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TOWARDS RIEMANNIAN EEG CLASSIFIERS TO DETECT AWAKE AND ANESTHETIZED STATES USING MEDIAN NERVE STIMULATION

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ABSTRACT: Among all the operations carried out under general anesthesia worldwide, some patients have had the terrible experience of Accidental Awareness during General Anesthesia (AAGA), an unexpected awakening during the surgical procedure. The inability to predict and prevent AAGA before its occurrence using only conventional measures, such as clinical signs, leads to the use of brain activity monitors. Given AAGA patients' first reflex to move, impeded by neuromuscular-blocking agents, we propose using a new Brain Computer Interface with Median Nerve Stimulation (MNS) to detect their movement intentions, specifically in the context of general anesthesia. Indeed, MNS induces movement-related EEG patterns, improving the detection of such intentions. In this article, we compared MNS effects on the motor cortex before and during surgery under general anesthesia. Then, a Riemannian Minimum Distance to the Mean classifier achieved 97% test balanced accuracy in distinguishing awake and anesthetized states. Additionally, we observed how the classifier's response evolves with anesthesia depth, in terms of distance to the awake class centroid. This distance appears to track the patients' awareness level during surgery. This holds promises for developing a future one-class classifier using only awake EEG data, as anesthesia EEG data are usually unavailable for classifier training, to detect AAGA.

INTRODUCTION

Accidental Awareness during General Anesthesia (AAGA) is an unexpected awakening during surgery that can be a truly traumatic experience for the patients. It occurs in about 1% of high-risk interventions [1], although the incidence remains controversial as it is a subjective experience that may be underestimated in the absence of the necessary questionnaires to follow the patients [2]. During an AAGA, the patient may experience pain, and recall events related to the surgery, which can lead to potentially devastating psychological sequelae, such as Post-Traumatic Stress Disorder (PTSD) [3]. The risk of AAGA is higher with Total Intravenous Anesthesia (TIVA), such as propofol, in comparison to volatile-based anesthesia [4]. In addition, the use of Neuromuscular-Blocking Agents (NMBAs) further increases this risk [2]. The first reaction to noxious stimulation when anesthesia depth is insufficient is the patient's movement, which may act as a potential detector of AAGA, but this response is suppressed by NMBAs, which paralyze the patient [5]. Besides, traditional clinical signs like hypertension, tachycardia and lacrimation are also unreliable indicators of anesthesia depth [5]. As a result, electroencephalography (EEG) has been used to monitor the depth of anesthesia [6], but awareness may still occur with current monitors [7, 8].

Since the first reflex of a patient experiencing AAGA is to attempt to move to prevent what is happening [2], using a Brain-Computer Interface (BCI) based on motor imagery could be relevant [9, 10]. Indeed, the power variations within the mu and beta frequency bands, called Event-Related Desynchronizations (ERD) and Event-Related Synchronizations (ERS) could be useful markers for detecting whether the patient is experiencing AAGA [11]. Interestingly, Median Nerve Stimulation (MNS) is a painless stimulation of the median nerve that generates a similar ERD/ERS pattern to the one induced by an intention to move (MI) [12]. Combining both MI and MNS has a significant impact on the patterns generated by the MNS, resulting in a better classification accuracy in MI detection [9, 13]. Also, MNS intrinsically provides a trigger to know when to analyze the signal [14], which leads to better classification (+18%) results than those obtained with asynchronous BCI [9]. The originality of this BCI paradigm is to exploit this MNS induced phenomenon to accurately detect the patient's motor intention during an AAGA. In preliminary results, we have shown that propofol sedation (at 0.5 µg/ml and 1 µg/ml) has no negative impact on the ability of an MNS-based BCI to detect movement intention. Concretely, at relatively low propofol concentrations, ERD/ERS patterns are still present in the sensorimotor cortex [15, 16]. However, it appears that

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high doses of propofol strongly affect the oscillatory activity generated by the MNS [17], which makes it difficult to detect MI under anesthesia.

