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Correlation of EEG spectra, connectivity, and information theoretical biomarkers with psychological states in the epilepsy monitoring unit — A pilot study

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ABSTRACT

At the level of individual experience, the relation between electroencephalographic (EEG) phenomena and subjective ratings of psychological states is poorly examined. This study investigated the correlation of quantitative EEG markers with systematic high-frequency monitoring of psychological states in patients admitted to the epilepsy monitoring unit (EMU).

We used a digital questionnaire, including eight standardized items about stress, energy level, mood, ward atmosphere, seizure likelihood, hopefulness/frustration, boredom, and self-efficacy. Self-assessments were collected four times per day, in total 15 times during the stay in the EMU. We extracted brainrate, Hjorth parameters, Hurst exponent, Wackermann parameters, and power spectral density from the EEG. We performed correlation between these quantitative EEG measures and responses to the 8 items and evaluated their significance on single subject and on group level.

Twenty-one consecutive patients (12 women/9 men, median age: 29 years, range: 18–74 years) were recruited. On group level, no significant correlations were found whereas on single-subject level, we found significant correlations for 6 out of 21 patients. Most significant correlations were found between Hjorth parameters and items that reflect changes in mood or stress.

This study supports the feasibility of correlating quantitative EEG measures with psychological states in routine EMU settings and emphasizes the need for single-subject statistics when assessing aspects with high interindividual variance. Future studies should select samples with high within-subject variability of psychological states and examine a subsample with patients encountering a critical number of seizures needed in order to relate the psychological states to the ultimate question: Are psychological states potential indicators for seizure likelihood?

1. Introduction

Admission to the epilepsy monitoring unit (EMU) constitutes the diagnostic gold standard in epileptology to confirm seizure diagnosis and seizure localization, to differentiate epilepsy syndromes, and to choose or optimize therapeutic approaches. The procedure consists in long-term inpatient video-electroencephalogram (EEG) monitoring [1-3] and includes periictal testing [4]. Qualitative EEG is the key method used in an EMU. While it was Hans Berger's original intent to gain insight into mental states [5], we now know that qualitative EEG analysis has little to add to the investigation of the nature of particular psychological states and processes. When qualitative EEG assessment is combined with the observation of seizure semiology and patient's reports of focal seizures or other seizure-related experiences, it allows to link qualitative characteristics of the EEG

Abbreviations: AED, antiepileptic drugs; EEG, electroencephalogram; EMU, epilepsy monitoring unit; PSD, power spectral density; SNS, Synergetic Navigation System.

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to behavioral and mental states. The routine assessment of mental states in the EMU is usually limited to periictal testing of cognitive functions [4], which can inform an epileptologist about the localization of the seizure [6]. The practices in EMUs exhibit a considerable diversity [7], and therefore, it is not surprising that a standardized systematic psychological assessment procedure that provides high-frequency data of psychological states alongside with the continuous video and EEG recordings is not available, so far. Up to date, only very few studies have integrated systematic psychological assessments into inpatient video-EEG monitoring [8]. None of these have obtained high-frequency psychological assessments yielding time series of psychological dynamics and actually correlated these with quantitative EEG measures. In healthy participants, it was shown that quantitative EEG measures, namely measures of connectivity, may be used to predict different emotional states [9]. While the biotechnical prediction of epileptic seizures with quantitative biomarkers from the EEG and modern means such as artificial intelligence and deep learning networks is not yet reliable [10], some patients report to be able to predict their own seizures [11]. Regularly sampled seizure expectations in 19 patients with epilepsy demonstrated significant predictability in a subgroup of patients [12].

Epileptic seizures may be precipitated by the interaction of various electroclinical factors that are subject to current technical endeavors of predicting seizures with a very low false prediction rate [13]. Given the promising results from patient self-reports and current advances in quantitative EEG analysis, the potential applications of correlating regularly sampled psychological states with EEG biomarkers in epileptology are manifold: Possible applications for research include, for instance, the investigation of the relationship between stress and mood states on the one hand and preictal, early ictal, and postictal EEG changes on the other hand. More reliable seizure prediction methods would facilitate the application of nonpharmacological (e.g., behavioral) and pharmacological seizure prevention and seizure interruption methods. These therapeutic methods might alleviate the patients' sense of being delivered to the unpredictability of seizures, which poses a major negative influence on our patients' quality of life [14].

This study aimed at characterizing the potential correlation between psychological states, monitored by high-frequency time-stamped electronic questionnaires, and quantitative EEG measures describing spectral properties, interactions, and informational content, extracted from continuous EEG over multiple days in the EMU. We demonstrate the feasibility of such an approach and aim to characterize the correlations across subjects as well as on a single-subject level and to provide directions for future research in this area.

2. Material and methods

This study is based on the same sample of a previously published pilot study, assessing the concept of the psychological sampling method, and compliance with this method, but did not investigate the correlation of the psychological states with the EEG measures [15].

2.1. Setting

This pilot study was conducted in the routine care of the EMU of the Department of Neurology, Christian Doppler Medical Center, Salzburg, Austria. Admitted patients undergo the usual diagnostic evaluations consisting of long-term video-EEG monitoring. Recordings are performed over a mean period of 5 days (Monday to Friday). In order to promote a timely occurrence of seizures during the monitoring period, it is common practice to taper the dosage of antiepileptic drugs (AEDs) and expose patients to sleep deprivation. Informed consent for serious adverse events was completed routinely upon EMU admission.

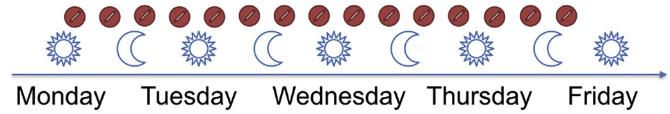

Fig. 1. Examination schedule in the epilepsy monitoring unit.

