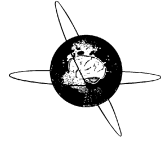




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Frontotemporal EEG to guide sedation in COVID-19 related acute respiratory distress syndrome



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ARTICLE INFO

Article history:

Accepted 6 January 2021

Available online 20 January 2021

Keywords:

Novel coronavirus

EEG

Severe acute respiratory distress syndrome

Limited electroencephalography

Consciousness

HIGHLIGHTS

- Novel coronavirus disease 2019 (COVID-19) complicates sedation guidance.
- Limited frontotemporal encephalogram (EEG) guided sedation in COVID-19 patients.
- A quantitative EEG machine learning algorithm classified patients' sedation depth.

ABSTRACT

Objective: To study if limited frontotemporal electroencephalogram (EEG) can guide sedation changes in highly infectious novel coronavirus disease 2019 (COVID-19) patients receiving neuromuscular blocking agent.

Methods: 98 days of continuous frontotemporal EEG from 11 consecutive patients was evaluated daily by an epileptologist to recommend reduction or maintenance of the sedative level. We evaluated the need to increase sedation in the 6 h following this recommendation. Post-hoc analysis of the quantitative EEG was correlated with the level of sedation using a machine learning algorithm.

Results: Eleven patients were studied for a total of ninety-eight sedation days. EEG was consistent with excessive sedation on 57 (58%) and adequate sedation on 41 days (42%). Recommendations were followed by the team on 59% (N = 58; 19 to reduce and 39 to keep the sedation level). In the 6 h following reduction in sedation, increases of sedation were needed in 7 (12%). Automatized classification of EEG sedation levels reached 80% ($\pm 17\%$) accuracy.

Conclusions: Visual inspection of a limited EEG helped sedation depth guidance. In a secondary analysis, our data supported that this determination may be automatized using quantitative EEG analysis.

Significance: Our results support the use of frontotemporal EEG for guiding sedation in patients with COVID-19.

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Abbreviations: qEEG, quantitative EEG; ARDS, acute respiratory distress syndrome; ICU, intensive care unit; IQR, interquartile range; RASS, Richmond Agitation-Sedation; GCS, Glasgow Coma Scale; CAM-ICU, Confusion Assessment Method for the ICU.

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<https://doi.org/10.1016/j.clinph.2021.01.003>

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1. Introduction

Every fifth patient that is hospitalized with novel coronavirus disease 2019 (COVID-19) is critically ill and most of these patients require mechanical ventilation for severe acute respiratory distress syndrome (ARDS) (Cummings et al., 2020). Prolonged sedation and neuromuscular blockade are two mainstays of treatment in severe ARDS (Alhazzani et al., 2020; Berlin et al., 2020). COVID-19 ARDS patients also have a particularly high rate of agitation and

encephalopathy which can necessitate prolonged use of sedatives (Mao et al., 2019; Kotfis et al., 2020). Minimizing sedative use in patients receiving neuromuscular blocking agents is paramount as this may be associated with shorter times on mechanical ventilation, shorter stays in the intensive care unit (ICU) (Kress et al., 2000), and potentially decreased mortality (Watson et al., 2008). Reducing ICU length of stay and sedation usage may also be beneficial in a pandemic surge situation resulting in medication shortages, as has been seen in the current pandemic (Mazer-Amirshahi et al., 2020; Food and Drug Administration, 2020). However, minimizing healthcare provider contact when managing highly contagious diseases such as COVID-19 (Waldman et al., 2020) creates additional challenges in utilizing behavioral assessments to guide sedation in these patients. EEG is widely available and offers a continuous assessment of the depth of sedation (Akeju et al., 2014; Brown et al., 2010). However, connecting patients to EEG and maintaining electrode integrity in COVID-19 patients is time-consuming, resource intensive, and significantly increases staff exposure (Gélisse et al., 2020).

Limited montage EEGs have been utilized for the rapid assessment of patients in the ICU and have the benefit of a faster connection and less maintenance time (Tanner et al., 2014). It has been demonstrated to reduce the total exposure time by nearly 50% in COVID-19 patients (Haines et al., 2020) when compared to a standard EEG connection.

Here we describe a cohort of COVID-19 patients managed with EEG guided sedation titration using a limited number of EEG electrodes requiring minimal time to set up and perform lead maintenance. Primarily we determined how often EEG guided sedation reduction would require rebound dose adjustments in the following 6 h. Secondarily, we analyzed quantitative features of the recorded EEG signal that correlated with sedation levels and used these to train a machine learning algorithm to classify sedation levels.

