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Resolving and characterizing the incidence of millihertz EEG modulation in critically ill children

Maren E. Loe [a,b], Sina Khanmohammadi [a], Michael J. Morrissey [c,d], Rebekah Landre [d], Stuart R. Tomko [c], Réjean M. Guerriero [c], ShiNung Ching [a,*]

[a] Department of Electrical and Systems Engineering, Washington University in St. Louis, USA
[b] Medical Scientist Training Program, Washington University School of Medicine, USA
[c] Division of Pediatric Neurology, Department of Neurology, Washington University School of Medicine, USA
[d] St. Louis Children's Hospital, USA

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HIGHLIGHTS

- Millihertz modulation of 5–15 Hz EEG activity was identified by parametric bilevel spectral analysis.
- Strong modulation, quantified by a nonparametric index score, was associated with worse outcomes in a high clinical suspicion cohort.
- Intracranial pressure and heart rate recordings from one patient with strong modulation suggest a potential physiological mechanism for millihertz EEG modulation.

ABSTRACT

Objective: We analyze a slow electrographic pattern, Macroperiodic Oscillations (MOs), in the EEG from a cohort of young critical care patients (n = 43) with continuous EEG monitoring. We construct novel quantitative methods to quantify and understand MOs.
Methods: We applied a nonparametric bilevel spectral analysis to identify MOs, a millihertz (0.004–0.01 Hz) modulation of 5–15 Hz activity in two separate ICU patient cohorts (n = 195 total). We also developed a rigorous measure to quantify MOs strength and spatial expression, which was validated against surrogate noise data.
Results: Strong or spatially widespread MOs appear in both high clinical suspicion and a general ICU population. In the former, patients with strong or spatially widespread MOs tended to have worse clinical outcomes. Intracranial pressure and heart rate data from one patient provide insight into a potential broader physiological mechanism for MOs.
Conclusions: We quantified millihertz EEG modulation (MOs) in cohorts of critically ill pediatric patients. We demonstrated high incidence in two patient populations. In a high suspicion cohort, MOs are associated with poor outcome, suggesting future potential as a diagnostic and prognostic aid.
Significance: These results support the existence of EEG dynamics across disparate time-scales and may provide insight into brain injury physiology in young children.

1. Introduction

Electroencephalography (EEG) is used to characterize neurological events and identify abnormal brain activity in critical care patients with brain injuries and those at risk for recurrent seizures. In these settings, EEG monitoring frequently spans multiple days, generating large volumes of brain electrical activity data (Payne and Hahn, 2014). Clinical EEG analyses typically involve

Abbreviations: 1LS, first-level spectrogram; 2LS, second-level spectrogram; CDSA, color density spectral array; CEEG, continuous EEG; HR, heart rate; ICP, intracranial pressure; ICU, intensive care unit; ISMO, Index for the Strength of Macroperiodic Oscillations; LASSO, least absolute shrinkage and selection operator; mHz, millihertz; MOs, macroperiodic oscillations; PAC, phase-amplitude coupling; PCPC, pediatric cerebral performance category.

* Corresponding author at: 1 Brookings Drive, St. Louis, MO 63130, USA.
E-mail address: shinung@wustl.edu (S. Ching).

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characterizing activity over tens of seconds, often using power spectral density methods. However, increasing evidence suggests that clinically informative EEG dynamics may manifest at much longer, minute- and hour-length time scales (Guerriero et al., 2021; Hashimoto et al., 2020; van Putten et al., 2015; Rodin et al., 2014; Vanhatalo et al., 2004). We recently identified a novel millihertz (mHz) dynamical phenomenon in the time–frequency spectrograms of EEG from pediatric patients in intensive care with EEG monitoring (Guerriero et al., 2021; Mitra and Bokil, 2007). This phenomenon, which we termed Macroperiodic Oscillations (MOs), is characterized by a slow oscillatory amplitude modulation of the power spectrum with periodicity of many minutes. Modulatory interactions in the EEG, including phase-amplitude coupling (PAC), have most often been described at commensurate time-scales (e.g., "alpha-delta" interactions) (Frauscher et al., 2015; Gong et al., 2021; Grigorovsky et al., 2020; Munia and Aviyente, 2019; Yeh and Shi, 2018). Our observed modulatory interaction spans several order of frequency magnitude, presenting a number of challenges in terms of detection and analysis.

The overall goal of the present study is to develop and deploy methods for characterizing the millihertz modulation of MOs, in order to better understand their expression and clinical relevance. To this end, we developed parametric and nonparametric signal processing methods for extracting modulatory EEG dynamics, which we applied to long EEG recordings from critically ill pediatric patients to quantitatively describe MOs. These methods are novel in their approach to identifying and characterizing minutes-long modulation of fast brain electrical activity. We previously described patients with MOs as typically young, previously healthy children with acquired brain injuries (Guerriero et al., 2021). Now, using these computational methods, we demonstrate how MOs manifest in a pediatric intensive care population of patients undergoing clinical EEG monitoring and show that the strength of their expression is correlated with patient outcomes.

2. Methods

2.1. Patient population

We considered two retrospective EEG datasets from patients in intensive care units (ICUs), with the goal of validating our detection methods and further studying the MOs phenomenon.