2.2. Ethical aspects

The study was designed and conducted in accordance with the World Medical Association Declaration of Helsinki and Good Clinical Practice Guidelines. Prior ethical approval was obtained from the ethical committee Salzburg (415-E/2206/9-2017). Written informed consent was obtained from all participants.

2.3. Process questionnaire

Our nonvalidated process questionnaire included eight standardized items. Patients were asked to rate the following items on visual analogue scales:

Stress level: *I feel nervous and stressed.* (0 = not at all to 100 = very much).
Energy level: *I have energy.* (0 = none at all to 100 = very much).
Mood: *My mood is...* (0 = very bad to 100 = very good).
Ward atmosphere: *The atmosphere is...* (0 = very bad to 100 = very good).
Seizure likelihood: *The likelihood of me having a seizure within the next hours is...* (0 = very low to 100 = very high).
Hopefulness/frustration: *I am...* (0 = frustrated to 100 = hopeful).
Boredom: *I am bored.* (0 = not at all to 100 = very).
Self-efficacy: *I can make use of things that help me to get along with the situation.* (0 = not at all to 100 = very well). This item probed the use of resources that had previously been identified during a short resource-oriented interview at admission.

Paper-based questionnaires may decrease data validity as they may allow patients to record or modify data retrospectively [12]. In order to increase data validity, we used an electronic data capture, the Synergetic Navigation System (SNS), which has already been used in outpatient settings and provides a more reliable time-stamped data collection method [16]. The SNS was used to collect daytime self-assessments every five hours, three times daily prior to meal times (6: 30 am, 11: 30 am, and 4: 30 pm) and at 9: 30 pm, using the process questionnaire outlined above (see Fig. 1). Each patient was provided with a tablet. The participating patients were made aware of the measuring times by an alarm set in the tablet and were free to access the questionnaires via internet through a personalized account whose password had to be changed upon first log-in. Each time that the questionnaire was accessed, the items appeared in random order. More details about item development and SNS are summarized in a pilot study [15].

As has been outlined above, patients were prompted to fill in the process questionnaire four times a day during their five-day inpatient hospitalization (including three full and two half days). As illustrated in Fig. 1, the maximum number of measurement points between admission on the first day and discharge on the fifth day was 15 measurement points (1st day: two measurement points (afternoon and evening), 2nd–4th day: four measurement points each, 5th day: one measurement point in the morning).

2.4. Recruitment of patients

A consecutive sample was enrolled: All patients who were 18 years and older and who were admitted to the EMU between November 6th 2017 and January 22nd 2018 were approached on the first day of admission.

2.5. EEG acquisition

A Micromed system (System Plus Evolution) for video-EEG monitoring and standard scalp electrodes were used routinely in the EMU Salzburg. Scalp electrodes were applied according to the 10–20 system. For the recording, 32 channels were used, including five non-EEG channels, each one for electrocardiogram, blood oxygen level, electromyogram, and two for the electrooculogram. These five channels were not submitted to the quantitative analysis. We performed the analysis on 19 selected EEG channels: F3, F3, F7, F8, Fz, C3, Cz, C4, T7, T8, T11, T12, P3, P4, P7, P8, Pz, O1, and O2. The sampling rate was 256 or 1024 Hz, as two out of 4 beds in this EMU were equipped with a higher sampling rate.

2.6. EEG analysis

From routine EEG recordings, we extracted 2 min prior to the time stamp of the completion of the questionnaire. These 2 min were chosen according to the median time of 3 min it took the participants to fill in the form. This period provides a consistent activity across patients while any other period would be biased by diverse activity such as reading, watching TV, talking, sleeping, etc. Patients were usually sitting on their beds and filled out the questionnaire by selecting responses on the touch screen of their tablet with their index finger. Since the questionnaire was very short, this activity was usually not interrupted by other activities such as talking, drinking, etc. Moreover, qualitative inspection of the EEG (performed by RM) revealed that these periods were at relative advantage to other periods in terms of artifacts. Furthermore, in these segments, we found local or diffuse slowing in some patients (N = 10) but no signs of epileptic activity. The data were imported to MATLAB (The Mathworks, Massachusetts, USA).

We used the BioSig toolbox [17,18] in order to extract the following features:

Brainrate: Brainrate [19], as a measure for the brain's basic activity, was calculated in stationary mode for each channel.

Hjorth parameters: Hjorth parameters as proposed by Hjorth [20,21] include activity, mobility, and complexity. Activity is the squared standard deviation of the amplitude, i.e., the variance of the mean power. Mobility can be understood as a mean frequency. Complexity describes deviation from the sine wave, i.e., degree of irregularity of the signal. Each of these features was evaluated in stationary mode separately for each channel. Thus, the result was a feature per channel.

Hurst exponent: The Hurst exponent was estimated via the rescaled range [22]. The Hurst exponent, also known as index of long-range dependence, measures long-term memory of time series in the sense of autocorrelations. In other words, it measures the repetition of patterns in the EEG. It was calculated for each channel.

Wackermann parameters: Global field strength σ, denoting the mean square of the global field power integrated over the length of the EEG epoch, global frequency ϕ, as a measure of general frequency, and a measure of spatial complexity ω, which is a global measure of spatial synchronization [23,24] were evaluated in stationary mode separately for each channel. These parameters characterize the potential field across the scalp, by taking into account the correlations between electrodes. I.e., these measures can be interpreted as global measures of connectivity.

