Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Quantitative EEG markers to prognosticate critically ill patients with COVID-19: A retrospective cohort study

There is an unmet need for biomarkers to monitor therapy responses and prognosticate neurological recovery in comatose patients with coronavirus disease 2019 (COVID-19). Acute encephalopathy is increasingly recognized in critically ill mechanically ventilated patients with COVID-19 (Helms et al., 2020). As brain injury is often the principal determinant of functional outcomes in critically ill patients (Tasker and Menon, 2016), we sought to assess if cortical electrophysiological markers can prognosticate neurological recovery. Continuous electroencephalography (cEEG) allows noninvasive monitoring of neural activity over time that can permit prognostication in real-time at the bedside. In this single-center, retrospective cohort study, we tested the hypothesis that quantitative EEG (QEEG) features extracted from cEEG can predict neurological outcome in critically ill patients with COVID-19 after sedation is withdrawn.

Ten consecutive patients (mean age 61.3 years, Table 1) met the inclusion criteria- a) mechanically ventilated and defined critically ill as in (Shen et al., 2020); b) polymerase chain reaction confirmed COVID-19; c) had cEEG monitoring (21 channels sampled at 250 Hz) over 48 hours, and d) had a definitive outcome at discharge as determined using Cerebral Performance Category Scale (CPC). Outcomes were grouped into good (CPC < 2) and poor (CPC 3–5). Multiple epochs of EEG collected over 37 patient-days were labeled for analysis as- a) EEG reactivity- 40 seconds epoch following voice and noxious-sensory stimuli; and b) baseline-epochs prior to reactivity. As part of the approved institutional protocol, EEG reactivity is tested after sedative and paralytic medications are withheld for clinical examination. The sound stimuli included calling out the patients' names and clapping. Tactile and noxious stimuli included sternal rub, trapezius pressure, and nose stimulation with a swab. The epileptologists reported EEG reactivity as "present" or "absent" or "indeterminate". If a change in the EEG frequency or amplitude was present post stimuli, the epileptologists reported as positive EEG reactivity. In the study, we have only used quantitative metrics.

The QEEG parameters included were spectral power changes and temporal-variance in different bandwidths (delta, theta, alpha, spindle, and beta) at baseline and during EEG-reactivity. Multichannel time-frequency decomposition was performed using multitaper spectral analysis (1–30 Hz in 2 s windows with 25% overlap, 3 time-half bandwidth product, and 5 tapers) in artifact-free, preprocessed EEG (Babadi and Brown, 2014). The average of the baseline segments was used to z-score normalization on all clear segments. The normalized spectrograms were averaged in delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), spindle (12–16 Hz), beta (16–25 Hz) frequency bands. Three channels of the bipolar montage were used for the analyses: P3-O1, Fz-Cz, P4-O2. Visual inspection was performed to select artifact-free epochs from all baseline and EEG reactivity recordings (mean length: 85.85 s, range: 40–120 s, s.d. 28.98 s). The frequency-specific differences in spectral power between patients with good and poor outcomes were estimated using multiple independent t-tests with false discovery rate (FDR) correction to accommodate for multiple comparisons. The institutional review board approved this study.

Spectral power in the delta-theta bands was significantly higher (P_{FDR} < 0.005, t's > 2.93, effect-sizes > 0.33) in the good outcome group (N = 5) for all channels, both at baseline and during EEG reactivity. Patients with good outcome had higher temporal-variance with greater diversity in frequency bands and spatial extents (Levene's F > 6.32, P_{FDR} < 0.005) (Fig. 1A). Of the QEEG parameters, an increase in both the theta power and it's temporal-variance during EEG reactivity was associated with the highest odds of predicting a good outcome (P_{FDR} < 0.005, odds ratio > 2.39) (Fig. 1C). Spectral-heat maps comparing 2 patients with good and poor outcome, respectively, depict higher EEG activity in theta-alpha range in the patient with a good outcome compared to the patient with poor outcome, in particular in the EEG-reactivity condition (Fig. 1B).

In summary, we confirm that QEEG features at baseline and reactivity can prognosticate neurological recovery in critically ill patients with COVID-19. QEEG parameters, including EEG reactivity, has been shown to prognosticate neurological outcome in patients with hypoxic-ischemic encephalopathy (Amorim et al., 2019). The ubiquity of cEEG monitoring allows rapid translation in the clinical practice to facilitate decision-making to mobilize or withhold limited resources, guide patient selection, and plan-

Table 1
Demographic details of the studied COVID-19 patients.

	Good outcome (N = 5)	Poor outcome (N = 5)
Age (years)	Mean: 56.2 Range 48–68	Mean: 66.4 Range 47–85
Sex (Male: Female)	2:3	3:2
Ethnicity	African American = 4	African American = 4
BMI[$] at admission	31.1	33.65
Dialysis	N = 1	N = 2
cEEG[#] monitoring	Total: 12 days Mean: 2.4 days	Total: 25 days Mean: 5 days
Survival	All 5 survived	Only one survived

$ – BMI: Body Mass Index; # – cEEG – continuous electroencephalography.

