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ORIGINAL PAPER

Combined cognitive, psychomotor and electrophysiological biomarkers in major depressive disorder

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Abstract

The diagnosis of major depressive disorder (MDD) should be based on multimodal evidence, because MDD not only affects mood, but also psychomotor and cognitive functions. Clinical markers such as executive dysfunctions and a reduction in daily motor activity have been observed in MDD. Neurophysiological biomarkers have also been described. In this study, we investigate the utility of combining biomarkers related to executive dysfunctions, motor activity, neurophysiological patterns (i.e. alpha power asymmetry and EEG-vigilance as indicators of brain arousal), and the interaction of these parameters in the diagnosis of MDD. Twenty (female: 11) patients with MDD (age: 51.05 ± 10.50) and 20 (female: 13) healthy controls (HC; age: 47.15 ± 12.57) underwent a 10-min resting EEG. Executive dysfunctions were assessed using the Trail Making Test B (TMT B). Motor activity was analysed by actigraphy measurements. MDD patients displayed significant impairments in executive functions and reduced daily motor activity. In the EEG, MDD patients showed more right than left frontal activity and lower brain arousal relative to HC. TMT B and asymmetrical frontal alpha power alone discriminated between MDD patients and HC with an accuracy of 78%. The interaction of motor activity and the EEG-vigilance stage alongside TMT B increased the accuracy of the discrimination test to 81%. This improved accuracy suggests that the combination of these biomarkers in a discriminant analysis resulted in a more reliable identification of MDD patients.

Keywords EEG · Major depressive disorder · Biomarkers · Executive dysfunction · Actigraphy

Introduction

Major depressive disorder (MDD) is a mood disorder that affects 1.3–19% of the world population [1]. An accurate diagnosis of MDD may prevent the risk of developing chronicity of depressive symptoms and attendant physical and neuropathological complications such as cardio- and cerebrovascular disease or dementia [2, 3]. The search for suitable biomarkers for depression is still at the forefront of biological research in the field. A biomarker is by definition "a characteristic that is objectively measured and evaluated as an indicator of normal biological process, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [4]. Research is underway to determine the diagnostic threshold for biomarkers in depression [5–7]. However, to date, there is no single candidate that can serve as a definite diagnostic marker for depression due to the heterogeneous nature of the disorder [8]. Notwithstanding, a few studies have shown phenotypes and indicated they may be helpful in the diagnostic procedure of MDD. For instance, 20–30% of individuals with MDD exhibit pronounced executive dysfunctions [9], and several studies demonstrated that executive dysfunctions in MDD are associated with altered frontal brain activity [10, 11] and anomalies at the frontal brain lobe [see review 12, 13]. Furthermore, executive

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dysfunction often persists after remission of depression and may be associated with increased relapse risk [14, 15, but see also 15]. Already during the first episode of depression, MDD patients showed significantly worse executive performance than HC [16].

Psychomotor abnormalities have also been reported in depression [17–19, see also review 19], and could potentially serve as a prognostic tool [20]. Psychomotor abnormalities in depression have been linked to alterations in frontostriatal dopaminergic neurotransmission [21–23]. Furthermore, it has been observed that greater neural activation in the frontal, limbic, and temporal regions during motor tasks may predict better treatment response in MDD patients [24]. Therefore, psychomotor characteristics such as retardation or agitation may constitute a further important clinical marker to diagnose MDD.

In addition, a particularly promising EEG finding in MDD during the resting state is frontal alpha power asymmetry, i.e. lateralized hemispheric power within the alpha frequency band [25, 26]. This finding was first reported in depression in 1991 [27]. It has also been reported that patients became more depressed after damage to the left than after damage to the right frontal hemisphere [28]. Further, Schaffer and co-workers [29] showed that depressed subjects exhibit higher left than right frontal alpha power. Schaffer and collaborators suggested that a dysfunction of the right frontal hemisphere leads to vulnerability to properly react to withdrawal-behaviour while the left hemisphere serves the function to correspond to appropriate approach-behaviour during various circumstances [29]. Since alpha rhythm is inversely associated with regional brain activity, the lower the alpha power, the higher the brain activity [30]. Parietal asymmetry has also been reported in MDD and has been linked to higher levels of anxiety [31]. In summary, alpha power asymmetry may serve as a neurophysiological indicator of depression.