Finally, we calculated **power spectral density (PSD)**, as the most classical quantitative estimate of EEG characteristics. The PSD indicates the amplitudes of EEG oscillations at specific frequencies by means of the Matlab function fft.m, and the resulting vectors for each channel were averaged in frequency bands centered at frequency bands delta (1–4 Hz), theta (5–7 Hz), lower alpha (8–10 Hz), upper alpha (11–13 Hz), beta (14–30 Hz), and gamma (31–48 Hz).

2.7. Statistics

The patients' clinical characteristics and compliance are summarized using descriptive statistical methods. We aimed to assess the correlation between the subjective ratings on the eight items for each patient and EEG measure, but also group-level correlations. For this purpose, we conducted correlation and statistical evaluation individually for each patient and also on group level for each of the seven EEG measures. Because of high dimensionality of the features such as, for example, PSD (6 frequency ranges times 19 channels), we chose to perform maximum statistics randomization tests. For the single-subject setting, this nonparametric test worked as follows: Consider that for each EEG measure and for each item on the psychological questionnaire, we have a list of 15 EEG values and a list of the corresponding 15 subjective ratings. The entries of both lists were shuffled. The resulting randomly permuted vectors were then correlated with each other using Spearman's correlation. Consequentially, this means that a given psychological measure was most likely assigned to an EEG segment from a different time and/or day. That is, for PSD, we obtained eight (for the eight items) times 19 (for the 19 channels and combinations) times 6 (for the 6 frequency ranges) correlation coefficients. From these coefficients obtained under random conditions, we recorded the maximum value and the minimum value (for negative correlation coefficients). This procedure of randomly permuting and correlating was performed 1000 times, thus yielding 1000 maximum and minimum correlation coefficients under random conditions. Some of the responses of participants (participants 10 and 15) were not eligible for Spearman correlation, as participants did answer only few (i.e., 9) measurement points, and indicated the same response (e.g., 100 out of 100) for several measurements. This problem was solved by adding random noise with values between 0 and 1 to the answers of these participants.

From the 1000 permutations, we obtained a distribution of maximum and minimum results under random conditions. Then, the data were correlated according to its original chronological order, in order to obtain the correlation coefficients under test conditions. Each of the obtained test values was compared to the maximum (when its sign was positive) or minimum distribution (when its sign was negative). Then, the proportion of more extreme values (larger for positive correlations and smaller for negative correlations) was considered as the p-value of this test value. Please note that this separate evaluation of positive and negative extrema should be considered to be one-tailed significance.

As this is a single-subject statistic, we could look at single-subject results. In order to summarize these results, we counted the number of participants whose correlation coefficients were significant on single-subject level ($p < .05$). We performed the same statistical test on group level by conducting the permutation across all measurement points of all participants. Because all tests were repeated for the 9 biomarkers, we provide also evaluation of significance at the Bonferroni-corrected level of significance, i.e., $p < .0056$.

3. Results

3.1. Sample

During the 10-week enrolment period, a total number of 40 patients had been referred to the EMU. Eleven patients had not been eligible with the main reasons being a) motor deficits and/or aphasic dysfunctions that severely limited the handling of the tablet and/or comprehension of the items of the questionnaire (n = 6), or b) underage (n = 3), or c) already felt too distressed by the EMU inpatient situation (n = 2). Eight patients declined to participate. Consequently, the sample included a consecutively recruited cohort of 21 participants (see Fig. 2).

The majority of the participating patients were admitted to the EMU within the first year after their first paroxysmal event (see Table 1 for sample characteristics).

During their stay in the EMU, 15 patients (71%) underwent sleep deprivation at least once. Medication was tapered in 12 patients (57% of all 15 patients who had been taking at least one AED upon admission to the EMU), and at least one epileptic seizure was recorded in four patients (19%).

3.2. Submitted questionnaires

The median number of submitted questionnaires was 13 (range: 9–15). Seven patients (33%) completed the questionnaire at all measurement points. Altogether, 14% (43 measurement points) of the total number of measurement points was missing. In a few cases, patients filled out the questionnaire more than once in a row. In such cases, only the first submission was examined. It took the participants a median time of 3 min[range: <1 min to 12 min] to fill out the questionnaire.

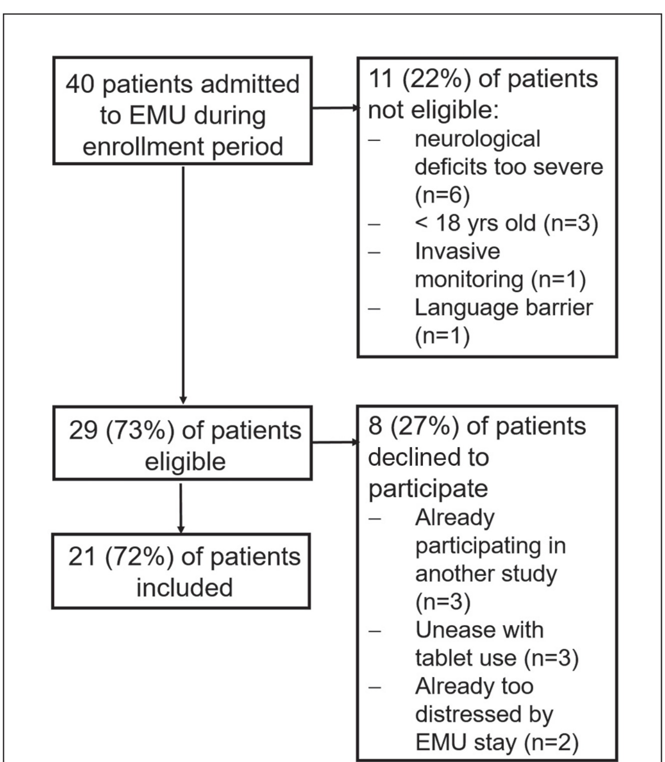

Fig. 2. Recruitment flow chart. EMU: epilepsy monitoring unit, yrs.: years.