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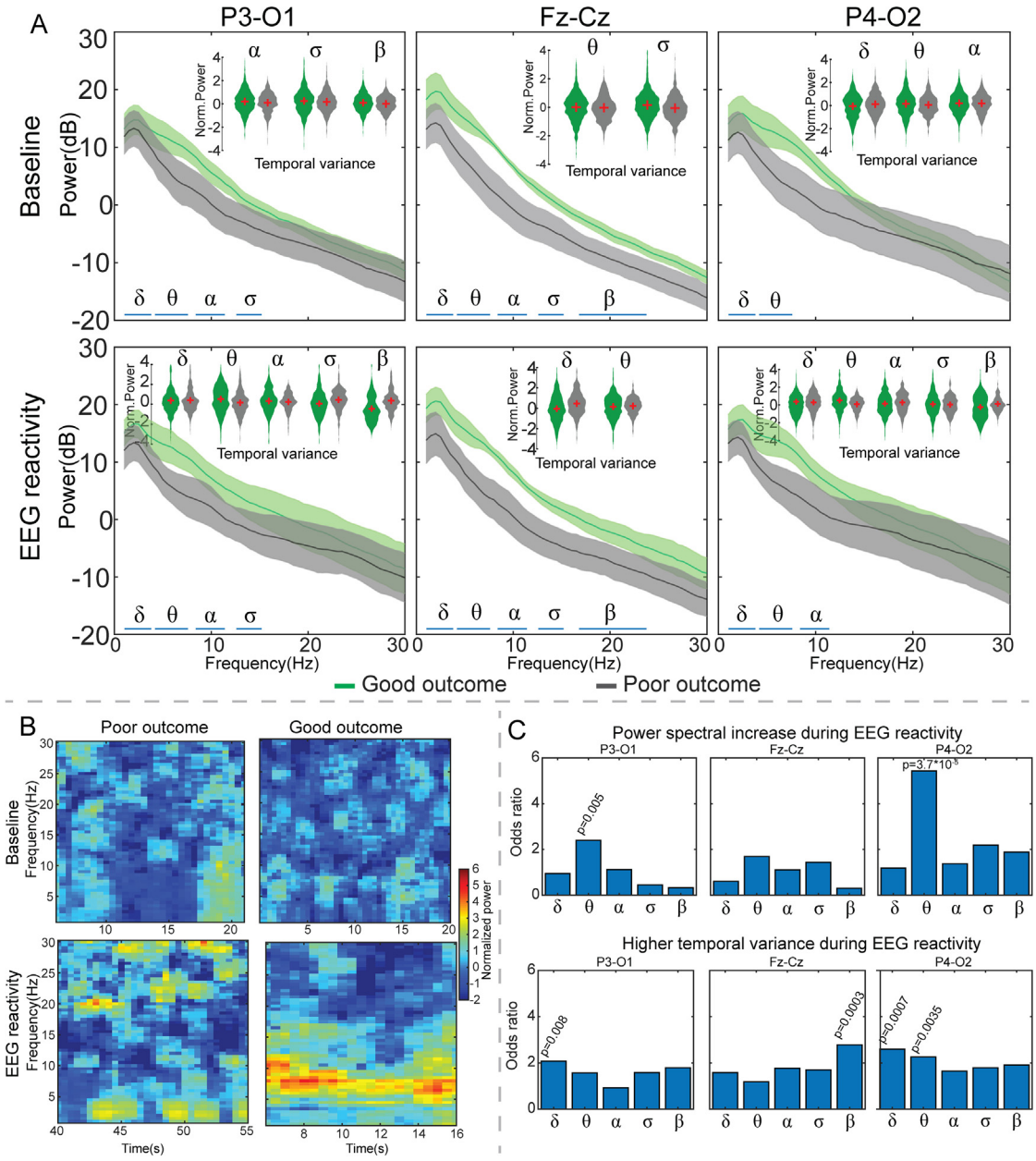

Fig. 1. Quantitative EEG (QEEG) assessment of neurological recovery in continuous EEG (cEEG) monitoring: (A) Average multitaper spectral power of baseline and EEG reactivity epochs. Frequency bands in which there was a significant difference between patients with good (green) and poor (grey) outcome are enumerated as Greek letters on the frequency axis (X-axis) [Delta-δ, Theta-θ, Alpha-α, Spindle-σ, Beta-β]. Violin Plots in insets depict the frequency bands, which showed greater temporal-variance of EEG activity in good outcome patients compared to poor outcomes. (B) Example of the typical time-frequency differences between a patient with good and another with poor outcome at baseline (upper row) and EEG reactivity (bottom row). (C) Upper row shows that patients who demonstrated increased theta power during EEG-reactivity had higher odds of being associated with a good outcome. Lower row shows that patients who show higher temporal-variance in theta-delta activity (and in beta activity over midline leads) had higher odds of being associated with a good outcome. Electrodes are parietal (left P3, right P4), occipital (left O1, right O2) and midline frontal (Fz) and central (Cz). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

ning adaptive clinical trials. More data in larger prospectively studied cohorts are needed to corroborate our findings.

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.

References

Amorim E, van der Stoel M, Nagaraj SB, Ghassemi MM, Jing J, O'Reilly UM, et al. Quantitative EEG reactivity and machine learning for prognostication in hypoxic-ischemic brain injury. Clin Neurophysiol 2019;130:1908–16.

Babadi B, Brown EN. A review of multitaper spectral analysis. IEEE Trans Biomed Eng 2014;61:1555–64.

Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, et al. Neurologic features in severe SARS-CoV-2 Infection. N Engl J Med 2020. https://doi.org/10.1056/NEJMc2008597. Apr 15;NEJMc2008597.

Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, et al. Treatment of 5 critically Ill patients with COVID-19 with convalescent plasma. JAMA 2020;323:1582–9.
Tasker RC, Menon DK. Critical care and the brain. JAMA 2016;315:749–50.

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