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A Prewarning Signalling in Motor Evoked Potentials Monitoring for Insular Glioma Surgery: A Preliminary Study

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■ OBJECTIVE: **Insular gliomas are surgically challenging. Intraoperative neurophysiological monitoring assists surgical excision. Although still controversial, a reduction of Motor Evoked Potential (MEPs) signal>50% correlates with postoperative impairment. However, this reduction often occurs too late. Identifying pre-warning indicators, anticipating MEPs drop>50%, could optimize surgery of insular gliomas.**

■ METHODS: **Monocentric retrospective study, collecting clinical, surgical and neurophysiological data of patients harboring insular intra-axial lesions. I) MEPs tracking included the baseline, compared with all subsequently recorded signals. Upper limb muscles were analyzed. II) The Fourier transform was used to modulate the recorded signals. III) The dynamic time warping was then applied followed by logistic regression.**

■ RESULTS: **Out of 300 patients operated on for supratentorial lesions (January 2023-September 2024), 30 patients with insular tumors were finally enrolled. The efficacy of the logistic regression model resulted in high accuracy [91.45%]: it allowed us to identify a pre-warning signal (PWS), anticipating the decrease in MEPs>50% (i.e. warning sign = WS), by considering new parameters of DTW. Comparing MEPs tracks and the identified parameters, our results revealed that PWS compared to WS has the same Se[83.3%]and negative predictive value [93.8%] in identifying MEPs drop and correlating with the postoperative clinical outcome. Compared to WS, PWS has superimposable Sp and positive predictive value correlating with prediction of motor deficits (Sp:62.5%, positive predictive value: 35.7%). Therefore, PWS may be more reliable than WS to interpret intraoperative monitoring variations and predict the clinical outcome.**

■ CONCLUSIONS: **Based on our preliminary data, PWS is reliably predictive of motor outcome, and more accurate than WS to identify intraoperative monitoring variations.**

INTRODUCTION

The primary purpose of neurosurgical oncology consists of achieving a complete resection of pathologic tissue while preserving the functional integrity of patients. Therefore,

Key words
- Brain tumors
- Insula
- Insular glioma
- Intraoperative monitoring
- Motor evoked potentials
- Neuro-oncology
- Vascular damage
- Warning signs

Abbreviations and Acronyms
DTW: Dynamic time warping
FT: Fourier transform
IOM: Intraoperative monitoring
LR: Logistic regression
MEPs: Motor evoked potentials
MRI: Magnetic resonance imaging
NPV: Negative predictive value
nTMS: Navigated transcranial magnetic stimulation
PPV: Positive predictive value
Se: Sensitivity
Sp: Specificity
WS: Warning sign

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it is crucial to maintain a balance between complete tumor resection (determining longer overall survival-OS- and progression free survival-PFS), and preservation of functional integrity to ensure patients a satisfactory quality of life.[1-7]

To achieve this goal, an excellent knowledge of the anatomical structures of the brain is essential,[4,5,8-11] and the intraoperative technological support is pivotal.[6,7,12] The region of the insula is complex because of the vasculature and the integration of several functions (i.e. somato-motor, homeostatic, behavioral, emotional, and cognitive ones), and because of the relationship of the insular cortex with the basal ganglia and internal capsule in the depth of the Silvian fissure (**Figure 1A—D**, drawings by Dr. Alice Esposito MD). Intraoperative neurophysiological monitoring (IOM) plays a major role, as its use is associated with a reduction in neurological deficits in the postoperative period. As far as we know, amplitude reduction of the motor evoked potentials' (MEPs) signal over 50% of the baseline value[13] is associated with the presence of neurological damage, although this cut-off value is still debated.[14] Based on the surgical experience, this reduction occurs late and/or abruptly, not allowing the surgeon to act in time, changing the surgical strategy and preventing the neurological impairment. Therefore, the identification of signals that may constitute prewarning elements could allow the implementation of alternative surgical plans, thus making the excision of brain tumor lesions safer.