3.3. Correlation of EEG biomarkers with psychological states

The correlation coefficients were in general very small on a group level. Consequently, none of the biomarkers showed significant correlation with items from our questionnaire on a group level, not even at the uncorrected level of significance. However, on a single-subject level, there were significant correlations in 12 out of 21 patients on the uncorrected level of significance, and in 6 out of 21 patients on the corrected level of significance, as shown in Table 2.

Because on group level we found no significant differences, the figures show the correlation coefficients on group level alongside with the number of patients showing significant differences on the single-subject level of statistical analysis (uncorrected level of significance).

Fig. 3 shows the group-level correlations and single-subject statistics for brainrate. On the single-subject level of 4 patients, we found most correlations between brainrate and reported stress, and occasionally also for reported energy and hopefulness/frustration.

Fig. 4 shows the group-level correlations and single-subject statistics for Hjorth features activity, mobility, and complexity. Again, most correlations were found with stress, especially for complexity and even more so for mobility, where the correlations of several patients overlapped regionally. But also for mood and boredom as well as hopefulness, regionally widespread correlations were found. Other correlations were rather occasional. Compared with brainrate, more correlations reached significance (uncorrected) on the single-subject level.

Fig. 5 shows the group-level correlations and single-subject statistics for Hurst exponent. Compared with the other features, correlations were rare and rather occasional. Only energy and hopefulness/frustration yielded significant (uncorrected) correlations.

Fig. 6 shows the group-level correlations and single-subject statistics for Wackermann parameters global field strength σ, global frequency ϕ, and spatial complexity ω. Again, group-level correlation coefficients were so small that it does not warrant to interpret them. Correlations on single-subject level were found for most items but not for ward atmosphere and mood. Stress was found to correlate for two patients as well as seizure likelihood.

Table 1
Patient characteristics and characteristics of the EMU stay.

	nr.	Rage/percent
Demographics		
Sample size	21	
Age in years median [range]	29	[18–74]
Gender (female) total (%)	12	(57%)
Years since 1st event median [range]	0	[0–17]
Reason for admission		
Classification of epilepsy syndrome	9	(43%)
Investigation of differential diagnosis	6	(29%)
Assessment of seizure frequency	3	(14%)
Optimization of medication	3	(14%)
Diagnosis		
Structural epilepsy	12	(52%)
Idiopathic generalized epilepsy	3	(14%)
Psychogenic nonepileptic seizures	3	(14%)
Syncope	2	(10%)
Migraine with aura	1	(5%)
Medication total		
None	6	(29%)
1 antiepileptic drug	14	(71%)
2 antiepileptic drugs	1	(5%)
> 2 antiepileptic drugs	0	(0%)

Table 2
Patients showing significant correlations between psychological state and biomarkers.

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Brainrate									x				+			+		x			
Activity[a]			x								x					x					
Mobility[a]			x										+	x		x		x	x	+	
Complexity[a]	x							x					+	x		x		x	+	x	
Hurst				x				x					x								
σ[b]			+								+			x		x		x			
ϕ[b]								x					x	x		+		x			
ω[b]											x										
PSD			x								x		x					+	x		

PSD = power spectral density. x: one-tailed significant, uncorrected ($p < .05$); +: significant, corrected ($p < .0056$).
[a] Hjorth parameters.
[b] Wackermann parameters.

Fig. 7 shows the group-level correlations and single-subject statistics for PSD. On single-subject level, we found significant correlations for all items, except for ward atmosphere and boredom. Significant correlations did not overlap in region/frequency but spread across 5 out of 21 patients. Most correlations were found for stress, mood, and hopefulness/frustration. Significant correlations extended across all frequency ranges but were most pronounced in the theta and alpha range.

4. Discussion

The results of this pilot study illustrate diversity across subjects when correlating quantitative EEG biomarkers with high-frequency psychological states in the EMU. According to the presented analysis, in several patients, the subjective ratings of stress, mood, boredom, hopefulness/frustration, and seizure likelihood correlated with quantitative EEG parameters, but the responses were so diverse that