EEG-based vigilance regulation is another approach to differentiate between patients with various psychiatric, particularly with affective disorders, and healthy subjects [32–34]. EEG vigilance is an indicator of brain arousal and can be used to quantify subjective alertness during the resting state, ranging from high alertness, relaxed wakefulness (i.e. EEG-stage A1–A3, high alpha power), to drowsiness (i.e. EEG-stage B1–B2/3, low-amplitude EEG) and, finally, sleep onset (EEG-stage C, K-complexes or sleep spindles) [35]. The different vigilance regulation patterns of HC were used for definition of standard templates and for comparisons to MDD patients [36]. It has been reported that depressive patients stayed stable at the alert stage (EEG-stage A) without high regulation, in comparison to healthy subjects who became drowsier during the EEG recordings. Using this EEG based vigilance regulation model, depressive patients could be distinguished from the healthy population with a sensitivity of 67–73% and a specificity of 67–80%. Furthermore, it has been found that MDD patients spend more time at vigilance stage A1 than control subjects, and have a longer latency to reach drowsier stages [37]. These results suggest that EEG vigilance regulation could also be used to distinguish depressed patients from healthy individuals.

The main aim of our study was to combine clinical and neurophysiological variables measured in MDD patients related to frontal brain dysfunctions, and thus to derive composite biomarkers for depression with a view to increasing the sensitivity and specificity of these markers for MDD. We focused on executive and psychomotor dysfunctions which critically depend on the integrity of the frontal brain. Psychomotor alterations were assessed by measuring total daily motor activity with actigraphy. In addition, we used quantitative EEG analysis to identify dysfunctions in frontal brain activity and vigilance regulation. In this naturalistic clinical study, we hypothesize an asymmetry in frontal alpha power, suggesting asymmetry in brain activation in MDD patients in comparison to HC. Furthermore, dysregulation of EEG-based vigilance in MDD accompanied by psychomotor and cognitive impairments was also expected to be more pronounced in MDD than in HC. Furthermore, we hypothesized that the combination of the above-mentioned biomarkers increases the diagnostic discrimination to healthy subjects. To note, although we applied simultaneous EEG and MRI scan as an integration of another extended study, only EEG is the main interest in this paper.

Materials and methods

Subjects

Twenty inpatients with a diagnosis of major depressive disorder (MDD) according to ICD-10/DSM IV criteria were recruited after admission to the Department of Psychiatry and Psychotherapy, Rostock University Medical Center, and enrolled into the study. Exclusion criteria included a history of major medical or neurological illness according to the assessment of a senior psychiatrist based on patient history and clinical examination. Furthermore, patients with major psychiatric comorbidity such as substance abuse, anxiety, psychotic disorders, or dementia (DSM-IV—SCID I) [38] were excluded, as were patients with personality disorders (SCID-II, Axis II) [39]. Age-matched healthy control subjects (HC) did not have any history or current symptoms of a neurological or psychiatric disorder as determined by a senior psychiatrist using a clinical interview. Furthermore, both patients and controls were thoroughly examined by a neurologist. Neither the MDD nor the HC group received psychopharmacological treatment such as antipsychotics, anticonvulsants,

antiparkinsonian medications, anticholinergic drugs, or benzodiazepines. However, medication for treatment of medical disorders such as hypertension, diabetes, cardiovascular disorders, or hyperlipidemia was allowed. In the MDD group, the current antidepressants, only consisting of SSRI or SNRI, were discontinued 3 days before the investigation was started. None of the patients took extended-release antidepressants or antidepressants with a long half-life such as fluvoxamine or fluoxetine. Moreover, only one patient had a lithium-prophylaxis for prevention of depressive episodes. We excluded this patient from the EEG investigation (see in the Results section below). None of the patients displayed withdrawal symptoms after discontinuation of antidepressant treatment as assessed by recordings of blood pressure, heart rate, and body temperature. Upon completion of the study, patients were set on a new antidepressant treatment setting. The study protocol had been approved by the local ethics committee and all procedures conformed to the Declaration of Helsinki. All participants provided written informed consent before enrolment.