Current BCIs require a subject-specific calibration due to large between-subject variabilities. However, before a surgery, patients' EEG examples of MNS during anesthesia are not available. In the long term, we thus need to develop new machine learning tools that can detect MI under anesthesia without any EEG example from this patient. With this future objective in mind, in this paper, we first propose to use a Riemannian Minimum Distance to the Mean (MDM) classifier [18] to differentiate the EEG activities induced by the two types of stimulations: preoperative MNS when the patient is awake (MNS-awake), from intraoperative MNS when the patient is under different stages of general anesthesia (MNS-anesthesia). Our findings suggest that an MDM classifier is indeed capable of distinguishing between these two classes with high accuracy. Additionally, the distance to the MNS-awake class centroid (which does not require data under anesthesia) varies according to the concentration of propofol throughout the surgery. These results are promising for the future development of a one class MNS based-BCI that detects AAGA, as EEG covariance matrices appear to contain information related to the patients' level of awareness throughout the surgery under propofol.

MATERIALS AND METHODS

Participants: 13 volunteers (7 females; 50 ± 7.39 years old) were enrolled for surgery at the CHU Brugmann, Brussels, Belgium, and accepted to participate in this protocol. This study was approved by the ethical committee of the CHU Brugmann (CE 2021/225) and was registered at EUDRACT (2021-006457-56). The study protocol [14] was also registered on ClinicalTrials.gov (NCT05272202) and follows the principles of the Declaration of Helsinki and the Medical Research Involving Human Subjects Act [19]. Subjects 1, 2, and 5 were excluded either due to technical issues or because the surgery was canceled, resulting in only 10 subjects being included. 2 of them (subjects 10 and 11) were stimulated on the right median nerve, and the remaining 8 on the left. This was due to difficulties in placing the electrodes on the left median nerve and limited time in order not to delay the surgical intervention.

Protocol: The patients were equipped with a TMSi 64-channel EEG cap covering the entire scalp, and the signals collected through an eego mylab system (ANT Neuro) at 4096 Hz. MNSs consisted of square electrical pulses of 0.2 milliseconds of duration, and were generated by Micromed device SD Ltm Stim Energy and delivered through a pair of grass gold cup electrodes (cathode [-] placed proximally) to the right/left median nerve at the wrist [12]. The intensities were adjusted to elicit visible small thumb twitches, below 15 mA [14].

First, a preoperative EEG recording session (approximately 1 hour) was conducted by stimulating the median nerve of the awake patient during 1 or 2 runs. This was followed by a second intraoperative session recorded during the entire surgery under general anesthesia; the duration and number of runs depended on the length of the surgery (from 3 to 10 runs, depending on the subject). One run consisted of 150 stimulations, spaced by 3 to 4 seconds. The anesthesia protocol was left at the anesthesiologist's discretion, except for the loss of consciousness, which was achieved using propofol with a Target-Controlled Infusion (TCI) pump with the Schnider pharmacokinetic model designed to predict propofol concentration at the effect-site [20]. If necessary, NMBA agents were used (patients n°4, 6, 7, 8, 11, 13). Data collection of the target propofol concentration administered to the patients was directly recorded alongside the EEG signals. After the surgery, sedation was discontinued, allowing the patient to recover and to be monitored afterward in the post-anesthesia care unit.

Time-frequency EEG analyses: Time-frequency analyses to identify the differences in MNS patterns between preoperative and intraoperative sessions were performed using the EEGLAB toolbox [21] and MATLAB R2023a (The MathWorks Inc). EEG signals have very low amplitudes and are thus susceptible to external interference. For example, the use of electrocautery during a surgery produces visible noise in the EEG signals [22]. In order to clean these electrocautery-related artifacts, all trials were visualized and those affected were rejected. Then, EEG signals were downsampled to 128 Hz and epoched into 4.5 s windows (1.5 s before and 3 s after MNS).

Because Event Related Spectral Perturbation (ERSP) time-frequency analyses are conducted at the group level, it is essential for the subjects to have homogeneity, meaning they should be stimulated in the same hand. Therefore, ERSP time-frequency analyses were averaged only across the 8 participants where the left median nerve was stimulated, the electrode of interest being C4 (Fig. 1).

Classification: Offline BCI performances for MNS-awake vs. MNS-anesthesia classification were analyzed to determine if the MNS pattern might be used to track the patient awareness level throughout surgery. Classifications were performed using the MNE [23], Scikit-learn [24] and pyRiemann [25] packages in Python 3.10. EEG signals, with trials affected by electrocautery-related artifacts rejected, were downsampled to 128 Hz, band-pass filtered (8-30 Hz), and epochs for MNS-awake and MNS-anesthesia were extracted from 250 to 1000 ms after the stimulation. Epochs do not start at time 0 ms to avoid MNS-induced electrical artifacts. All 64 electrodes were used for the classification, and since the algorithm calibration is subject-specific, all 10 subjects were included.