In this retrospective work, we considered patients with intra-axial lesions in the anatomic region of the insula, and we proposed an algorithm, based on machine learning analyses, to identify prewarning signals that anticipate the standardized warning sign, i.e. a decrease in MEPs signal amplitude over 50%.[14,15] This model has been elaborated to provide innovative technical aspects to consider in MEPs traces before amplitude reduction, and to modulate the surgical strategy, minimizing the risk of postoperative motor deficits.

MATERIALS AND METHODS

We designed a retrospective, monocentric clinical study, collecting data from patients with intra-axial insular lesions, who

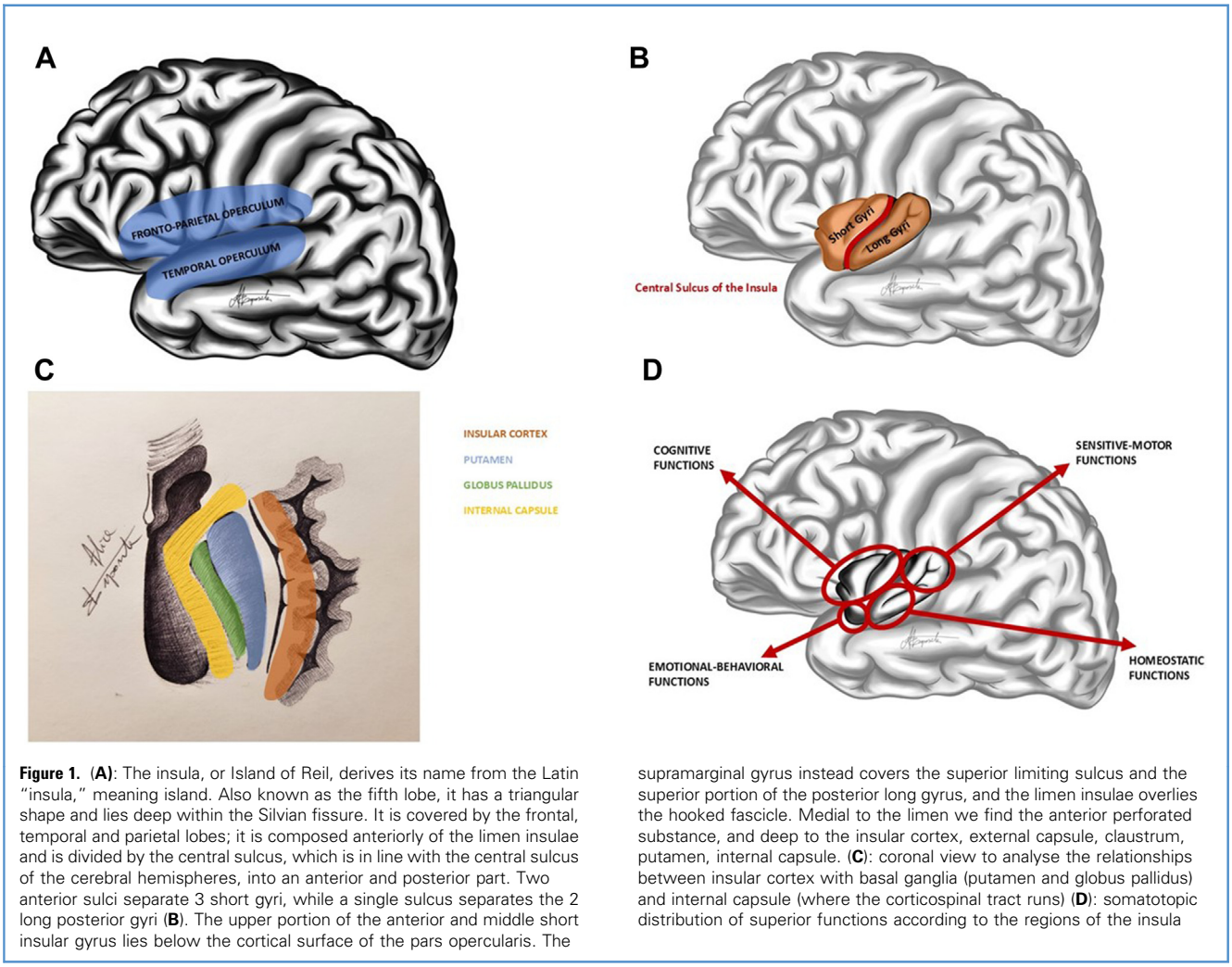

Figure 1. (**A**): The insula, or Island of Reil, derives its name from the Latin "insula," meaning island. Also known as the fifth lobe, it has a triangular shape and lies deep within the Silvian fissure. It is covered by the frontal, temporal and parietal lobes; it is composed anteriorly of the limen insulae and is divided by the central sulcus, which is in line with the central sulcus of the cerebral hemispheres, into an anterior and posterior part. Two anterior sulci separate 3 short gyri, while a single sulcus separates the 2 long posterior gyri (**B**). The upper portion of the anterior and middle short insular gyrus lies below the cortical surface of the pars opercularis. The supramarginal gyrus instead covers the superior limiting sulcus and the superior portion of the posterior long gyrus, and the limen insulae overlies the hooked fascicle. Medial to the limen we find the anterior perforated substance, and deep to the insular cortex, external capsule, claustrum, putamen, internal capsule. (**C**): coronal view to analyse the relationships between insular cortex with basal ganglia (putamen and globus pallidus) and internal capsule (where the corticospinal tract runs) (**D**): somatotopic distribution of superior functions according to the regions of the insula

underwent surgery between January 2023 and September 2024 at the Neurosurgical Department, University Hospital of Careggi, Florence.

Study Population