2. Methods

2.1. Subjects

We studied all patients admitted to the neurological ICU at Columbia University Medical Center between April 14th and May 5th that fulfilled the following inclusion criteria: (1) A positive SARS-CoV-2 nasopharyngeal swab; (2) severe ARDS requiring invasive mechanical ventilation, sedation, and neuromuscular blockade to achieve ventilator synchrony, and (3) no known pre-existing neurological condition. Data were collected as part of a prospective observational cohort study approved by the local institutional review board.

2.2. General management

Medical management was in accordance with the institutional guidance on COVID-19 related ARDS, as well as recommendations by the European Society of Intensive Care Medicine and the Society of Critical Care Medicine (Alhazzani et al., 2020). Management included endotracheal intubation, sedation and neuromuscular blockade to allow ventilator synchrony, and prone positioning (Table 1).

2.3. Behavioral assessments and outcomes

Neurological assessments were performed by nursing staff throughout the day and documented in the medical record at least twice daily. Assessments were done using the Richmond Agitation-Sedation Scale (RASS) (Sessler et al., 2001), Glasgow Coma Scale

Table 1
Characteristics of the 11 Patients.

Demographics	Value
Age – yr	60 (±9)
Female sex – no. (%)	4 (36)
Common comorbidities – no. (%)	
Any	9 (82)
Hypertension	7 (64)
Diabetes	6 (55)
Lung Disease	3 (27)
Common complications during hospitalization – no. (%)	
Shock (septic, cardiogenic, secondary to sedatives)	11 (100)
Superimposed pneumonia	7 (64)
AKI, with or without renal replacement therapy	7 (64)
Diabetic ketoacidosis	5 (46)
ICU interventions	
Deep sedation with neuromuscular blockade – no. (%)	11 (100)
Underwent Prone positioning – no. (%)	9 (82)
Median APACHE II score per patient (IQR) – no.	29 (15–33)
Median number of neuromuscular blockade days per patient (IQR) – no.	11 (3–19)
Median number of prone trials patient (IQR) – no.	3 (2–4)
Median number of total ICU days per patient (IQR) – no.	25 (17–41)
Outcome at end of hospitalization – no. (%)	
Deceased	7 (64)
Inpatient rehabilitation	3 (27)
Home	1 (9)

Data reported as mean +/- standard deviation or n(%) as appropriate. AKI = acute kidney injury; IQR = interquartile range

(GCS) (Teasdale and Jennett, 1974), and Confusion Assessment Method for the ICU (CAM-ICU) (Inouye et al., 1990; Ely et al., 2001). Nursing staff also performed basic neurological examinations several times per day, including assessments of the pupillary size, pupillary light reflex (present or not for each eye), gag reflex, and the best motor response.

2.4. Electrophysiological data collection

Electrode placement followed the international 10–20 system but was limited to five frontotemporal EEG leads (Fp1, Fp2, F7, F8, Fpz, using Fpz as the reference electrode) and a ground electrode. EEG was recorded using a digital video EEG bedside monitoring system (Xltek; Natus Medical, Oakville, ON, Canada; low-pass filter = 70 Hz, high-pass filter = 1 Hz, sampling rate = 200 Hz) (Claassen et al., 2016). Electrodes were routinely checked to keep impedances <5 kΩ and to ensure high signal quality.

2.5. EEG interpretation

1–2 h of EEG were reviewed by an epileptologist each day and an assessment of sedation status was categorized into either being consistent with adequate sedation or consistent with a high level of sedation. Sedation was deemed adequate if the EEG showed predominantly continuous background activity. If the EEG was markedly attenuated or discontinuous (with periods of attenuation lasting approximately three seconds or longer), it was considered consistent with a high level of sedation.

2.6. Sedation adjustments

The sedative infusions used were fentanyl, midazolam, propofol, and dexmedetomidine. Rocuronium was used for neuromuscular blockade. The decision to reduce sedation was guided by the EEG assessment but implementation was left to the Critical Care attending responsible for the care of the patient. All changes to sedation or neuromuscular blocking agents within six hours of

the EEG assessment were recorded. If sedation was decreased, any subsequent increases in sedation within six hours of the decrease were recorded. Each patient-day while on EEG was treated as a separate trial but in the statistical modeling analyses were corrected for repeated measures.