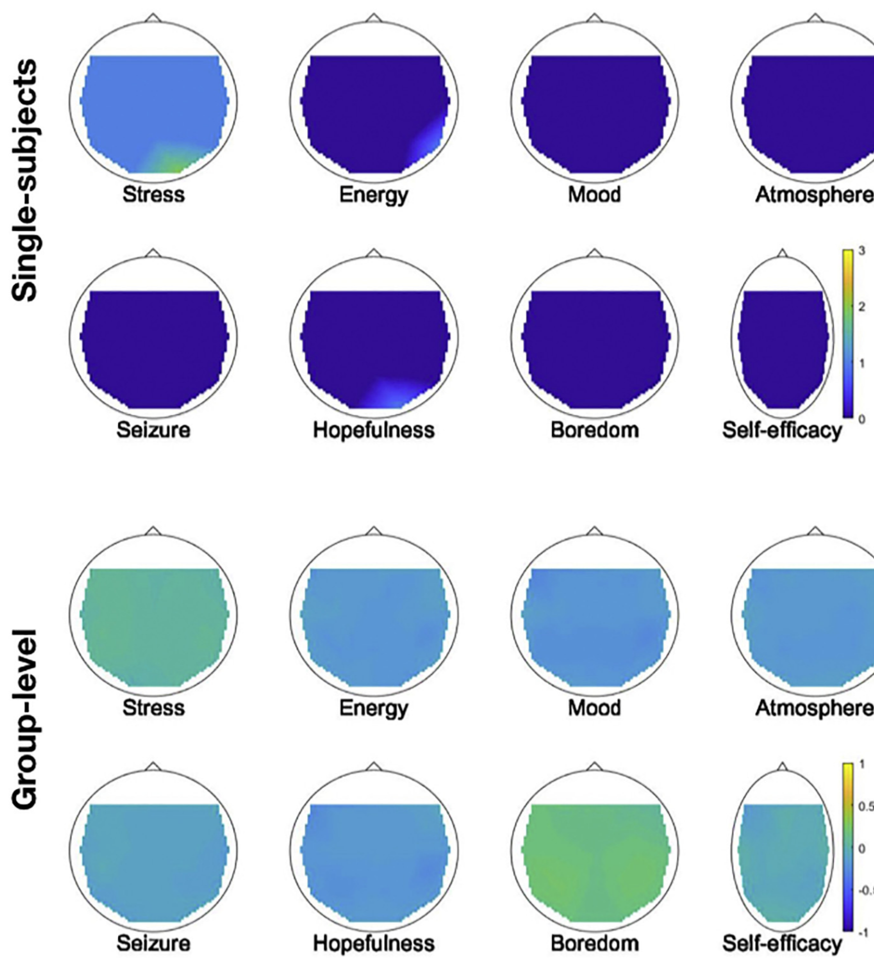

Fig. 3. Statistical results for brainrate: Number of subjects with significant ($p < .05$, uncorrected level of significance) correlations (top) and group-level correlation coefficients (bottom).

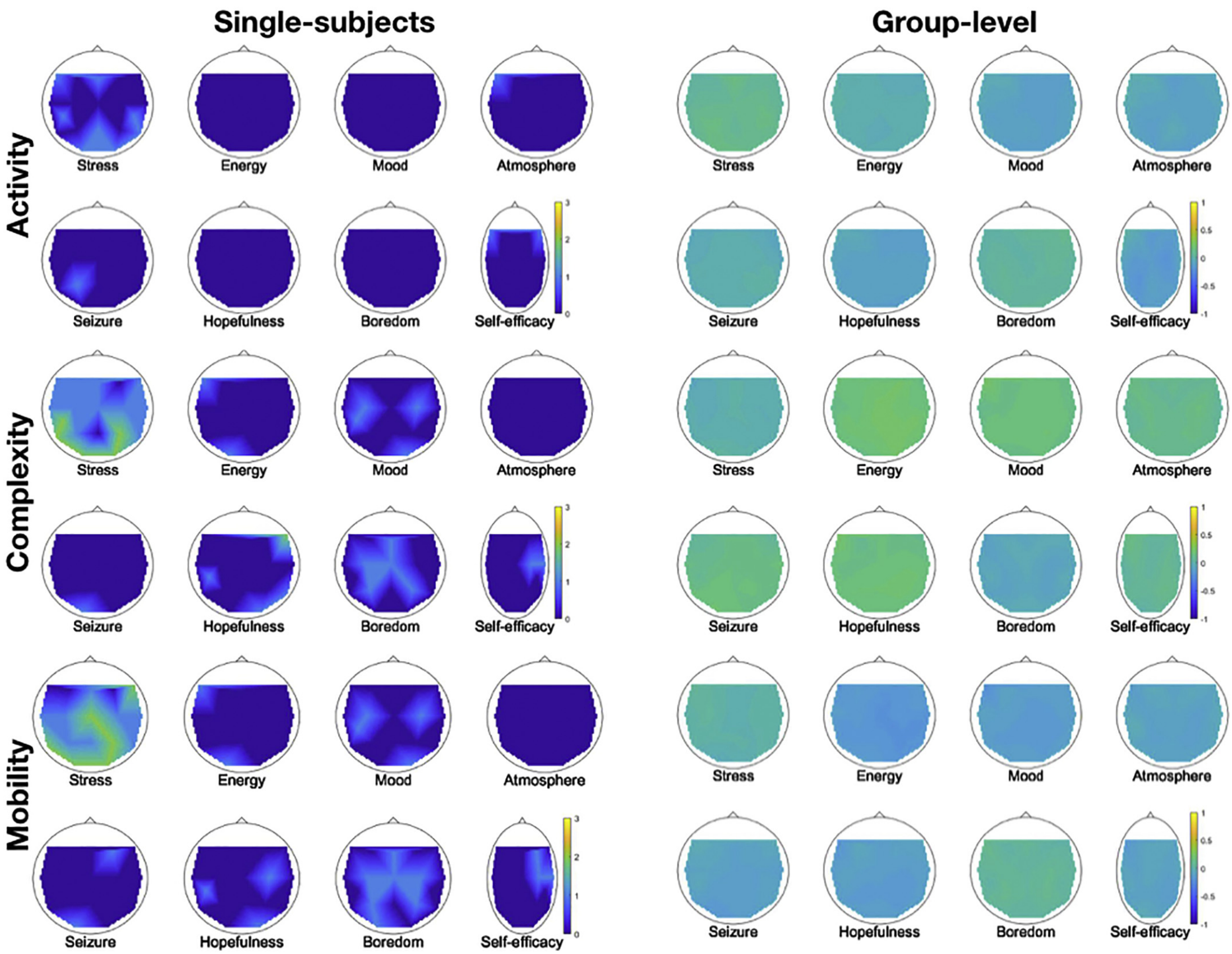

Fig. 4. Statistical results for Hjorth features activity, complexity, and mobility: Number of subjects with significant ($p < .05$, uncorrected level of significance) correlations (left) and group-level correlation coefficients (right).

on group level, no consistent pattern emerged. We also found that no single biomarker revealed correlations for all patients, and no patient's subjective experience correlated with all biomarkers. This finding encourages the use of a battery of quantitative EEG measures.