Intraoperative Neurophysiological Monitoring data of 350 patients, operated on for supratentorial intra-axial lesions were initially identified. From these, n = 43 patients with purely insular lesions were selected by collecting and filtering clinical, surgical and neurophysiological data. For each patient, MEP tracings were considered, especially those of the upper limb muscles. Thirteen (n = 13) patients were excluded since their MEPs tracings were not adequately interpretable. Finally, we considered a cohort of n = 30 patients with insular lesions and having MEPs tracks homogenously comparable. In addition, upper and lower limb motor impairment was assessed preoperatively and postoperatively (at 5 and 30 days). Muscle strength was measured by means of the Medical Research Council Manual Muscle Testing scale.[16] Follow-up was performed up to 30 ± 10 days postoperatively (clinical and radiological evaluation) (Figure 2 and Table 1).

Although motor function was evaluated for both upper and lower limbs, intraoperative MEPs from the lower limbs were excluded from the analysis due to the insufficient number of usable traces available in our patient cohort. This limitation could be related to the higher stimulation intensity required to evoke lower limb responses,[18] which often induces movements that may interfere with the surgical procedure and compromise the stability and interpretability of the recorded signals.

Data Analysis (Engineering Model)

Data analyses included MEPs of the upper limb, with a selection of specific muscles (i.e. common extensor digitorum, abductor pollicis brevis, biceps brachii). To define a MEP, a train of stimuli equal to n = 5, capable of evoking a motor response in the recorded muscle, was considered. All stimuli in groups of n = 5 that were not capable of eliciting a MEP were then eliminated. As there is considerable variability in the signals, we chose to use the Baseline, i.e. the first signal recorded after the dural incision, set as the Reference. The tracings were evaluated to identify the exact time of incision of the dura mater (recorded in the tracing), and then to identify the exact time of Baseline, excluding signals recorded prior to this time. The Baseline signal was therefore compared with all subsequently recorded MEPs, called Trials. Each patient has a different number of Trials, ranging from 10 to 900, depending on the duration of the surgical procedure. The analyses of MEPs which involved colleagues from the Department of Computer and Biomedical Engineering (Prof. Bocchi and his team), was conducted in 3 main steps: MEP signal representation, baseline-trial comparison using dynamic time warping (DTW), and classification of MEPs (Figures 3–5).