2.6.1. EEG preparation

For quantitative analysis, we sought to understand what measures on EEG correlated with adequate or inadequate sedation. Based on visual screening, artifact-free 15-min-long EEG clips were selected as close as possible to the time of the epileptologist’s assessment. EEG analysis was carried out in MATLAB (MathWorks, Natick, MA) using the Fieldtrip (Oostenveld et al, 2011), as well as custom scripts. Then EEG clips were split into nonoverlapping epochs of 10-s duration. All epochs were converted to Hjorth Laplacian montage by subtracting the distance-weighted average of up to three nearest neighbors from each channel (Goldfine et al., 2011).

2.6.2. EEG acquisition and processing

Building on studies analyzing EEG correlates of consciousness in disorders of consciousness as well as anesthesia models, we selected Power Spectral Density (PSD) as a measure of interest. PSD for frequencies from 1 to 50 Hz was calculated for each trial using Welch’s power spectral density estimation. In line with previous studies, data were analyzed in frequency bands: delta (1–4 Hz), theta (4–8 Hz), alpha (8–14 Hz), beta (14–24 Hz), and gamma (26–50 Hz) (Claassen et al., 2016). The average across all epochs for a given patient and day were used to train a machine-learning algorithm (an ensemble of decision trees implementing the random forest algorithm (Breiman, 1984)) to distinguish between the EEG signal according to the level of sedation. We applied a leave-one-out procedure to evaluate the quality of the model. Training of the algorithm was performed on all subjects minus one and then tested only on the subject that was left out. This process was repeated for each subject prior to averaging across all subjects.

2.7. Statistical analysis

Performance of the machine-learning algorithm was estimated using classification accuracy. To evaluate the significance of the classification accuracy, a one-tailed permutation test was performed (training and evaluation of the classifier 1000 times after random shuffling of the sedation level labels) (Noirhomme et al., 2014; Good, 2005). The model was considered as successfully distinguishing the classes if it significantly outperformed the random classifier. The influences of the predictor variables in the model at predicting the sedation level was estimated (Breiman et al., 1984). The scaled coordinates corresponding to the first two eigenvalues were generated by the multidimensional scaling of the proximity matrix of the random forest classifier (Seber, 1984). All EEG analyses were performed with the use of MATLAB (MathWorks, Natick, MA).

3. Results

3.1. Study cohort

Eleven patients were included in the study. The mean age of patients was 60 years old, and all were critically ill, requiring prolonged ICU stays, deep sedation, neuromuscular blockade, and prone positioning on several days. Seven (64%) patients died during their hospitalization, and four (36%) survived to hospital discharge, either to home or to a rehabilitation facility (Table 1). Of

the four who survived, one was extubated and three underwent tracheostomy placement. Two were decannulated within two months of their ICU stay and one remains ventilator-dependent.

3.2. Behavioral assessments

In >90% of days with available behavioral assessments, the GCS score was 3 or 4 and RASS score was –4 or –5. This was true in patients regardless of their EEG findings and epileptologist recommendations. The CAM-ICU was not applicable to most patient days as they scored a RASS of –4 or –5 and was positive in the five patient days with a RASS \geq –3 in both sedation classifications (Table 2).

3.3. EEG sedation assessments

We recorded a total of 98 days of EEG guided sedation assessments across 11 patients. The epileptologist’s assessment deemed 57 (58%) EEG recordings consistent with high levels of sedation, and 41 (42%) were considered consistent with adequate sedation. The primary team followed the recommendation to reduce or maintain sedation 59% of the time (33% of the time for reduction and 95% of the time for maintaining current sedation). In 12% of the cases where the primary team followed the epileptologist’s recommendation the sedation subsequently needed to be increased (Fig. 1).

3.4. Quantitative EEG features

PSD was significantly different between the two classes in the alpha, theta, and delta bands across leads F7, F8, Fp1, and Fp2. In the beta band, F7 and F8 leads were significantly different (two-sided Wilcoxon rank sum test, $p < 0.01$) (Fig. 2).