A Riemannian MDM [18, 26] was used, as Riemannian classifiers are currently the state-of-the-art in EEG-based BCIs [27, 28]. Each EEG trial $\mathbf{X}$ is represented by a covariance matrix $\mathbf{P} \in \mathrm{R}^{n \times n}$, with n the number of electrodes, s the number of sampled time points in each trial and the superscript ^{T} as matrix transposition:

$$\mathbf{P} = \frac{\mathbf{X}\mathbf{X}^T}{s-1} \tag{1}$$

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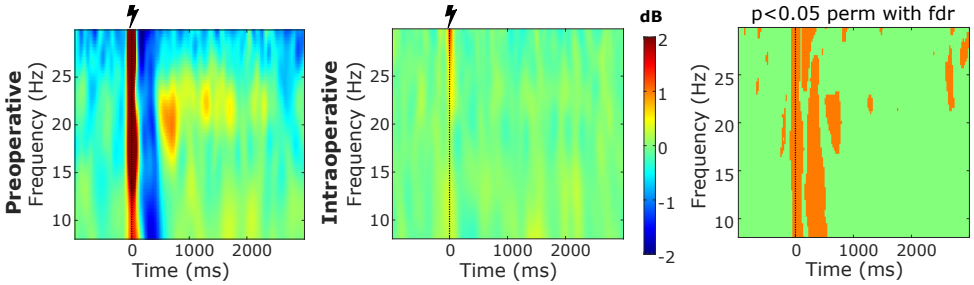

Figure 1: Grand average Event-Related Spectral Perturbation (ERSP) time-frequency analysis across 8 subjects for both conditions: preoperative (left figure) and intraoperative (central figure) median nerve stimulation, for electrode C4. The flash icon indicates the beginning of the stimulation. Statistical differences at a significance level of 0.05 are shown on the right figure. Red color corresponds to a strong ERS and blue to a strong ERD.

Such matrices are symmetric-positive definite matrices, that can be manipulated using Riemannian geometry, and compared using a dedicated Riemannian geodesic distance δ_R:

$$\delta_R(\mathbf{P}_1,\mathbf{P}_2) = ||log(\mathbf{P}_1^{-1/2}\mathbf{P}_2\mathbf{P}_1^{-1/2})||_F \quad (2)$$

where $||\mathbf{A}||_F$ is the Frobenius norm of a matrix A. For algorithm training, the MDM algorithm first estimates the mean covariance matrix $\mathbf{P}^k_{\mathfrak{G}}$ for each class k (here, MNS-awake or MNS-anesthesia). This is performed using the covariance matrices of the $I \geq 0$ training EEG signals from class k, as follows:

$$\mathbf{P}^k_{\mathfrak{G}} = \arg\min_{\mathbf{P}^k} \sum_{i=1}^{I} \delta^2{}_R(\mathbf{P}^k,\mathbf{P}^k_i) \quad (3)$$

These two mean covariance matrices, one for each class, can then be used as class centroids. For algorithm testing, covariance matrices are also estimated for each trial. Thus, the class $\hat{k}$ of an unseen EEG covariance matrix $\mathbf{P}$ is determined based on the nearest centroid's class:

$$\hat{k} = \arg\min_{k} \delta_R(\mathbf{P},\mathbf{P}^k_{\mathfrak{G}}) \quad (4)$$

The number of training and testing trials differs among subjects, depending on the quantity of clean trials recorded preoperatively or during their surgery. The classifier was trained with the first half of preoperative trials for the MNS-awake class (65 to 148 trials), and the first half of deep-anesthesia intraoperative trials for the MNS-anesthesia class (113 to 535 trials). It was then tested on the remaining trials (279 to 1192 trials). Standard cross-validation was not used to remain realistic and more similar to an actual online use, where no future data would be available for cross-validation. Employing this technique might lead to an overestimation of the accuracy [29].