The present study is one of the first that tries to link the variability in the EEG to subjectively rated psychological states of patients in the EMU. Therefore, it is of interest to take a closer look at the diverse results and give recommendations for future research endeavors. In the following, we would like to point out how these results can be related to what has been done so far in similar areas of research, how our study could stimulate further investigations, and what limitations need to be considered.

4.1. Individual response patterns

We were not able to demonstrate a relation between psychological states and EEG measures in the EMU on group level. However, single-subject correlations supported considerable variability across participants. Several reasons can explain these circumstances.

First, the correlation is highly dependent on the variability of a patient's answers in regard to his or her feelings. If a patient exhibits no variation over time in the respective domains, correlation analysis does not yield a meaningful result. This might have been specifically true for the item about seizure likelihood, as only four patients experienced seizures. Moreover, in qualitative terms, the result may also depend on the accurateness of a patient's indications of feelings. Furthermore, by having corrected for multiple comparisons, the power is reduced. And finally, the patient's clinical background is diverse, which could be addressed in future studies by selecting a homogeneous sample of patients.

Interindividual variability of EEG measures is a known phenomenon. For example, gender affects the power of frequency bands [25], and variability was reported for attention-related activation [26], or responses to music [27]. Interindividual EEG variability is indeed so large that the EEG is subject to intensive research of using it as a new biometric modality [28,29]. However, a problem for EEG-biometrics as well as longitudinal studies such as the present one is variability over time [30,31]. The EEG's variability over time might be affected by several unknown factors, such that the systematic variation with psychological states is hard to be detected in the noise of other moderators. Pathological activity such as diffuse changes as noted in the present data may contribute to this variation over time.

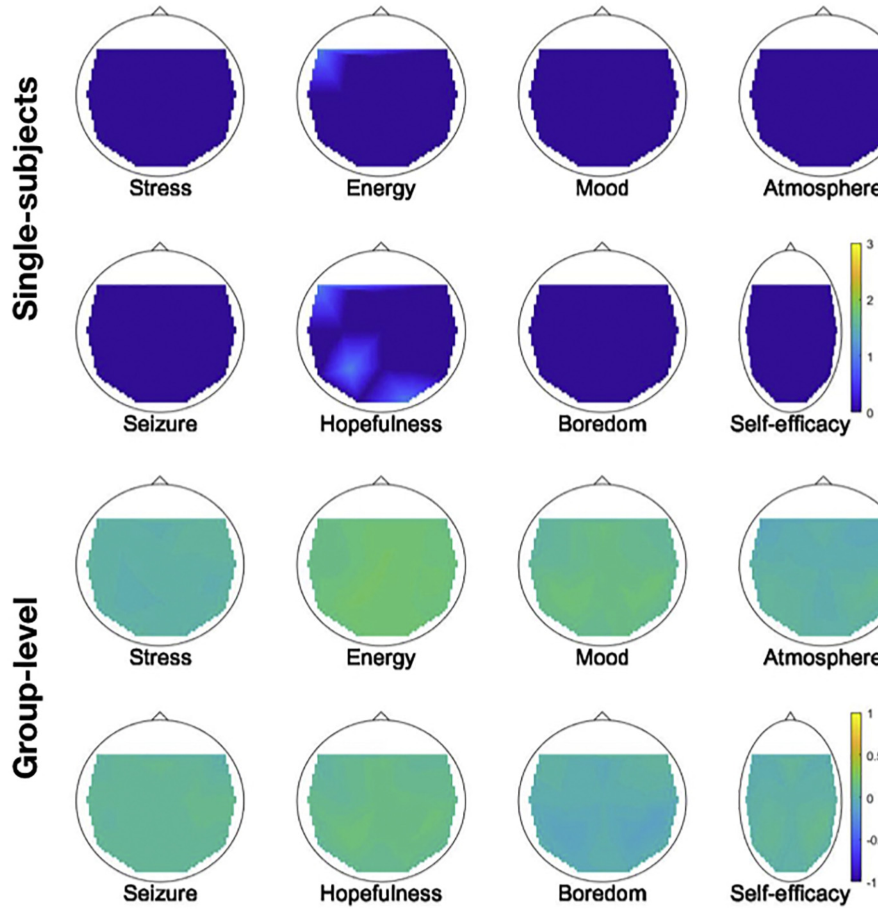

Fig. 5. Statistical results for Hurst exponent: Number of subjects with significant ($p < .05$, uncorrected level of significance) correlations (top) and group-level correlation coefficients (bottom).

4.2. Correlation of EEG biomarkers with psychological states

We found correlations of EEG biomarkers with psychological states that match reports about previous efforts into this direction. It was shown that EEG spectral properties correspond to stress states [32-35]. However, the exact EEG-frequency range, where this stress response might be found, varies over the full range of frequency bands from delta to gamma across studies. Alonso et al. [32] reported that with stress, approximate entropy is decreased while EEG interactions measured by coherence are increased. In another study, multivariate multiscale entropy analysis was used to characterize states of stress in the EEG [36]. Most interestingly, in patients with stress-sensitive epilepsy, cortisol levels measured in saliva correlate significantly with global functional connectivity, whereas this effect was not significant in patients without this sensitivity [37].