3.5. EEG-based classifier

Classification accuracy of $80\% \pm 17\%$ was achieved using PSD features, with a sensitivity and specificity of $68\% \pm 0.17$ and $68\% \pm 0.21$, respectively (area under the receiver operating characteristic curve, $AUC = 0.85 \pm 0.19$; Fig. 3). The result significantly outperformed the random classifier prediction, which had a classification accuracy of $53\% \pm 6\%$ and a sensitivity and specificity of 0.55 ± 0.1 and 0.48 ± 0.1 , respectively (permutation test, $p < 0.001$). The influences of the predictor variables in the model at predicting the sedation level are given in Fig. 4. The influence of a predictor increases with the value of this measure. Fig. 5 represents the scaled coordinates corresponding to the first two eigenvalues.

Table 2

Behavioral assessment scores for commonly used intensive care unit tools for available sedation days. If multiple assessments were present on one day, the assessment closest to the time of the EEG read was used.

Behavioral assessment	EEG consistent with over-sedation	EEG consistent with adequate sedation
no. of patient days (%)		
GCS = 3 or 4	52/55 (95)	39/40 (98)
GCS \geq 5	3/55 (5)	1/40 (2)
RASS = –4 or –5	52/55 (95)	35/37 (95)*
RASS \geq –3	3/55 (5)	2/37 (5)*
CAM-ICU positive**	3/3	2/2

GCS = Glasgow Coma Scale; RASS = Richmond Agitation-Sedation Scale; CAM-ICU = Confusion Assessment Method for the Intensive Care Unit.

*RASS scores were missing for 3 patients in the adequate sedation group.

** CAM-ICU is not assessable in patients with a RASS score of –4 or –5. Therefore, the test is only reported for those patients with a RASS score of \geq –3.

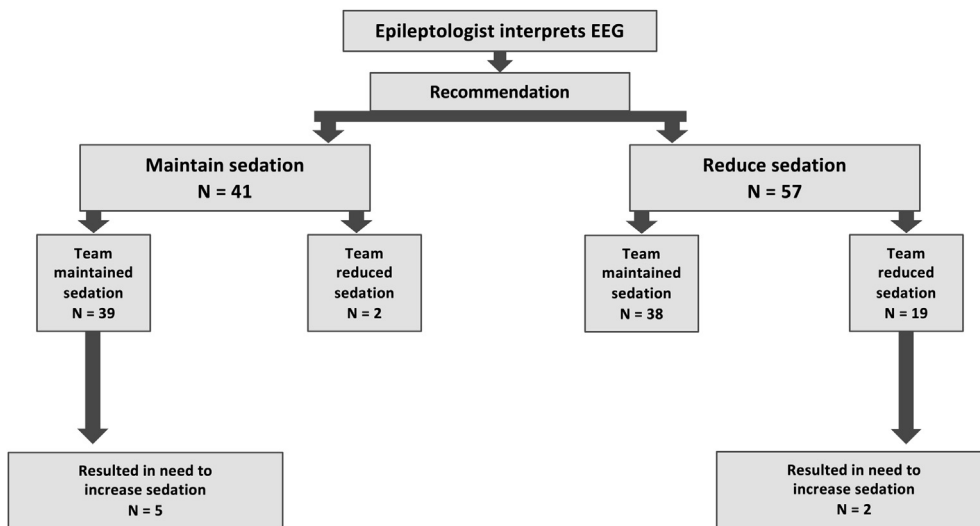


Fig. 1. Recommendations based on EEG and treatment/response algorithm.