Clinical scales

Cognitive tasks and the severity of depression were assessed by a clinical psychologist. Cognitive functions included: psychomotor speed (Stroop task: colour word naming and colour naming [40], trail making test A (TMT A) [41]); executive functions (Stroop interference, Trail Making Test B (TMT B)]; and word fluency (Regensburg Word Fluency Test) [42]. Clinical depressive symptoms were assessed by standard questionnaires: Beck Depression Inventory (BDI) [43] and the Hamilton Depression Rating Scale (HDRS) [44]. Psychomotor dysfunction was measured by the use of Motor Agitation and Retardation Scale (MARS) [45]; and previous sleep rhythm was assessed by the Pittsburgh Sleep Quality Index (PSQI) to monitor previous sleep patterns [46].

Actigraphy

We used actigraphy to record the daily motor activity of the participants (Actiwatch 2, Philips Respironics®) as a potential measure of psychomotor dysfunction [47]. Participants wore the Actiwatch on their non-dominant wrist consecutively for 5 days. Activity was recorded at 1-min intervals. The sensitivity of the actigraphy was 0.1 g (G-force). Data were evaluated using the Respironics software (Respironics Actiware). Daytime activity across 5 days was averaged into "total activity" for further analysis. The root mean square successive difference/standard deviation (RMSSD/SD) ratio was used to investigate the variability in motor activity.

EEG recording and analysis

The EEG was recorded simultaneously with an MRI scan. The MRI data are beyond the scope of this preliminary analysis. We placed 31 Ag/AgCl EEG electrodes (10/20 international system) using hypertonic, abrasive and conductive gel through EEG cap (BrainCap MR, EasyCap, GmbH, Breibrunn, Germany) along with an additional ECG channel. EEG data were recorded using Brain Vision Recorder (Brain Product, Gilching, Germany) with MR-compatible EEG system. Participants were in supine position and their head was stabilized using square memory foam placed around their head. Participants were instructed to stay relaxed but not asleep during the 10-min eye-closed resting state recording. All of them wore earplugs to reduce the MRI noise. The participants were contacted twice during the whole procedure by the MRI staff via speakers.

Acquisition

EEG data were obtained simultaneous to MRI scanning using 5 kHz sampling rate and online band pass (0.1 to 1 kHz). Position AFz was determined as ground while position between Fz and Cz was used as online reference. Impedances were kept below 5 kΩ.

Analysis

EEG data were pre-processed using Brain Vision Analyzer (Brain Products, Gilching, Germany). Movement artefacts were excluded manually from analysis. ECG and ocular artefacts were excluded via independent component analysis (ICA). Artefact-free EEG was filtered with 0.5 Hz high pass and 70 Hz low pass. Data were subsequently re-referenced to the average across all 31 electrodes and down-sampled to 250 Hz for further analysis. We obtained the normalized asymmetry index using $(R-L)/(R+L)$ formula for frontal and parietal regions. We included medial (F3–F4, P3–P4) and lateral (F7–F8, P7–P8) electrodes for the analysis. The EEG spectral power and asymmetry indices were calculated from 8 min of artefact-free data for each frequency bands: general alpha: 8–12 Hz, lower alpha: 7–10 Hz, upper alpha: 10–13 Hz.

Analysis of the vigilance regulation was performed using built-in Vigall toolbox for Brain Vision Analyzer (VIGALL 2.0 Leipzig). This toolbox classified each second of resting state EEG to one of the seven brain arousal stages (http://research.uni-leipzig.de/vigall/). The total amount of time spent on each stage (A1, A2, A3, B1, B2/3) ranged from alertness to drowsiness. To note, sleep-onset stage (C) was

omitted here, because no occurrence of sleep-related pattern (i.e. sleep spindles and K-complexes) was detected in the data.

Statistical analysis

Values are presented as mean ± SD. To identify differences in the EEG between HC and MDD groups on the asymmetry of alpha power at the frontal and parietal regions, vigilance regulation, total daily motor activity as well as the cognitive abilities, we performed Mann–Whitney *U* test. The non-parametric test was chosen as Kolmogorov–Smirnov analysis revealed that most of the dependent variables (DVs) mentioned above were not normally distributed. $P < 0.05$ was considered statistically significant. To further investigate the discriminative power of the significant DVs obtained from non-parametric testing, a regression analysis was performed. Binary logistic regression with conditional forward step method was chosen as we attempted to examine which factor entered as the most powerful risk factor in a stepwise fashion. Spearman's correlation (significance level at 0.05) was further used to control for multicollinearity[1] of the regressors in the model.