While an "objectifying" biological correlate of the mental state of stress can, so far, be obtained by measuring cortisol, no such direct marker exists for mood. It was, nevertheless, shown that patients with major depressive disorder show changes in EEG spectra that are correlated to treatment response [38]. Moreover, in a more general approach, Wyczesanz et al. [39] were able to demonstrate a covariation of subjective mood indications and EEG spectral power. However, while this study also performed a single-subject analysis, it did not employ any means to correct for multiple comparisons.

We calculated several information theoretical measures, based on findings that entropy was shown to be informative for pathology [40], and to be a correlate of successful seizure therapy for depression [41]. Similarly, our results reflected a correlation with hopefulness. Furthermore, in line with our findings, it was recently found that information theoretical measures correlate with stress [42].

The presented measures were shown in the past to be potential biomarkers for the classification of disorders of consciousness [43]. Brainrate was intended to serve as a standard indicator of activation and mental arousal [19], and was found to be indicative for attention deficit hyperactivity disorder [44]. Wackermann parameters were used for assessing sleep and pharmacological effects [23], in brain computer interfaces [45]. Dynamical Hurst analysis assessing the autocorrelation of EEG signals found differences between patients with posttraumatic stress disorder and healthy controls [46], and it was also used to identify nonlinear features in patients with epilepsy during seizures vs. interictal periods [47], to diagnose epilepsy [48], and to detect seizures in the EEG [49].

Comparing channel-wise features to global features (Wackermann-features) does not allow the general conclusion that channel-wise features are more informative, although most correlations were found for Hjorth parameters mobility and complexity on a channel-wise level. We encourage the use of a meaningful battery of complementary features, but an optimal set of features should

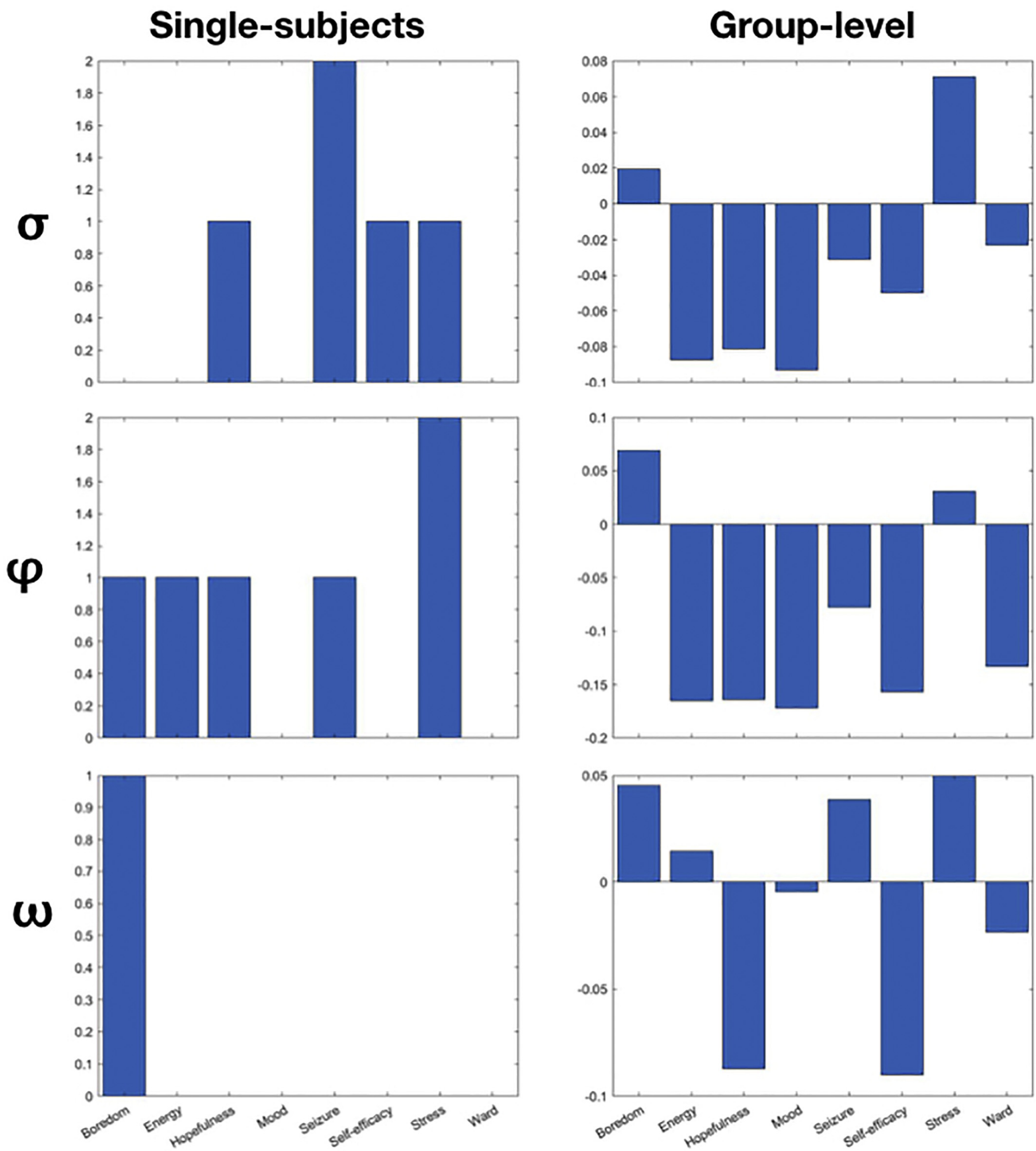

Fig. 6. Statistical results for Wackermann parameters: Number of subjects with significant ($p < .05$, uncorrected level of significance) correlations (left) and group-level correlation coefficients (right).

be validated in future studies with a carefully selected sample of patients.