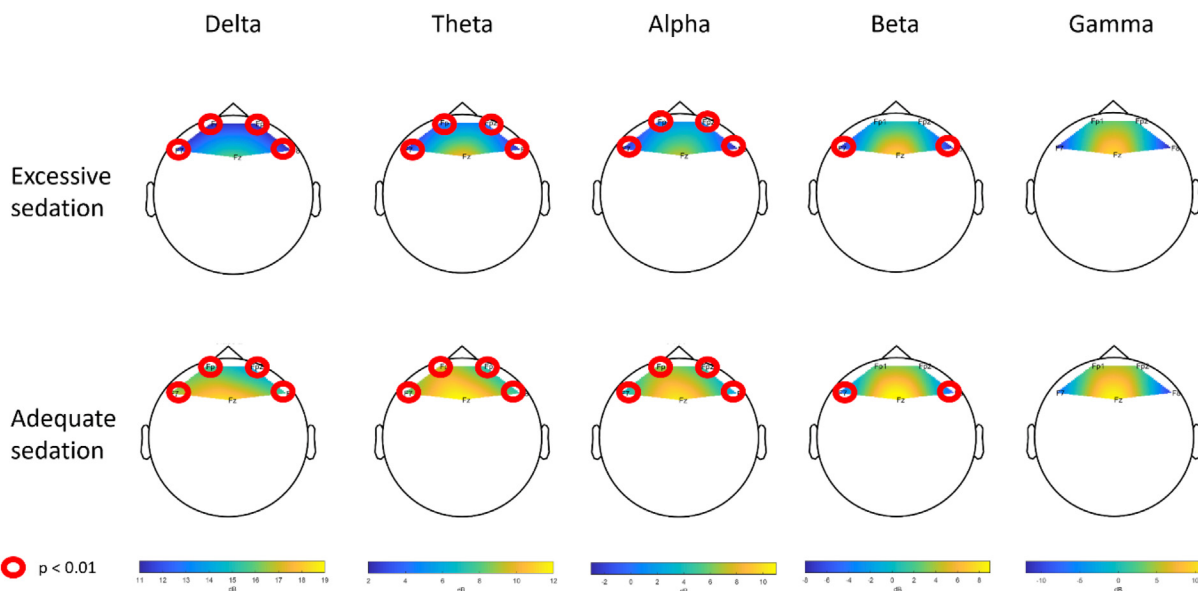


Fig. 2. Layout of frontotemporal leads and corresponding power spectral density within the labeled bands, between the two groups. Red circles indicate significant.

The scaled coordinates are generated by the multidimensional scaling of the proximity matrix of the random forest classifier.

4. Discussion

In this study we showed that visual inspection of a limited EEG-montage can be used to classify sedation depth and help with sedation depth guidance. Secondly, we were able to use quantitative EEG to train a machine learning algorithm with good classification accuracy, supporting the concept that the process could potentially be automated. These methods may have applications in the management of patients with COVID-19 given the high sedation burden and the need to minimize patient contact.

4.1. Severity of illness

The chosen cohort is not representative of most COVID-19 patients, and not even of the majority of COVID-19 patients in

the ICU, but represents the most challenging subset of critically ill patients with COVID-19. The severity of their illness warranted near-continuous attention from nurses and physicians. We found that a limited frontotemporal EEG montage could be a useful adjunct for guiding sedation changes in these patients. We showed differences in qEEG based on depth of sedation and modeled a random forest machine learning algorithm from quantitative data using the PSD that had good classification accuracy.

4.2. Interpreting the raw EEG signal

The raw EEG interpretation used by epileptologists are in line with existing literature about sedative effects on EEG (Chander et al., 2014; Hight et al., 2019; Hesse et al., 2019). As deeper levels of sedation are achieved, EEG power shifts from high- to low-frequency bands. In states of very deep sedation a burst-suppression pattern will appear (Hagihira, 2015). Burst-suppression as a reflection of disease states may be encountered in the context of brain injury or as a result of sedation

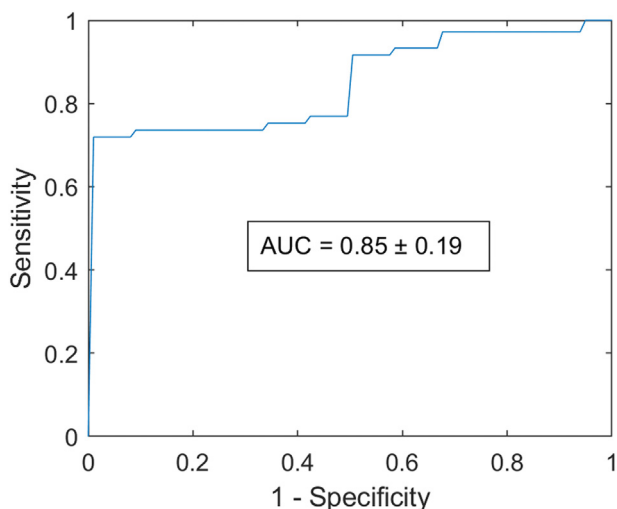


Fig. 3. Area under the receiver operating characteristic curve (AUC) for the random forest classifier.