RESULTS

Impact of general anesthesia on ERD/ERS induced by MNS: During the preoperative condition (i.e., before the general anesthesia), the ERSP analysis (Fig. 1) revealed the usual EEG pattern associated with median nerve stimulation [9, 30]. In particular, immediately after the MNS, a powerful ERS appears between 0 and 250 ms, in the whole 8 to 30 Hz frequency band. For the remainder of this article, this very first ERS will be referred to as the post-stimulation rebound (PSR; see [9, 30]) and could be due partially to an electrical artifact. The PSR is followed by an ERD period of approximately 500 ms in both the alpha and beta frequency bands (8-30 Hz). Finally, a post-movement beta rebound (PMBR) occurs in the beta frequency band (18-23 Hz) about 500 ms after stimulation and lasts 1 s. According to a permutation test comparing the two surgical conditions, for $p \leq 0.05$ with a correction for false discovery rate for multiple comparisons, both ERD and PMBR seem to disappear significantly during the intraoperative condition.

MNS-awake vs MNS-anesthesia classification: The MDM algorithm is able to correctly distinguish the preoperative MNS pattern (MNS-awake) from the intraoperative pattern (MNS-anesthesia), with an average test set balanced accuracy of 97% (Fig. 2). The test set balanced accuracy for each subject is never below 85%, which is not surprising given the clear difference in the MNS pattern between these two sessions (Fig. 1).

Distances to the MNS-awake class centroid: The distances to the MNS-awake class centroid of the test trials of subjects S6, S8 and S9 over the whole experiment are shown in Fig. 3. When a trial is classified as MNS-awake by the MDM classifier, a bar is presented below it, beneath the graph. The corresponding test set balanced accuracies of subjects 6, 8 and 9 are 96%, 98% and 86%, respectively, with the latter being the lowest accuracy among the 10 subjects. For S6 and S8, the MDM classifier correctly identified the patients as awake during the preoperative session and at the beginning of the intraoperative session. For S6, this prediction persisted until the propofol concentration reached approximately 1.5 µg/ml, and for S8 until it reached 3 µg/ml. At the end of the intraoperative session, S8 was also identified as awake for a few trials. As for S9, the preoperative session was accurately labeled. Towards the end of the surgery, with propofol below 1.5 µg/ml, the subject was identified as awake, which is consistent with reality, as the patient was already responding. However, the classifier associated some trials that were part of the induction (with propofol concentration between 2 and 8 µg/ml), as part of the MNS-awake class. The evolution of the distance is congruent with anesthetic concentration evolution, suggesting that covariance matrices might indeed reflect the progression of the MNS pattern throughout the surgery.

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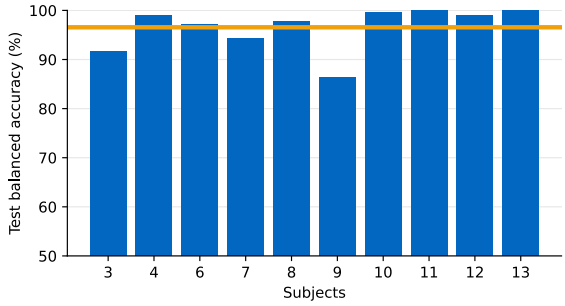

Figure 2: Riemannian MDM test set balanced accuracy of the 10 subjects, for MNS-awake vs MNS-anesthesia classification, where the EEG signals were filtered in the mu+beta band (8-30 Hz), and all 64 electrodes were used. The yellow line indicates the average test set balanced accuracy (97%).

DISCUSSION

According to these results, a Riemannian MDM is indeed capable of distinguishing the MNS pattern of an awake patient from the MNS pattern when the same patient is under propofol. This distinction varies throughout the surgery, according to the propofol concentration. The classifier accurately identifies the patient as awake during the preoperative session, at the beginning of the induction and at the end of the emergence phases. Furthermore, trials of deep anesthesia are farther away from the MNS-awake class centroid than trials corresponding to induction or emergence. We will suggest a few hypotheses that may explain the changes in MNS patterns between the two sessions and how to make the algorithm more robust. Additionally, we will discuss the possibility of evolving this algorithm into a one-class model, as well as future analyses to be explored.