Results

Clinical characteristics

Twenty MDD (f: 11) patients (mean age: 51.05 ± 10.50 years) and 20 (f: 13) age-matched HC (mean age: 47.15 ± 12.57 years) were enrolled in the study. One patient was excluded from EEG analysis due to a patient-related medication mistake before the EEG investigation (i.e. lithium intake). This patient was the only patient who had received lithium before the investigation. The actigraphy data of two HC could not be analysed due to severe technical artefacts, which were identified only during data analysis.

The MDD patients who participated in the study were moderately to severely depressed (BDI = 27.90 ± 7.85). None of the patients displayed psychotic symptoms or suffered from melancholic, chronic, catatonic, atypical or postpartum depression. Including the current depressive episode, patients had experienced 2.68 ± 2.21 numbers of depressive episodes. The duration of the current episode was 6.81 ± 1.83 months. No patient had presented with suicidal ideation during the current episode.

MDD patients showed impaired attention and reduced psychomotor speed as measured with the TMT A ($p = 0.008$). They also showed disturbed divided attention as measured with TMT B ($p = 0.001$) and Stroop interference ($p = 0.004$). The Motor Agitation and Retardation Scale (MARS) revealed that psychomotor functions in MDD patients were significantly altered in comparison to HC, both regarding agitation (MDD: 14.63 ± 9.15; HC: 9.15 ± 16.42, $p < 0.001$) and retardation (MDD: 16.42 ± 4.14; HC: 10.15 ± 0.49, $p < 0.001$). PSQI scores showed that MDD patients had had significantly worse sleep quality over the four weeks prior to investigation ($p < 0.001$). Actigraphy indicated a significantly lower total activity in the MDD patients in comparison to HC ($p = 0.028$). The RMSSD/SD ratio (for investigation of movement variability) was not significantly different in patients in comparison to healthy subjects. All clinical and neurocognitive characteristics of study subjects are given in Table 1.

EEG-alpha asymmetry at frontal and parietal brain regions in MDD

Mann–Whitney *U* test indicated a significant difference of asymmetry in upper alpha power (10–13 Hz) between MDD and HC at the lateral frontal (F7–F8) region (MDD: 0.07 ± 0.03; HC: −0.03 ± 0.04, $U = 119.00$, $p = 0.047$, Fig. 1). As the formula to calculate asymmetry is (R − L)/(R + L), a negative value indicates higher power at the left than at the right hemisphere. Therefore, MDD patients showed greater right than left frontal activity as compared to the HC group.

None of the other potential EEG asymmetries in all frequency bands tested reached significant differences between groups ($p > 0.10$).

EEG-vigilance regulation

Using the built-in toolbox of Vigall, vigilance analysis revealed that the MDD group spent significantly less time at stages A2 (MDD: 6.63 ± 4.14; HC: 51.05 ± 18.24, $U = 90.50$, $p = 0.004$) and A3 (MDD: 1.68 ± 0.96; HC: 10.35 ± 3.87, $U = 85.00$, $p = 0.003$). Conversely, MDD patients spent significantly more time at stages B2/3 (least alertness; MDD: 565.21 ± 18.64; HC: 412.65 ± 48.79, $U = 102.50$, $p = 0.01$). Time spent at each vigilance stage is illustrated in Fig. 2.

Interaction between clinical and neurophysiological characteristics

In total, there were four independent variables that entered the regression model: TMT B (executive function), total activity measured by actigraphy, lateral frontal upper alpha power, and vigilance stage A3. In total, there were

[1] Only one variable was selected for logistic regression if inter-correlation occurred amongst variables; e.g. correlation between Stroop interference and TMT B, r = .629, p = 0.004, TMT B was selected as it has higher significant value from the Mann–Whitney U test.

Table 1 Clinical and neurocognitive characteristics of study participants

	HC ($N=20$)	MDD ($N=20$)	Significance
Gender (male)	13 (7)	11 (8)	$p=0.747$
Age	47.15 (12.57)	51.05 (10.50)	$p=0.448$
RWT[b] (number of words)	25.40 (7.41)	21.65 (7.57)	$p=0.104$
BDI score	2.50 (3.25)	27.90 (7.85)	$p<0.0005$
HDRS score	0.75 (1.45)	26.10 (6.22)	$p<0.0005$
MARS score	19.30 (0.80)	30.10 (5.70)	$p<0.0005$
PSQI score	4.30 (2.03)	12.15 (4.64)	$p<0.0005$
Total daily motor activity	267495.21 (81392.86)[a]	210228.17 (66495.03)	$p=0.028$
Total sleep (min)	341.73 (71.91)	385.56 (54.87)	$p=0.050$
TMT[c] A (s)	28.20 (9.90)	38.70 (13.86)	$p=0.008$
TMT B (s)	53.35 (11.70)	79.80 (32.28)	$p=0.001$
Stroop CWN[d] (s)	29.30 (4.55)	35.00 (8.74)	$p=0.020$
Stroop CN[e] (s)	43.00 (6.55)	51.20 (12.99)	$p=0.035$
Stroop INT[f] (s)	73.35 (11.55)	93.15 (26.41)	$p=0.004$

