseline (Schmidt et al., 2017).

In summary, our findings show that the severity of depressive symptomatology correlates with EEG measures of brain arousal in SSRI-medicated MD patients, and may indicate that SSRIs counteract arousal upregulation, as posited in the Arousal Model of Affective Disorders (Hegerl and Hensch, 2014).

A main limitation of the current study is the cross-sectional and retrospective design which does not allow to link individual changes in brain arousal during SSRI treatment to changes in psychopathology. Another limitation is the lack of a professional rating at the time of the EEG recording.

In conclusion, the findings provide further evidence that brain arousal regulation plays an important role in the pathophysiology and treatment of MD. VIGALL 2.1 is an EEG-based algorithm for objectively assessing and monitoring brain arousal regulation in MD patients.

Author contributions

Concept and design: Hegerl, Hensch, Spada, Ulke, Wittekind. Acquisition, analysis, or interpretation of data: All authors. Statistical analysis: Ulke, Spada. Drafting of the manuscript: Ulke, Wittekind. Critical revision of the manuscript for important intellectual content: All authors.

Additional contributions

The authors would like to thank Alexander Groβ for his help with obtaining the data.

Conflict of interest disclosures

Dr. Hegerl was an advisory board member for Lilly, Lundbeck, Servier, Takeda and Otsuka; a consultant for Bayer and Nycomed; and a speaker for Bristol-Myers Squibb, Medice Arzneimittel, Novartis, and Roche. No other disclosures are reported.

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Appendix A. Supplementary data

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