ERD/ERS differences between preoperative and intraoperative conditions: As mentioned, sensorimotor modulations after stimulation are strongly modulated by general anesthesia. First, the amplitude of the PSR (i.e., ERS following the MNS) completely disappears in the presence of propofol. This is also the case for the post-MNS ERD and for the PMBR (Fig. 1). Our previous results had shown that with light propofol sedation (concentrations below 1.5 µg/ml), ERD/ERS patterns were still present in the sensorimotor cortex [16]. However, at deepest concentrations, propofol decreases excitatory inputs from the thalamus to the cortex [6], leading to a decrease in the metabolic activity of the central nervous system, thus making the ERD/ERS disappear after MNS.

In addition to the effects of general anesthesia, other factors could explain the modulations of ERD/ERS. For example, this could be attributed to a change in skin conductance, for instance due to stress. Skin conductance increases in response to stress [31], as is the case right before the intervention, and decreases during the surgery when the patient is no longer conscious. This remains a hypothesis to be further analyzed. It might also result from the change in environment between the two sessions, with the preoperative session conducted in a different room than the operating one because of the high cost of the operating rooms. Also, the position of the patient's arm was not exactly the same in the two sessions.

Robustness of the classification: The MDM classifier is indeed capable of correctly identifying the periods when the patient is awake (preoperative session, beginning of induction and end of emergence). It is important to note that the MNS-anesthesia class was trained with trials under deep anesthesia, which are not easily obtained under clinical conditions. Moreover, for certain subjects such as S9, it mistakenly classifies some trials where the patient is at a propofol concentration of 2 to 6 µg/ml as MNS-awake. During this period, some external elements occurred that could explain why these covariance matrices were closer to the centroid of the MNS-awake class rather than to the one associated with MNS-anesthesia. For example, the patient raised an arm, MNS electrodes were repositioned, the patient was intubated, and the medical team adjusted the patient's position on the operating table. Even though the biggest artifacts were rejected from the EEG, the signals remained considerably noisy. Furthermore, there is minimal difference between S9 and the other subjects, except for its age of 75, compared to an average of 50. Age-related variations in the effects of anesthesia on the EEG have already been shown to impact the effectiveness of EEG-based monitors [32]. Additionally, S9 had notably fewer training trials (77 for MNS-awake and 137 for MNS-anesthesia) compared to S6 and S8, which had 2 to 4 times more trials, making them the subjects with the highest number of training trials. Despite this, Spearman's correlation revealed no significant relationship between the number of training trials and accuracies. Thus, while S9's lower accuracy compared to S6 and S8 may be due to its fewer training trials, this explanation cannot be generalized across all subject's. Burst suppression, a high-voltage activity alternating with isoelectric flat EEG [33], is related to deep levels of general anesthesia [6, 34]. Thus, current depth of anesthesia monitors have a burst suppression sub-variable to avoid a paradoxical increase [5]. In our algorithm, we have not yet taken into account this paradoxical increase in amplitude.

One-class classifier: In a real-world application, the MNS-anesthesia class trained with deep anesthesia trials will not be available to calibrate the BCI. Therefore, a one-class approach [35] calibrated only with MNS-awake trials will be required. Given that the distance to class MNS-awake appears to evolve logically in relation to the anesthesia concentration evolution, one could imagine a one-class method that only takes into account preoperative data to compute an MNS-awake centroid using a Riemannian distance, as in the MDM algorithm. A threshold would then be defined, beyond which the trials of the testing set no longer match, meaning the MNS pattern corresponds to an anesthetized patient. We will explore this approach in future works.

Future analyses: To detect the propofol concentration at which the MNS patterns are no longer visible, we will further analyze an average time-frequency across subjects