All comparisons were performed using Mann–Whitney test. Significant p values are given in italics

[a]$n=18$

[b]Regensburg word test

[c]Trail making test

[d]Colour word naming

[e]Colour naming

[f]Interference

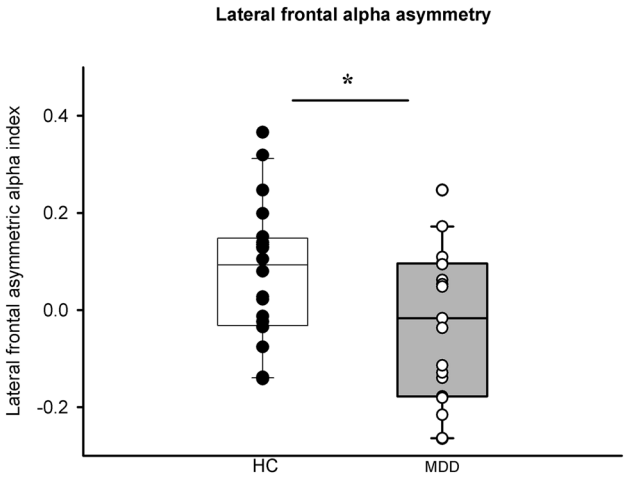

Fig. 1 Lateral frontal alpha asymmetry between HC and MDD. The horizontal line inside the box plot shows median value with bottom and top whiskers represent the 5th and 95th percentiles, respectively. Each dot denotes individual value. Asterisk indicates $p<0.05$

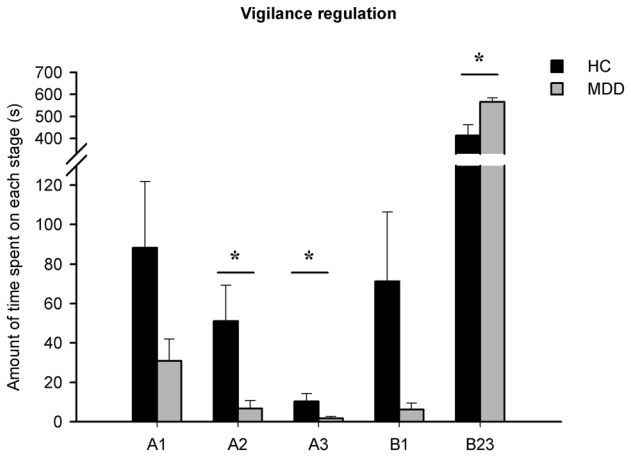

Fig. 2 Vigilance regulation during eye-closed resting state. Each bar represents different mean time (in seconds) that the HC (black) and MDD (grey) spent on each vigilance stage. Whiskers on each bar show the standard error mean values. Different EEG phenomena were characterized into different vigilance stages [35]: A1 (high posterior alpha power); A2 (high frontal and occipital alpha power); A3 (high frontal alpha power); B1 (desynchronised low amplitude EEG power); B2/3 (high theta and delta power). Asterisks represent $p<0.05$

two forward steps that were calculated. The first variable at step 1 was TMT B: OR = 1.18, 95% CI 1.03–1.22, $p=0.011$, and the second variable at the second step was asymmetric lateral frontal upper alpha power: OR = 0.00, 95% CI 0 -0.36, $p=0.025$. Using this analysis, 14 out of 19 (73.70%) patients were classified correctly as being depressed (true positive rate), yielding 78.40% accurate discrimination. Total activity and vigilance stage A3 were excluded by the algorithm due to the lack of a significant increase in prediction accuracy. In other words, these two factors alone did not serve any valuable prediction.