First, we studied a cohort of pediatric patients, identified in the cardiac, neonatal, and pediatric intensive care units (CICU, NICU, and PICU) at St. Louis Children's Hospital (St. Louis, MO, USA) between September 2016 and May 2019 with 21-channel EEG recorded and clinical suspicion of aberrant brain electrical activity during routine clinical review of raw EEG and color density spectral array (CDSA), as described previously. This cohort included the 38 patients previously identified with MOs during a retrospective observational study (Guerriero et al., 2021). An additional five studies were identified during ongoing clinical review following the same clinical criteria, visually apparent oscillatory pattern in the CDSA on a 12-hour EEG recording, without appreciable changes observed in the 10- to 20-second raw EEG. We refer to this entire cohort as the High Clinical Suspicion (HCS) cohort (n = 43). Clinical data collected included age, sex, reason for admission, indication and duration of EEG, location of monitoring (CICU, NICU, or PICU), pediatric cerebral performance category (PCPC) at discharge, and two measures of seizure load: peak seizure burden, the number of minutes with seizures in the hour recorded with the most seizures (out of 60), and seizure index, the number of hours with at least one seizure (out of 12). Peak seizure burden and seizure index were calculated by board-certified epileptologists (RMG and SRT) or a senior clinical neurophysiologist (MJM).

To assess the incidence of MOs in a standard ICU population and to examine the relationship with outcomes at hospital discharge, we reviewed 200 EEG files, recorded in consecutive patients from 7/28/2020 to 1/1/2021. Inclusion criteria was a 21-channel 200 Hz EEG recorded in an ICU (NICU, CICU, or PICU) at St. Louis Children's Hospital, with at least 12 hours of continuous data. We analyzed the first 12 hours for all patients included. Exclusion criteria were: if the patient was still admitted at the time patient data was analyzed or if the file was one of multiple EEGs for a given patient during the evaluation period. Clinical data collected included age, sex, reason for admission, indication of EEG, location of monitoring, and PCPC at discharge. Based on preliminary negative results from analyses of the HCS cohort and seizure measures (Supplementary Table S1), we did not obtain peak seizure burden and seizure index for these patients. For patients with multiple studies, the first study was selected. There were 152 EEG files analyzed. We refer to this set of EEG recordings from the ICU as the intensive care incidence (ICI) cohort (n = 152).

For both cohorts, PCPC was obtained on retrospective chart review from discharge summaries. All EEG was obtained with a Nihon Kohden platform, which had 21 channels sampled at 200 Hz, in the international 10–20 system of electrode placement. The amplifier was non-DC coupled with 32 channels (Model #JE-921). For one of the patients, physiological monitoring data, including heart rate (HR) and intracranial pressure (ICP), was recorded using BedMaster (Excel Medical, Inc., Jupiter, FL, USA). This study was approved by the Institutional Review Board (IRB) at Washington University in St. Louis.

2.1.1 Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to restrictions concerning the privacy of research participants.

2.2. Analyses

2.2.1 We developed a non-parametric analysis pipeline to characterize MOs. We obtained a multi-taper spectrogram of the bipolar montaged (standard longitudinal bipolar montage LB-18.1 (Acharya et al., 2016)) EEG data (Fig. 1A). We extracted a time-varying power envelope signal for the 5 to 15 Hz band for each channel. To characterize modulatory oscillations, we obtained a spectrogram of this envelope signal over long time windows (40 minute epochs, 30 minute overlap), which we refer to herein as the second level spectrogram (2LS). We summarized this observation in each patient by averaging the 2LS over time and channels between 0.001 Hz and 0.03 Hz (Fig. 1E). We identified differing levels of temporal heterogeneity within individual patients (Supplementary Information S1). We also computed the average 2LS for each of the 152 files analyzed in the ICI cohort; we plotted the 10 highest and lowest index scores (section 2.2.2) within the ICI cohort (Fig. 1F). We did not include duplicate files from the ICI cohort in our analyses (Supplementary Information S2).

2.2.2 We created an Index for the Strength of MOs (ISMO). This index quantifies the extent to which the envelope signal is sinusoidal over long time epochs. Specifically, we used linear regression to estimate the signal as a weighted sum of sinusoids across our frequency range of interest. We imposed sparsity on this sum of sinusoids by using least absolute shrinkage and selection operator (LASSO) optimization for our linear regression. A strongly sinusoidal envelope signal would be well-approximated by a weighted sum with one or two dominant components. The proposed method is a form of basis pursuit denoising (Charles et al., 2016) applied to the EEG amplitude envelope. This method provides a parametric estimate of power spectral density restricted to a discrete number of very slow frequencies of interest, determined *a priori* and is comparable to a wavelet analysis. To quantify