4.3. Limitations and future studies

The small sample size and inhomogeneity of included patients in this pilot study constitutes the major limitations to interpret our findings. Given the small number of patients, systematic variations between patients with different seizures and other paroxysmal disorders could not be determined. Optimal follow-up studies with more specific designs should include sufficient numbers of patients in well-selected homogeneous subgroups. Specifically, a study examining the correlation of stress with EEG factors in patients with stress-sensitive epilepsy such as in the study of Heijer et al. [37]

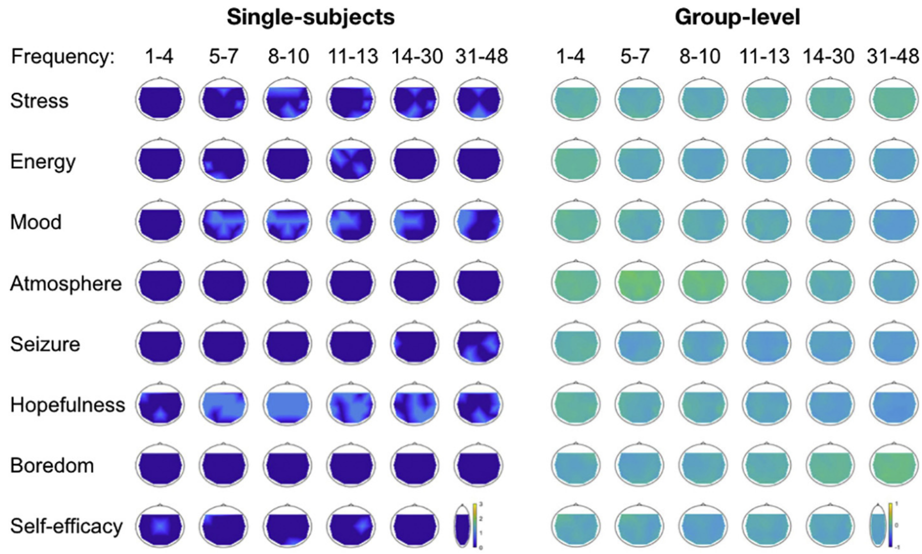

Fig. 7. Statistical results for power spectral density: Number of subjects with significant ($p < .05$, uncorrected level of significance) correlations (left) and group-level correlation coefficients (right).

could allow to test the concept in a sample where a relationship between seizures and stress was already established based on patient self-reports. Similarly, the examination of a sample of patients who report to be able to predict seizures could allow testing the relationship between EEG variables and subjective seizure prediction, such as in the study by Haut et al. [12]. This would also add to our understanding of the interaction between mental, behavioral, and neural correlates of the transitions between periictal, preictal, and early ictal states. So far, there are only hypotheses derived from the retrospective correlation of patient accounts' of seizure phenomena and EEG data [50]. The approach employed in this pilot study would allow for the correlation of psychological states obtained during real-time monitoring with simultaneously obtained EEG data. In addition, we propose that participants in future studies should be trained in introspective methods to increase their sensitivity towards subjective phenomena.

Another clear limitation is the selection of EEG segments. Patients responded autonomously to the questions on the tablet, the recording time was not controlled by an experimenter. In future studies, EEG segments with more standardized environmental conditions could be obtained. Ideally, we would have asked the patients to close their eyes and not to move for 2 min. This would require the presence of an experimental supervisor 4 times a day for each patient. This alternative would increase data quality, but at the same time clearly limit the feasibility and practical usability of the procedure.

Furthermore, we need to take a closer look at the inconsistency of correlations across measures. Despite similarity, e.g., for stress, there were also differences both in terms of which patients showed correlations as well as which items showed correlations. This inconsistency could ideally be interpreted such that the different measures assess different concepts, thus encouraging the use of a comprehensive battery of measures. However, the inconsistency can also be due to data quality and varying data quality across subjects whereas differential susceptibility of the measures towards artifacts and statistical bias could explain the inconsistencies. When reporting our results, we distinguished between those that were significant at the uncorrected and corrected level of significance. Increasing the number of biomarkers of interest decreases statistical power, because of the need to correct for multiple comparisons. However, the tendency of significant correlations was similar for the uncorrected and corrected level. Future studies should aim to select a-priori a shortlist of well-defined biomarkers.

Nevertheless, the strength and innovative character inherent to the analysis in this study is that we used robust nonparametric methods with correction for the multidimensional nature of the statistics, and we performed single-subject analysis. In field studies, such an approach is tremendously important, as over-interpretations of statistical artifacts easily arise.

For the future, we aim to integrate sampling of psychological states into routine monitoring at the EMU. That way, patients with high fluctuations of mood and stress could be selected for a study that correlates the fluctuations of quantitative EEG parameters and subjective psychological states. Furthermore, the occurrence of seizures was rare in this study. Only four patients experienced seizures, such that analysis of potential relationship between psychological states and seizures was not feasible. Future studies should involve a selected sample with seizures and address the question whether the combination of quantitative EEG measures and psychological state dynamics is a valid ground for seizure prediction models.

5. Conclusions

This study supports the feasibility of investigating the correlation between neural states and subjective ratings psychological experience by correlating EEG biomarkers with psychological states in the routine EMU setting. Conclusions are limited because of the pilot nature of this study, but the data encourage further research into the correlation of EEG biomarkers and psychological states of stress and mood. Future studies should aim at recruiting samples that allow to test the covariability of quantitative EEG markers and psychological dynamics more closely by hands of a high within-subject variability and a sample with a higher seizure rate over the sampling period.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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