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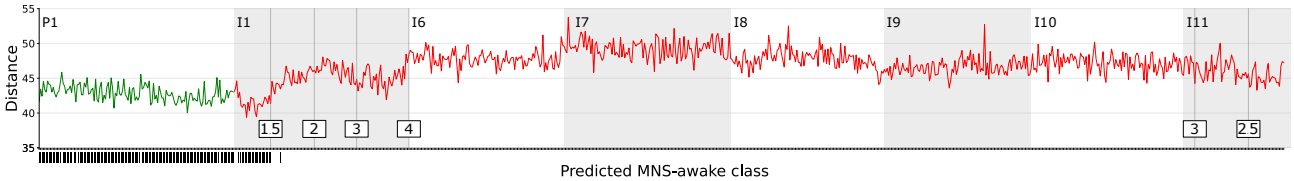
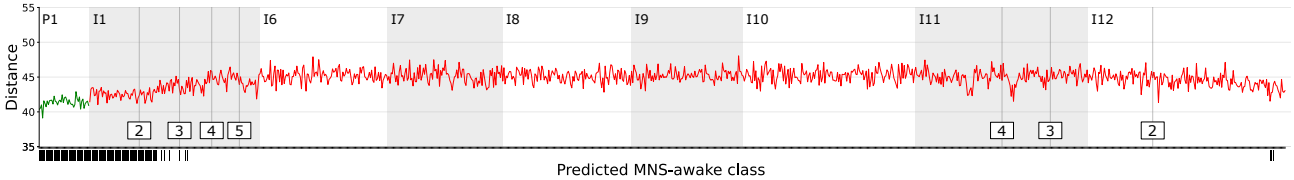
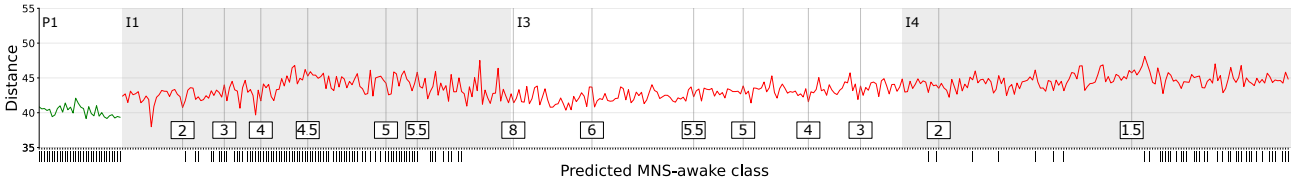


(a) Subject 6 (MDM test balanced accuracy: 96%, trained with P2, and I2 to I5)



(b) Subject 8 (MDM test balanced accuracy: 98%, trained with the last half of P1, and I2 to I5)



(c) Subject 9 (MDM test balanced accuracy: 86%, trained with the last half of P1, and I2)

Figure 3: Distances of each test trial to the MNS-awake centroid, for subjects 6, 8 and 9. The real labels are presented by colors: green for the preoperative session (MNS-awake) and red for the intraoperative session (MNS-anesthesia). Below, a bar indicates when the classifier predicted MNS-awake. When propofol reaches the target concentration, a gray line with a label indicating the corresponding concentration (in µg/ml) is displayed. Each run is differentiated by alternating background colors (white, gray), and labeled as preoperative (P) or intraoperative (I) runs.

for each concentration. This will allow us to observe the pattern evolution. An extension of this MNS-based BCI will also be explored by integrating other EEG features, still visible under deep levels of propofol. Some of these features might be the signal entropy, already used in some monitors [36], functional connectivity or somatosensory evoked potentials. Further analyses will also aim to identify the specific frequency band and the most relevant electrodes to correctly detect the changes in the MNS pattern when a patient is anesthetized. In order to validate this MNS-based BCI, a protocol will be carefully conceived to try to simulate an AAGA and observe if the BCI will indeed be able to detect it.

CONCLUSION

In this paper, we evaluated the feasibility of a new MNS-based BCI to detect intraoperative awareness during general anesthesia by tracking the EEG pattern in the motor cortex associated to MNS during the surgery. We compared this MNS pattern when the subject is awake (MNS-awake) with the MNS pattern when the same patient is undergoing a surgical procedure at different concentrations of propofol (MNS-anesthesia). The two patterns are indeed very different from each other, more particularly, the ERD and PMBR present after the stimulation seem to disappear at deeper concentrations of propofol. A Riemannian MDM was used to differentiate the MNS-awake and MNS-anesthesia classes. The average test balanced accuracy was of 97%, which was expected considering how different the two patterns are. The evolution of the classifier was further analyzed, by tracking the distance between the centroid of the MNS-awake class and covariance matrices of other trials throughout the surgery. This distance is greater during the maintenance phase, under deeper concentrations of anesthesia, compared to the induction or emergence phases. This indicates that covariance matrices associated with the MNS pattern seem to evolve consistently with the patient's level of awareness. Hence, a one-class approach only based on MNS-awake trials, utilizing this distance to detect when the patient is awake during the surgery might be developed. Such a one-class method will be necessary, as the MNS-anesthesia trials will not be available to calibrate the BCI.

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