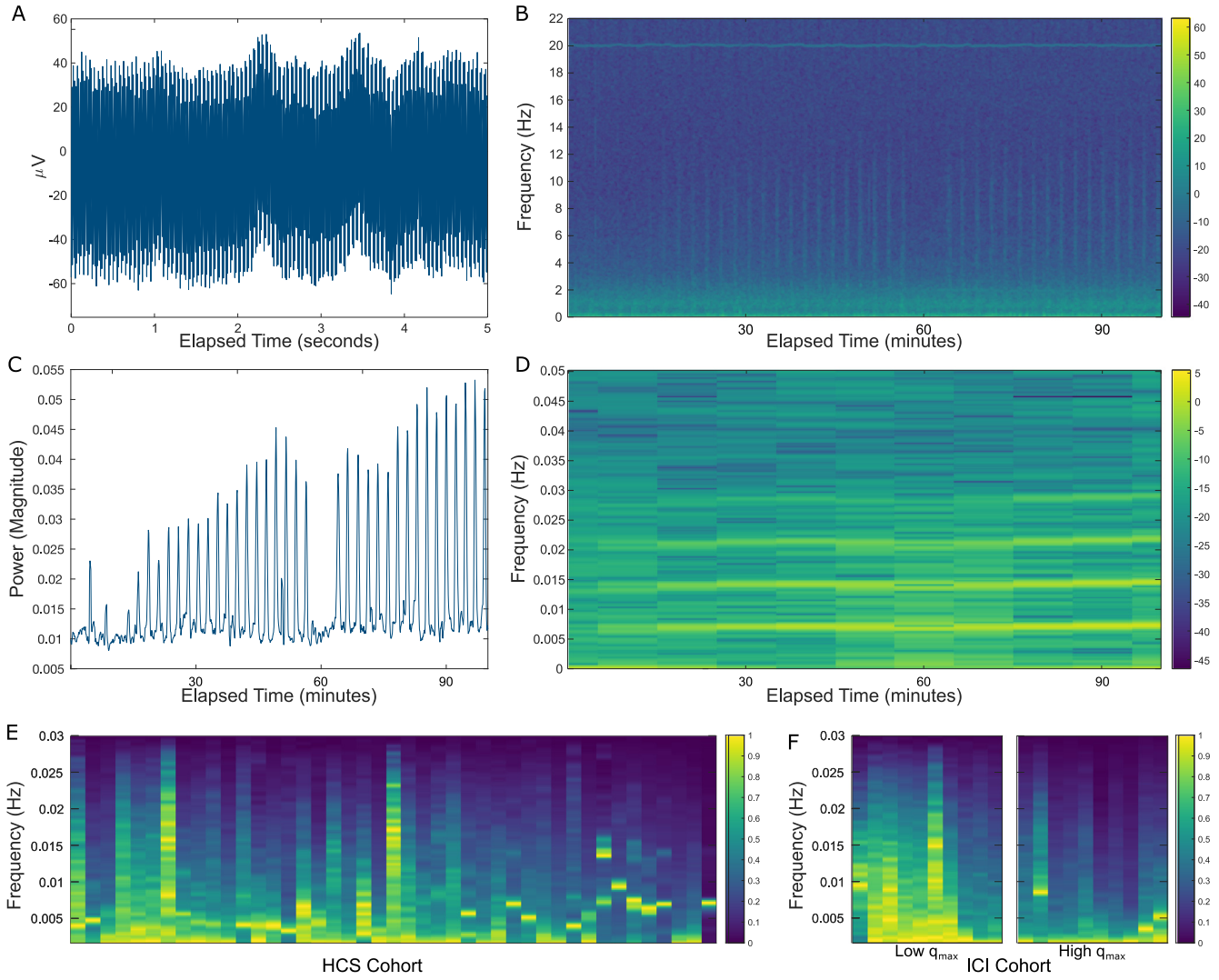

Fig. 1. Non-parametric analysis of EEG reveals narrowband phenomena on nested spectral analysis. A) 5 seconds of raw EEG (200 Hz) from one bipolar montaged channel, T7-P7. B) 100 minutes of multi-taper spectrogram, termed first level spectrogram (1LS), from the same channel in the same patient; waxing and waning in the power spectra was evident with a periodicity of ~ 2.5 minutes. C) The envelope signal of the 1LS from the same time period depicted in (B) was extracted via the Hilbert transform for power magnitude across the 5–15 Hz frequency band. The oscillations in the power spectrum are evident here as periodic oscillations in the power. D) The second level spectrogram (2LS) was calculated from the envelope signal, identifying high power, narrowband activity at the frequency of oscillations in the 1LS and envelope signal. In this example, the dominant frequency of the Macroperiodic Oscillations (MOs) was approximately 0.007 Hz. E) Summary spectra were generated for each patient in the High Clinical Suspicion (HCS) cohort by averaging the 2LS across time and channels. These spectra were then normalized and plotted according to their Index for Strength of MOs (ISMO) score, with the highest q_{max} on the right. MOs are clearly identifiable as narrow bands of high power between 0.003 Hz and 0.011 Hz. F) Summary spectra were generated as in E for the patients in the Intensive Care Incidence (ICI) cohort with the 10 lowest and 10 highest q_{max}. In some high q_{max} patients, similar narrowband activity was visually apparent, suggesting the presence of MOs.

the fit, we calculated Pearson's correlation, $J \in [0, 1]$ between the original and reconstructed envelope signals. To quantify the sparseness of the approximation, we calculated the entropy of the frequency distribution, $H = -\sum_i P(x_i) \log(P(x_i)) \in [0, 1]$. Strong MOs are characterized by high correlation ($J = 1$) and low entropy ($H = 0$); thus our index was calculated as $q = J(1 - H)$. The index value, q, was calculated channel-wise with a sliding window approach, generating an array of $q \in Q^{M \times T}$ for M channels and T time windows, for each patient. The strength of MOs, q_{max}, was defined as the channel-wise maximum of the average of the 90 minutes with the highest q values; we refer to that time window of interest as t_q. To evaluate the efficacy of q_{max} to identify strong MOs, we generated surrogate noise data by creating pairwise (for each patient and channel) time series with the same spectral content as the bipolar montaged EEG data for both HCS and ICI cohorts. We applied the same analysis pipeline to these noise data. The noise surrogate EEG was the same duration as the original data (12 hours for most patients); thus, for each patient we obtained a matrix Q of the same size and calculated the surrogate q_{max} as before.