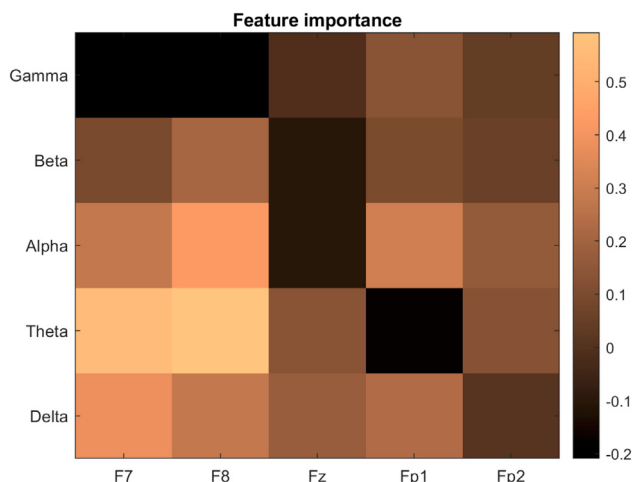


Fig. 4. Influence of predictor variables. Brighter color (more positive) represents increased influence.

(Fernandez and Claassen, 2012), and has been associated with increased mortality in a general ICU population (Watson et al., 2008). A number of EEG features have been incorporated into algorithms to guide depth of sedation primarily in the operating room context (Bennett et al., 2009; Sun et al., 2020). However, such systems may underestimate the amount of EEG suppression (Muhlhofer et al., 2017) and lead to deeper levels of sedation than intended. For this reason, interpreting the raw EEG may provide a more accurate assessment of sedation.

4.3. Utilizing quantitative EEG parameters

The use of quantitative EEG (qEEG) has been explored in anesthetics (Sun et al., 2020) where it has been shown to discriminate effectively between loss and recovery of consciousness (Purdon et al., 2013). It has also been applied in the study of disorders of consciousness in patients with brain injury, where it can properly classify comatose and non-comatose patients (Claassen et al., 2016). Although its main use is in the detection and monitoring of primary neurological disorders, qEEG and its derivations may see an expanding role in the monitoring of sedation levels in the critically ill (Ramaswamy et al., 2019). While burst-suppression

represents one pattern that can be detected by qEEG (Muhlhofer et al., 2017), sedative medications have other influences on qEEG dynamics as well. For example, sedation with both propofol and dexmedetomidine result in slow (0.1–1 Hz) and delta oscillation patterns, but the EEG of patients receiving propofol is characterized by a much larger slow oscillation power. Additionally, propofol induces prominent frontal alpha oscillations, whereas dexmedetomidine induces spindles which resemble natural sleep (Akeju et al., 2014). These differences could be used to guide proper sedative dosing in critically ill patients. In this study the level of sedation as classified by the epileptologist could also be discerned by using the PSD of the qEEG. Although we saw the pattern of increased PSD of slow and delta frequencies at higher levels of sedation, the distinct patterns associated with each sedative were not seen. The reason for this is likely multifactorial but could have been influenced by the patients' disease state as well as the need to use multiple sedatives at one time to achieve adequate sedation in many cases.

4.4. Machine learning algorithm

There is growing interest in machine learning algorithms that can correctly classify EEG signals with the aim of automating continual real-time assessments. Many methods have been employed to create algorithms that can accurately classify sedation status based on qEEG measures in healthy patients (Ramaswamy et al., 2019; Rathee et al., 2018), patients receiving general anesthesia (Liang et al., 2018), and in the ICU (Sanz-García et al., 2019). Here we utilized a random forest algorithm with a sedation classification accuracy of 80% ± 17% using PSD in the specified frequency bands. This method was used as this algorithm is robust to overfitting for small training sets (Hastie et al., 2009). In addition, it allows for a transparent and natural ranking of the importance of predictors (Breiman, 2001) and an understanding of which variables are most important in the model. In our study the lower frequencies (delta, theta, and alpha bands) were more informative, whereas beta and gamma frequencies were less informative. This is consistent with the known frequency shifts that occur with deeper levels of sedation (Hagihira, 2015) as well as with various sedatives (Purdon et al., 2013; Akeju et al., 2016).

4.5. Limitations

There are several limitations to this study worth mentioning. Firstly, the small sample size and study design limit the generalizability of the results. Further, constraints imposed by the pandemic provided challenges to more extensive data collection. For instance, as there was no control group, we were unable to quantify reductions in staff exposure and sedatives. While we did not record overall EEG connection time, the experience of the authors was that the limited montage significantly expedited this process, consistent with prior reports (Haines et al., 2020). This was felt to be especially relevant when connecting patients who were in the prone position. Nevertheless, a larger case-controlled study will be needed to draw definitive conclusions about these aspects.