Additionally, to investigate if the interaction of two variables could better predict MDD, all four independent variables were grouped into two combinations resulting in six pairs of interaction: lateral asymmetric frontal upper alpha power × TMT B; lateral asymmetric frontal upper alpha × vigilance stage A3; lateral asymmetric frontal upper alpha × total activity; TMT B × total activity; TMT B × vigilance stage A3; vigilance stage A3 × total activity. The interaction also resulted in two-step calculation. The first step was the interaction of vigilance stage A3 with total activity: OR = 1.00, 95% CI 1.00–1.00, $p = 0.030$, and the second step consisted of the interaction between vigilance stage A3 and TMT B: OR = 1.01, 95% CI 1.00–1.02, $p = 0.048$. Using this extended analysis, the sensitivity for detection MDD was increased to 18 out of 19 (true positive rate, 94.70%), whereas specificity decreased to 12 out of 18 (66.70%), yielding an averaged accuracy of 81.1%.

Discussion

This investigation used a combination of clinical and neurophysiological data to differentiate between MDD patients with a current depressive episode and healthy controls in a clinical study. Our results illustrate that MDD patients suffered from both executive dysfunctions (i.e. significant impairments on the TMT B and Stroop interference task) and psychomotor abnormalities (i.e. significantly longer reaction time on the TMT A, decrease in total activity, and higher sum score on the MARS). In addition, MDD patients showed more cerebral dysregulation compared to HC, as measured by EEG parameters (i.e. asymmetry in alpha power, reduction in alertness). Despite significant differences in these variables between the two groups, regression analysis showed that executive dysfunctions and alpha power asymmetry index in the EEG discriminated between the MDD and HC groups with accuracy of 78%. Combining two variables, TMT B and vigilance stage A3 along with vigilance stage A3 and total daily motor activity, an increase in the discrimination rate to an accuracy of 81% was attained.

Our results for the clinical symptoms are in line with previous studies, confirming that MDD patients show psychomotor abnormalities [19, 48], which means our patients had lower total activity and higher scores in the Motor agitation and retardation score (MARS). In addition, the variability of motor activity during the whole actigraphy procedure as described by Hauge et al. [49] was also investigated here in the form of the RMSSD/SD ratio. The absence of a significant difference in RMSSD/SD ratio between MDD and HC may indicate a continuous reduction in daily motor activity with fewer fluctuations in our sample of MDD patients. This observation fits well with the findings by Hauge and colleagues [49]. In the current study, MDD patients also showed impairments in executive functions, but not in verbal fluency (Regensburg word test). Specifically, executive functions involved in attention shifting and inhibitory processes were altered in MDD patients [50, 51]. Importantly, these two neurocognitive domains are highly dependent on the activity of prefrontal cerebral regions [52]. Using voxel-based lesion-symptom mapping, Tsuchida and co-workers found that Stroop colour naming and attention shifting tasks were mapped on the left ventrolateral prefrontal cortex in a highly similar manner, indicating the critical role of these particular regions in attention switching and inhibitory processes [53]. Given the frequently observed dysfunction in frontal lobe and executive dysfunctions in major depression [54], it is not surprising that the TMT B turned out to be the best candidate for the discrimination between MDD and HC groups.

Interestingly, EEG revealed a significant left-sided hypoactivity at the lateral frontal region in MDD which emerged as a less valuable, albeit significant predictive variable. As it is suggested by fMRI and EEG event-related studies, frontal asymmetry may reflect self-regulated motivational approach/withdrawal behaviours [55–57]. We, therefore, tested the hypothesis that frontal asymmetry may be used as a marker for depression. Indeed, there is already some evidence for this in the literature. In particular, several studies confirmed alpha asymmetry in MDD [57–62], see also review [63], and even a correlation between asymmetry index and depressive symptoms [64–67]. However, there are also some negative reports [68, 69]. Alpha power asymmetry has also been observed in healthy samples [70], and, in addition, inter-individual differences within depressive patients have been described [71]. These inconsistencies may be in part due to different sample characteristics. Crucially, psychopharmacological treatment has been shown to alter EEG alpha power [72]. Furthermore, it has been reported that alpha asymmetry may vary in an individual both on a diurnal basis and across the time of year [73]. Several genetic studies suggest that frontal alpha asymmetry may not be a reliable endophenotype because of the low interrelation to depressive mood [74] and also the high gender variability [75]. Finally, these clinical dysfunctions were also documented in other psychiatric disorders, especially in those with frontal brain abnormalities, such as schizophrenia [76]. On balance, alpha power asymmetry could be a useful, yet somewhat less stable marker of MDD requiring further investigation.