To quantify the spatial distribution of MOs, we defined q_{sp} as the percent of channels in which the channel-wise mean of $q \in Q$ during t_q is within one standard deviation of q_{max}; thus, we have a measure of spatial modulation $q_{sp} \in (0, 1]$ for each patient. We calculated surrogate q_{sp} values from the surrogate Q matrix and evaluated the significance of q_{sp} by comparison with surrogate data (Supplementary Information S3).

To assess the clinical utility of ISMO, we evaluated the relationship between q_{max} and PCPC. PCPC is a numerical outcomes categorization, in which patients are scored at hospital discharge on a scale from 1 (normal) to 6 (death); we binarized PCPC to "good outcome" (PCPC $\leq$ 3: normal, or mild to moderate

disability), and "poor outcome" (PCPC $\geq$ 4: severe disability, coma, or death) (Fiser, 1992). To evaluate the validity of q_{max}, we obtained the pairwise difference between patient q_{max} and their respective surrogate q_{max}, and we performed two-sample t-tests for significant differences with 95% confidence level. The same comparisons between patient and surrogate data were calculated for q_{sp} (Supplementary Information S3).

We also assessed whether there was a relationship between q_{max} and measures of seizure load and age, for the HCS cohort. We calculated the correlation between q_{max} and age, seizure index, and peak seizure burden.

2.2.3 For the patient with ICP and HR data, we identified two distinct, uninterrupted periods of time: MOs "on" and MOs "off." These epochs were established by identifying narrowband activity within the 2LS from each of the 18 channels and verified by q_{max} values during these epochs. HR, ICP, EEG envelope, and raw EEG were obtained for both epochs; multi-taper spectra were calculated with 7 tapers, yielding eight total spectra with 95% confidence intervals. For the raw EEG, we analyzed the channel from which q_{max} was identified (i.e. the channel-wise maximum of q during t_q).

3. Results

Patient demographics are summarized in Table 1. The 43 HCS patients were 0–15.83 years old; 79% were less than 1 year old (n = 34). 47% were female (n = 20). 40% of the patients (n = 17) had poor outcomes, indicated by PCPC of 4 or greater.

In the set of 200 EEG studies identified in the ICI cohort, there were 168 unique patients; 33 files were duplicates from 19 patients. An additional 15 files were excluded because those patients were not yet discharged from the hospital. Of the remaining 152 files, 55% were less than 1 year old (n = 84); 36% were female, and 26% had PCPC of 4 or greater.

Table 1
Characteristics of patients and normal controls.

	HCS cohort (n = 43)	ICI cohort (n = 152)
Age in years (st. dev.)	1.2 (3.0)	4.1 (7.6)
number below 1 year old (%)	34 (79%)	84 (55%)
Sex (% female)	46.5%	36%
Hospital location, number in each		
NICU	15	54
CICU	9	23
PICU	19	75
Indication for EEG		
Seizure	19	48
TBI	5	5
Neonatal Encephalopathy	3	26
Cardiac Arrest / ECMO	9	34
Altered Mental State	8	6
Characterization of Events / Other	4	43
Peak Seizure Burden in minutes out of 60	24.3 (16.1)	Not obtained
Seizure Index, hours out of 12 (st. dev.)	6.7 (3.1)	Not obtained
Pediatric Cerebral Performance Category (PCPC)		
% PCPC $\geq$ 4	39.5%	26%
PCPC mean (st. dev.)	3.3 (1.8)	2.6 (1.8)
q_{max}, mean (st. dev.)	0.55 (0.12)	0.46 (0.06)
q_{sp}, mean (st. dev.)	0.25 (0.22)	0.29 (0.21)
Surrogate q_{max}, mean (st. dev.)	0.36 (0.06)	0.35 (0.03)
Surrogate , mean (st. dev.)	0.06 (0.01)	0.06 (0.01)

Intensive care unit (ICU) patients with suspicion (HCS cohort) for aberrant EEG were very young, with poorer clinical outcomes and high seizure burden and index. HCS: High Clinical Suspicion; ICI: Intensive Care Incidence; NICU: neonatal intensive care unit; CICU: cardiac intensive care unit; PICU: pediatric intensive care unit; ECMO: extracorporeal membrane oxygenation

3.1. Systematic millihertz EEG modulation is found in ICU patients

In patients with suspected MOs, waxing and waning in the power spectrum was observed on a 1–5 minute timescale (Fig. 1B). We applied our analysis pipeline to all patients. For certain HCS patients, oscillations in the power spectrum were visually apparent (Fig. 1B), manifesting as narrowband oscillatory signatures in the envelope signal (Fig. 1C) appreciable in the 2LS (Fig. 1D). To summarize the 2LS, the spectrum was averaged over time and channels and normalized for comparison. In the HCS cohort, patients are ordered by lowest to highest q_{max} (Fig. 1E). The spectra from the 10 lowest and 10 highest q_{max} scores from the ICI cohort are also displayed (Fig. 1F). Some patients' 2LS revealed a well-defined peak in the 3–12 mHz range (i.e., MOs), as clearly seen across the HCS cohort and in the higher q_{max} subset of the ICI cohort. This analysis demonstrates a heterogenous manifestation of MOs in the ICU population, over a range of millihertz frequencies which can drift across time within subjects (Supplementary Information S1, Supplementary Figure S1).