Secondly, the clinical team did not follow the recommendation to reduce sedation in all cases. While the team had access to the EEG interpretation, they also incorporated the patient's clinical and neurological exam, other laboratory values, and the larger therapeutic goals when deciding whether to adjust the sedation. While this may have affected our overall results, it was deemed necessary for patient care. Additional studies are also needed to evaluate the specific reasons why the team deviated from the EEG recommendations.

Lastly, frontotemporal leads may show attenuation and discontinuity for reasons other than excess sedation, such as hypoxic-

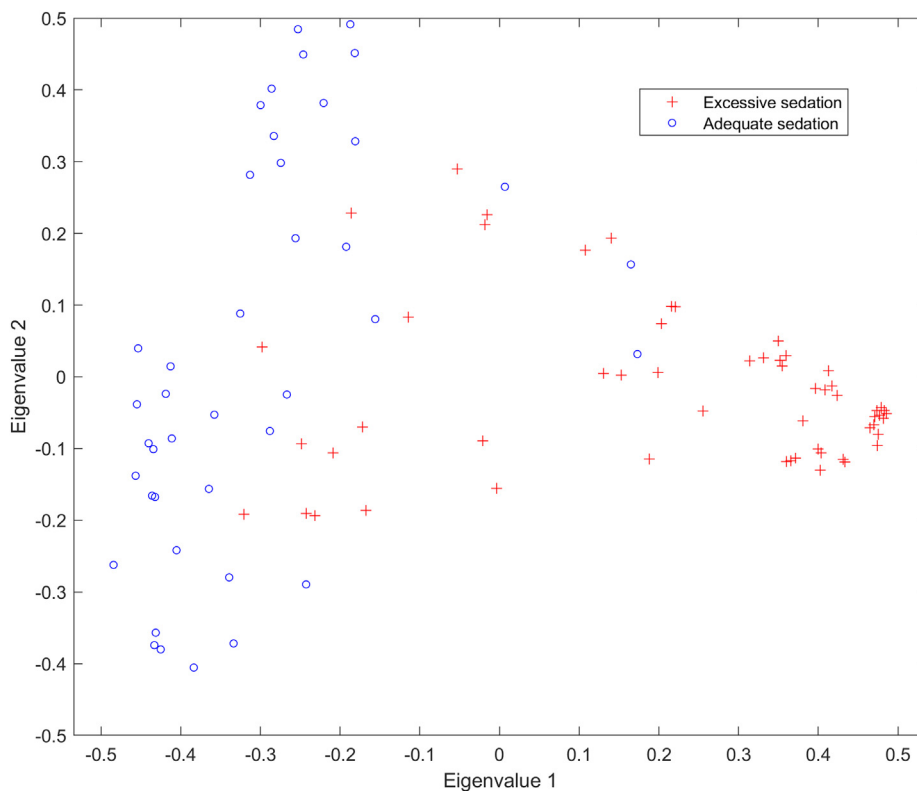


Fig. 5. Scaled coordinates corresponding to the first two eigenvalues, generated by multidimensional scaling of the proximity matrix of the random forest classifier.

ischemic injury or cerebral infarction. This could lead to inappropriate reduction of sedation and represents one potential contributor to the need to increase sedation in 12% of cases. None of the seven patients who died had been evaluated for stroke or hypoxic-ischemic injury. Of the four patients who recovered, one was later found to have multifocal punctate infarcts and a larger occipital lobe infarct. This was not apparent on or relevant to frontotemporal EEG monitoring. The limited montage might also miss epileptiform activity and would not be adequate for patients with suspicion for seizures. Although prior studies have shown varying levels of sensitivity and specificity for detecting epileptiform activity with limited montages (Pati et al., 2017; Ma et al., 2018; Tanner et al., 2014), it nonetheless remains a limitation that a direct comparison of this technique to a traditional full montage was not done. More studies are needed to evaluate the safety, efficacy, and applicability of this technique, as well as to compare it to a traditional montage.

5. Conclusion

A limited frontotemporal EEG montage can be helpful in guiding sedation dose guidance in highly contagious COVID-19 patients receiving neuromuscular blocking agents. Further studies at additional centers are warranted to evaluate the broader applicability of this technique.

6. Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Disclosure of conflicts of interest

JC is a minority shareholder at iCE Neurosystems.

Funding

JC is supported by grant funding from the NIH R01 NS106014 (including NS106014-S0202).

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