We did not find alpha power asymmetry in other brain regions, e.g. in the parietal region. A previous study suggested that asymmetry of parietal alpha power may reflect a different underlying mechanism than the asymmetry observed in frontal regions. While frontal asymmetry is linked to motivational approach/avoidance behaviour [77], parietal asymmetry of alpha power has been related to increased anxiety [31, 63, 78]. Lopez-Duran et al. found an

increase in lateral frontal asymmetry during the presentation of sad films, suggesting that lateral frontal alpha asymmetry may be a moderator regulating depressive or withdrawal behaviours during stressful events [57]. On the other hand, Bruder et al. followed up the offspring of depressed parents and grandparents and found greater parietal alpha asymmetry power and higher rates of anxiety disorders relative to the offspring of never-depressed parents and grandparents [79]. The authors hypothesized that asymmetry of parietal alpha power may constitute an endophenotype of increased risk for depression and anxiety disorders. Since patients with comorbid anxiety disorders were excluded from this study, we may not have detected asymmetry of parietal alpha power in our sample of MDD patients.

Contrary to previous findings [36, 80], our patients showed no constant alertness in vigilance EEG stages. We attribute this finding to their drowsiness during the time of EEG recording. Since EEG vigilance is an indicator of brain arousal, patients had a lower arousal, which might be due to increased fatigue or previous worse sleep quality as reflected by PSQI scores. Since the EEG investigations were performed in the morning, it is tempting to speculate that the diurnal variation of depression ('worse in the morning') may account for this observation. Our results suggest that MDD patients suffer from impaired regulation of vigilance stages. Further research with better valence-controlled and long-term EEG recordings is required to support this finding.

Our regression analysis indicated that two individual variables could discriminate the MDD from the HC group and yielded approximately 78% accuracy. Whereas executive dysfunction and alpha power asymmetry are two valuable candidates for discrimination, vigilance regulation and total daily motor activity alone do not provide significant predictive value. However, when two variables were merged into a single predictor, the interaction between total activity and vigilance stage A3 as well as the interaction between TMT B and vigilance stage A3 showed robust discriminative power and improved the accuracy of the prediction to 81%. The data suggest that reduced total activity and executive dysfunctions depend on brain arousal, which was low in our patients. Moreover, our data suggest that the combination of neuropsychological parameters and neurophysiological measures provides a better model to discriminate depressive patients from healthy subjects. Since the TMT B alone could already fairly reliably distinguish between MDD and HC, adding a second factor increased the accuracy of the prediction. Hence, taking either of these two combined factors could ultimately improve the discrimination rate of depressive patients from healthy controls, our results support the concept that the use of multivariate candidate analysis increases the diagnostic demarcation of MDD. The combination of special clinical symptoms and EEG parameters such as vigilance regulation as an indicator of brain arousal seems to be suitable in this process. Further research is needed to extend these results to earlier stages of MDD.

Conclusion

Major depression is a heterogeneous disorder with individual symptom complexes [81, 82]. A single biomarker to diagnose depression has not yet been defined, even with the help of modern technologies such as functional brain imaging. Hence, combining clinical and electrophysiological variables seems like the most viable approach for the diagnostic procedure of depression. We here show that using executive dysfunctions or frontal alpha power asymmetry alone could distinguish between MDD and HC with a sensitivity of 78%, which could be further improved to 81% if clinical ratings and EEG vigilance regulation were factored in. Our results support the notion that the heterogeneous symptoms of MDD lend themselves better to multivariate candidate analysis than to investigation of a single biomarker.

Limitations

The small sample size of this report limits its generalizability to a larger population. However, given the exploratory approach of our study, we rather aimed at including as many candidate variables as possible, thereby accepting some weaknesses in detection (power). The data are preliminary, we report in a first step the clinical and EEG data, only. Another limitation lies in the fact that our data only reflect the clinical and neurophysiological symptoms of a current depressive episode. Therefore, our results do not have clear implications for the 'state or trait' debate of major depression. Considering the limitations of the present study, further research will be needed to validate the biomarkers identified here. Most importantly, this clinical validation will have to include a comparison of MDD patients and patients suffering from other psychiatric disorders.

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Compliance with ethical standards

Conflict of interest The authors report no conflict of interest.

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