3.2. Strong spatiotemporal manifestation of MOs is associated with poor outcomes in HCS patients

To resolve this heterogeneity, we applied our ISMO method. Fig. 2A-C depict the procedure: the envelope signal was filtered and then estimated by a sparse sum of sinusoids; q was calculated for each time window in each channel, generating a time $\times$ channel Q matrix (Fig. 2D-F). The strength and spatial similarity (q_{max} and q_{sp}, respectively) of Q were plotted against each other (Fig. 2G). For the HCS cohort, q_{max} ranged from 0.40 to 0.98; q_{sp} ranged from 0.06 to 0.89. For the patients depicted in Fig. 2 D, E, and F, their ISMO values (q_{max}, q_{sp}) were (0.98, 0.78), (0.67, 0.06), and (0.42, 0.22); these values correspond to strong widespread MOs, strong focal MOs, and weak or no appreciable MOs, respectively.

We also plotted the mean q_{max} and q_{sp} for the surrogate data (0.36, 0.06) and the HCS cohort with poor outcomes (0.62, 0.30), with the 99% confidence interval for each shaded in gray. The q values for the surrogate data were significantly lower ($p < 10^{-4}$) for all populations, supporting the validity of ISMO as a method for evaluating slow modulation in the spectral domain.

The pairwise difference between patient and surrogate noise q_{max} was significantly higher for patients with poor outcomes (0.27 vs. 0.13, $p < 10^{-3}$) within the HCS cohort; the difference was not statistically significant for the ICI cohort (0.11 vs 0.12) (Fig. 2H). Patients with poor outcomes in the HCS cohort had significantly higher q_{max} values than those with good outcomes (0.62 vs. 0.50, p = 0.001); there was no significant difference in q_{max} by outcome in the ICI cohort (Fig. 2I) (see also Discussion 4.3).

Our initial description of MOs identified the phenomenon exclusively in patients with seizures (Guerriero et al., 2021), so we assessed whether q_{max} was correlated with seizure index, peak seizure burden, or age in the HCS cohort. None of the relationships were statistically significant (p > 0.05) (Supplementary Table S1). The lack of statistical relationship between q_{max} and seizure index or peak seizure burden is likely skewed by one important outlier: the patient with the strongest MOs expression (q_{max} = 0.98, Fig. 2A, 2D, Supplementary Figure S1A, S1D) had no seizures. This was the only patient in the HCS cohort without seizures. If this patient is excluded from the analysis, there is a significant correlation (r = 0.42, p < 0.01) between q_{max} and peak seizure burden, suggesting a potential weak relationship between MOs strength (q_{max}) and peak seizure burden (number of minutes with seizures in the

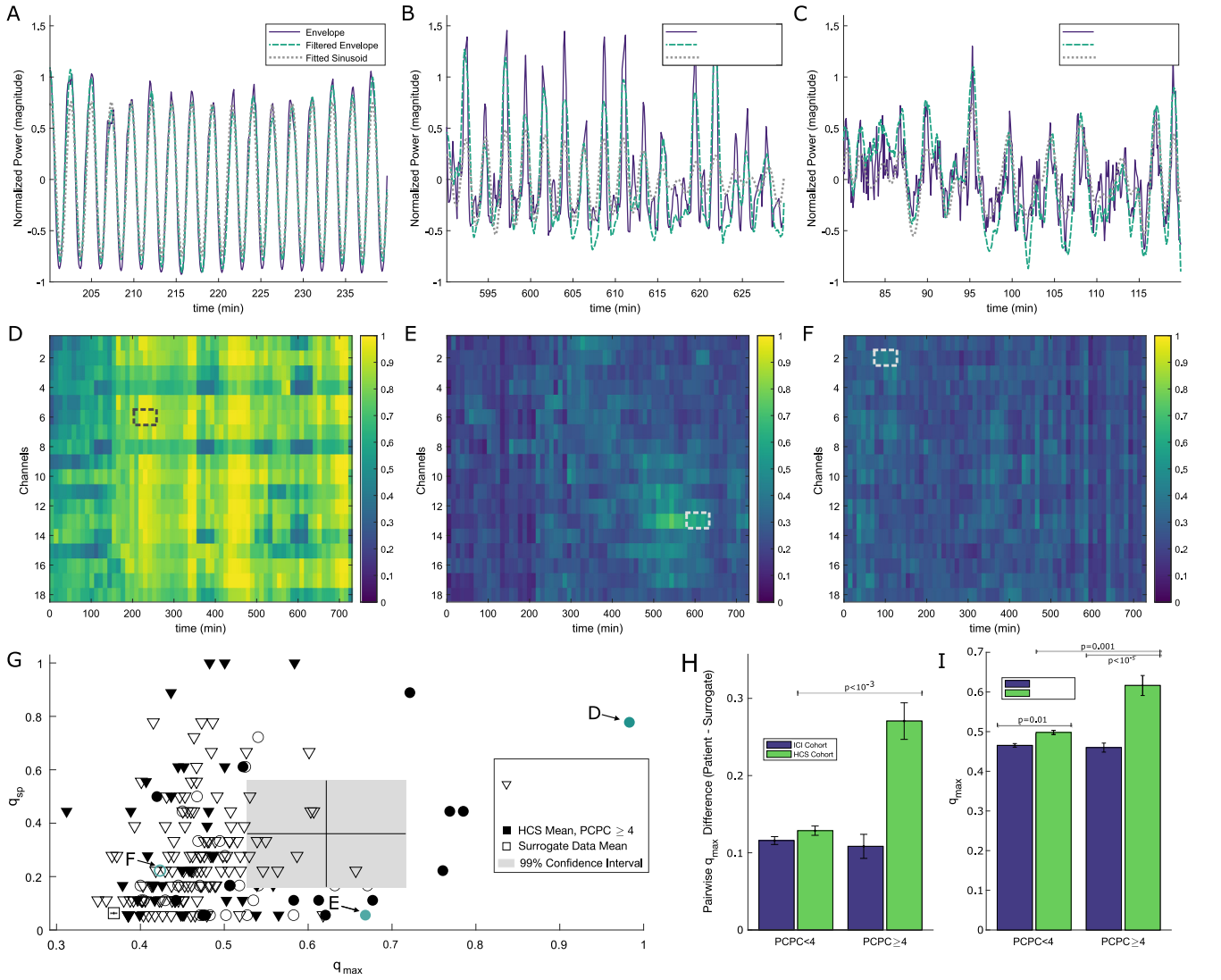

Fig. 2. Index for Strength of Macroperiodic Oscillations (ISMO) quantifies the strength and spatial homogeneity of Macroperiodic Oscillations (MOs). A, B, C) Three examples of an envelope signal (calculated as in Fig. 1C), overlaid with the filtered signal and the sparse sum of sinusoids that was fitted to the filtered signal during that time window. D, E, F) Heatmaps of the ISMO value, q, depicted over 12 hours for all 18 channels. The inlaid boxes identify the channel and time depicted in A, B, and C, respectively. G) A summary of MOs manifestation in patients across both cohorts. MOs strength is summarized by q_{max}, which was calculated by averaging q from the highest 90 minutes in each channel and selecting the channel-wise maximum. Spatial homogeneity was quantified by calculating q_{sp}, the percent of channels within 1 standard deviation of the channel from which q_{max} was selected. Clinical outcomes were binarized by pediatric cerebral performance category (PCPC) ≤ 3 (good outcomes) in open circles and PCPC ≥ 4 (poor outcomes) in closed circles. Higher q_{max} were associated with poor outcomes in the HCS cohort. H) Surrogate noise data was generated channel-wise for each patient, and q_{max} was calculated for each set of surrogate data as before. The pairwise difference between patient and surrogate q_{max} is depicted for each outcome group, with error bars for standard error ($p < 10^{-3}$). I) The average q_{max} for patients by outcome in each cohort is depicted, with error bars for standard error. For the High Clinical Suspicion (HCS) cohort, q_{max} was significantly higher for patients with poor outcomes (PCPC ≥ 4) ($p = 0.001$). There was no significant difference between outcome groups for the Intensive Care Incidence (ICI) cohort. The q_{max} was significantly lower in the ICI cohort than in the HCS cohort for both the good and poor outcome groups ($p = 0.01$ and $p < 10^{-6}$, respectively).

hour recorded with the most seizures), in patients with seizures (see also Discussion 4.4).

3.3. Mos are present in broader clinical populations

The ISMO facilitates objective comparison of MO temporal and spatial expression between patients, which we then applied to a set of ICU patients (ICI cohort), to assess manifestation of MOs in a heterogenous critical care population. For the ICI cohort, the indices ranged from 0.31 to 0.66, and 0.06 to 1, respectively. Patients with high values for q_{max} or q_{sp} had strong and widespread MOs. There are 22 patients from the ICI cohort whose q_{max} is above the lower bound ($q_{max} > 0.521$) of the 99% confidence interval for mean q_{max} from the HCS cohort with PCPC of 4 or greater. This strongly supports the existence of MOs within the general ICU population, which was qualitatively observed in the 2LS (Fig. 1F).

3.4. Mos may reflect coupled cyclic physiological mechanisms

One patient with strong MOs had ICP and HR data recorded simultaneously with EEG. For this patient, we identified uninterrupted epochs of 623 minutes with MOs present (“on”) and 972 minutes with no MOs (“off”). The ISMO value for the “on” epoch wasq_{max} = 0.75 and for the “off” epoch was q_{max} = 0.43 (Supplementary Figure S2). Spectral analysis with 95% confidence intervals identified significant differences between MOs off and MOs on epochs for ICP, HR, and 2LS between 6–8 mHz (Fig. 3A). This suggests that MOs (narrowband activity on 2LS), may be coupled with

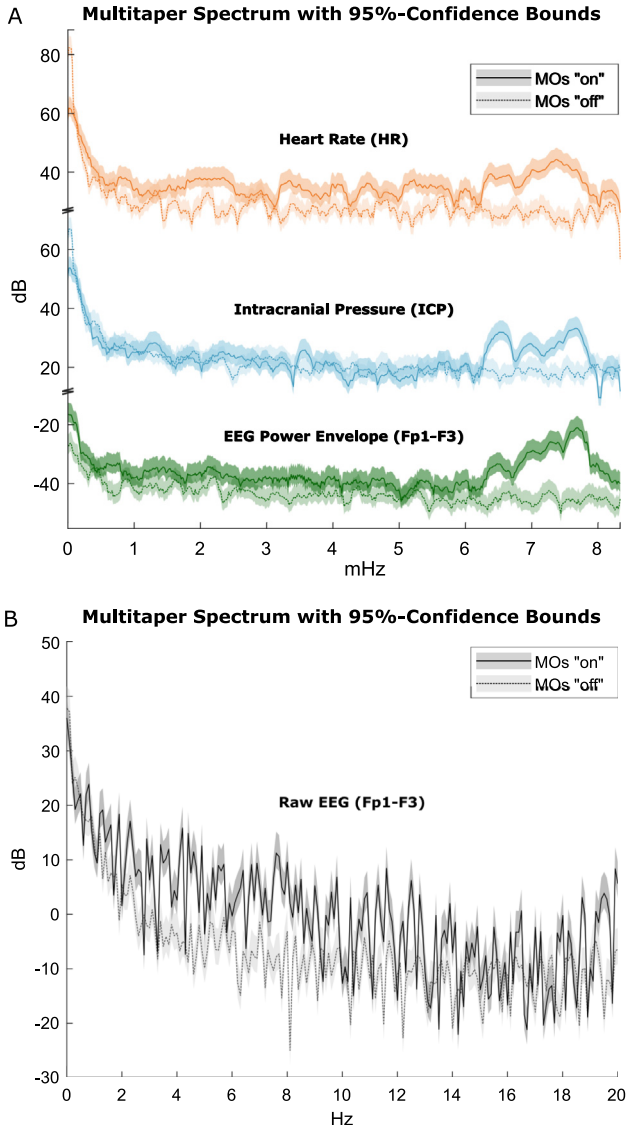

Fig. 3. Physiological correlates of Macroperiodic Oscillations (MOs) were identified in one patient with simultaneous monitoring. A) In the only patient with simultaneous intracranial pressure (ICP), heart rate (HR), and EEG recording, we first identified a MOs "on" epoch of 623 consecutive minutes and a MOs "off" epoch of 972 consecutive minutes. We calculated the multi-taper spectra with 95% confidence intervals for each epoch, for all three signals, and found a significant difference between the epochs for each signal at 6–8 mHz. B) The multi-taper spectra of the raw EEG during the same epochs as (A) depicted slightly higher power in the MOs "on" epoch at 3–12 Hz.

variation in HR and oscillations of ICP. Spectra of the raw EEG from the same channel revealed only slightly higher power in the theta and alpha bands during MOs "on" (Fig. 3B), further supporting the claim that spectral analysis alone is inadequate to identify MOs.

4. Discussion

4.1. Identifying EEG modulation across several orders of magnitude

We identified a novel phenomenon in the EEG of critically ill children, which we termed MOs. This phenomenon is primarily characterized by slow waxing and waning modulation of 5–15 Hz EEG power. We generated an index, ISMO, to quantify the strength of this modulation, and demonstrated its validity by the statistically significant difference between surrogate noise data and EEG with the same spectral content. Our approach successfully identified modulation in brain electrical activity on a much slower, millihertz scale than conventional spectral analyses. Across a pediatric population of ICU patients (HCS cohort), MOs were characterized by a well-defined peak in the 2LS, a power spectral analysis on the 5–15 Hz power envelope signal. While such a slow phenomenon may initially seem like artifact or noise, the physiological nature of MOs is supported by their temporal heterogeneity (both within and across patients), range of frequencies at which MOs manifested, the ISMO values, and the nature of recording EEG from multiple ICUs.

4.2. A potential biomarker for acquired injury and outcomes in young children

When the ISMO indicated strong or spatially widespread MOs, patients in the HCS cohort tended to have worse outcomes, suggesting potential value as a marker for poor prognosis. Some patients within the ICI cohort had q_{max} scores comparable to patients with MOs in the HCS cohort, with visually appreciable MOs on summary 2LS (Fig. 1F): 14% had q_{max} scores above the lower bound of the 99% confidence interval of the HCS cohort with poor outcomes (Results 3.2). However, higher q_{max} scores were not associated with poor outcomes in the ICI cohort. This discrepancy between the ICI and HCS cohorts may be due to the initial screening for clinical suspicion. It is possible that some patients with poor outcomes in the ICI cohort would not be at risk for aberrant brain activity like MOs, and by including these patients to gain perspective on MOs incidence, we diluted the strength of this quantification. We also note that the overall strength of MOs was larger in the HCS cohort relative to the ICI cohort and it may be that more ambiguity with outcomes occurs in these mid-range q_{max} values. The overall relationship between MOs and outcomes may be a pediatric variation on infraslow oscillations and slow electrophysiological depolarizations, which have been associated with poor outcomes in adult post-anoxic coma patients (Dreier et al., 2017; Lauritzen et al., 2011; van Putten et al., 2015).

Our data suggests that intracranial pressure and heart rate variability may be integral to understanding the physiological mechanisms underlying MOs. In this case, the slow modulation in the 5–15 Hz power envelope signal was observed at the same frequency as the oscillations in heart rate and intracranial pressure. Aberrant oscillations in intracranial pressure and heart rate occurring at the same frequency as MOs, potentially due to impaired hemodynamic autoregulation, would suggest severe injury and thus may be important for understanding brain injury prognosis and outcomes (Czosnyka and Pickard, 2004; Steiner and Andrews, 2006). This observation needs to be validated in larger cohorts. Further research into the mechanism of MOs may identify differential response to various treatments, which could be clinically beneficial in the ICU population.

In particular, it is as yet unclear whether this overall phenomenology is unique to young children. One previous study of a small number of adult brain injury patients demonstrated concomitant oscillations in ICP, mean arterial pressure, mean flow velocity in the right cerebral artery, and one measure of EEG power (Lescot et al., 2005). Other statistical analyses of the relationship between ICP and EEG phenomena do not fully encapsulate spatial and temporal variability, which dilutes the explanatory power of these relationships and have limited insights into physiological processes (Amantini et al., 2009; Sanz-García et al., 2018). The brain is not a closed system, thus it is possible that aberrant fluctuations in heart rate, cerebrovascular autoregulation, and ICP, like Lundberg B waves, have a dampening effect on brain electrical power, causing fluctuations in total power (Nag et al., 2019). Clarifying the mechanisms of MOs through further experiments and

modeling studies may also reveal pharmacological interventions to halt MOs, which may have key ramifications if MOs are indeed causal to adverse outcomes.

4.3. Relationship of MOs to related clinical phenomena

The relationship between MOs and seizures is also unclear. We believe that MOs are a marker of acquired injury, potentially related to edema and hemodynamics; like seizures and *status epilepticus*, MOs may manifest after severe injuries and be correlated with worse clinical outcomes (Chin et al., 2006; Ferro et al., 2014; Payne et al., 2014; Raspall-Chaure et al., 2006; Topjian et al., 2013). Among 22 patients in the ICI cohort with strong MOs (q_{max} scores above the lower bound of the 99% confidence interval of the HCS cohort with poor outcomes), 13 received EEG monitoring for seizures or *status epilepticus*, which is consistent with our initial description of MOs in young children with seizures (Guerriero et al., 2021).

However, seizures alone cannot mechanistically explain the phenomenon we described, particularly in relation to the aberrant hemodynamic oscillations. Of note, far fewer of these 22 ICI patients had poor outcomes (only 6 out of 22 with PCPC $\geq$ 4), than the HCS patients with similar ISMO values. These results from our ICI cohort support the importance of further study, as there was no clear relationship between ISMO values and clinical outcomes as measured by PCPC.

4.4. Methodological considerations and relationship to related analyses

We emphasize that MOs appears to be a genuine physiological phenomenon and not the product of electronic noise or other forms of artifact. There is substantial individual variation in the MOs spatiotemporal expression, which would not be expected in the latter case. Furthermore, the MOs frequency was observed in multi-modal recordings, involving several isolated hardware platforms.

It is tempting to ask whether MOs are equivalent to prior descriptions of EEG phase amplitude coupling. PAC is a general descriptor of a dynamical interaction in the EEG, wherein oscillatory power at a fast frequency is gated or modulated at a specific phase of a slower frequency (e.g., in a nested type interaction) (Bragin et al., 1995; Canolty et al., 2006; Mukamel et al., 2014; Shibata and Otsubo, 2020; Vanhatalo et al., 2004). Under this general descriptor, MOs might be considered a type of PAC. However, PAC is not a monolithic phenomenon and the specific frequencies involved may implicate very different underlying mechanisms, let alone functional salience (An et al., 2021; Canolty and Knight, 2010; Osipova et al., 2008; Tort et al., 2010, 2008; Te Woerd et al., 2015). In our present work, the vastly disparate time-scales of modulation in MOs necessitated novel analytic methods to overcome limitations of traditional analyses. Indeed, millihertz modulation of EEG is, to the best of our knowledge, a novel finding in PAC, as well as in EEG dynamics in general. This vast separation in time-scales required methodological innovation to reliably extract and characterize the millihertz MOs embedding signal, which was achieved by both our non-parametric bilevel spectral approach and our parametric ISMO.

4.5. Limitations

This was a retrospective analysis of ICU patients which aimed to characterize a novel phenomenon, thus it is limited in a several aspects. Most directly, there is currently no gold standard or "threshold" for identifying MOs; the ISMO characterizes MOs, but we refrained from identifying a hard cutoff for whether or not MOs are present in an EEG signal, opting rather for a graded quantification. Unfortunately, only one of the 43 HCS patients had ICP monitoring data available retrospectively, necessitating prospective data collection in the future. Finally, PCPC is a crude measure of outcomes and does not differentiate the relative contribution of seizures, MOs, or underlying brain injury on outcome.

4.6. Conclusion

In summary, we formally characterized MOs, a novel phenomenon in the EEG of critically ill pediatric patients and showed it to be associated with worse outcomes. We developed methods to identify and quantify MOs, which may have utility in future analyses of other EEG and biophysical data. Our findings from retrospective analyses suggest that MOs have strong potential for assisting prognostic and treatment decisions following future study.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2022.02.010.

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