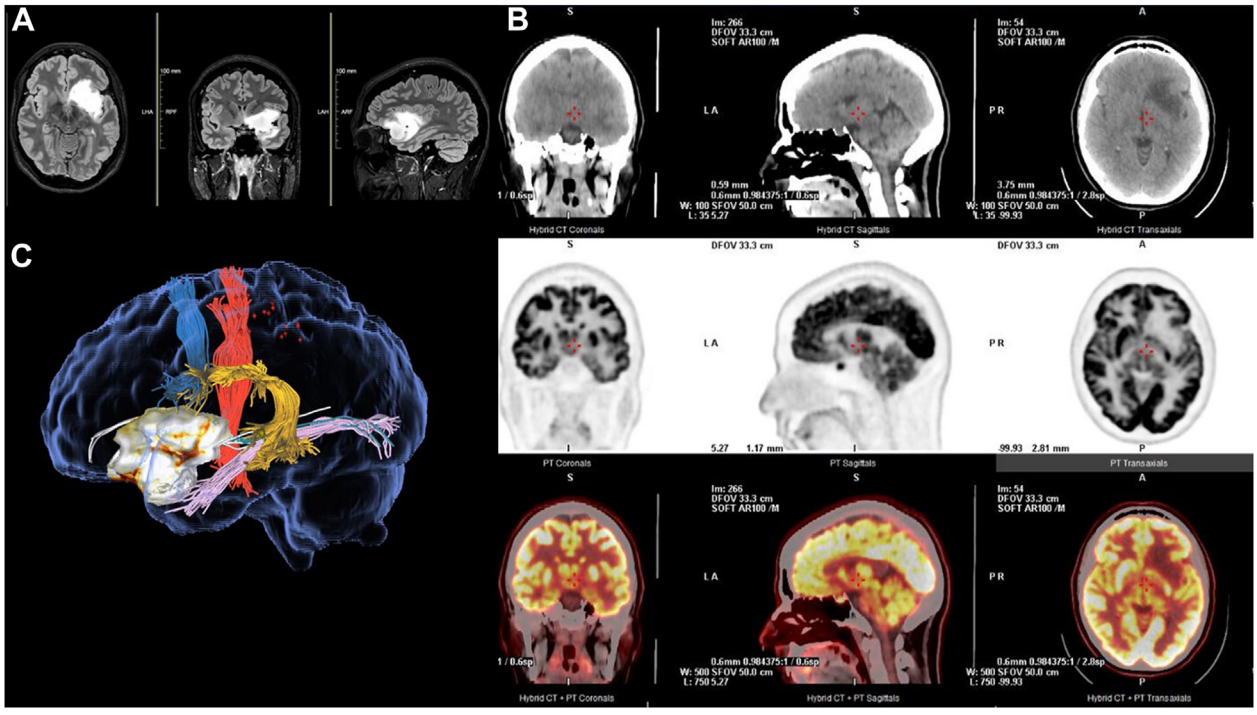

Figure 2. (**A**): MRI scan with FLAIR sequence showing an insular low grade glioma (axial, coronal and sagittal projections). (**B**): PET scan to study the metabolism of the lesion. (**C**): Final 3D reconstruction of the lesion, in relationship with the corticospinal tract (*red*), derived from the cortical points identified with navigated Transcranial magnetic Stimualtion (nTMS). Blue: Fronto-Aslant tract. *Yellow*: Arcuate Fasciculus. *Green*: Optic radiations. Pink: Inferior Longitudinal Fasciculus. MRI, magnetic resonance imaging.

Table 1. Patients' Characteristics

Pat Code	Age	Sex	Grade	MRC Preop	MRC Postop	Clinical Warning	Classifier Warning
"067"	77	f	HG	5/5	5/5	No	No
"031"	53	f	HG	5/5	2/5	No	Warning short abductor of the thumb 70
"063"	60	f	HG	5/5	5/5	Short abductor of the thumb 10:30:52 Trial 109	No
"077"	50	f	LG	5/5	3/5	No	Warning biceps 12
"044"	56	f	HG	5/5	5/5	No	No
"064"	76	f	HG	5/5	4/5	No	No
"055"	50	m	LG	5/5	5/5	No	No, warning biceps 75,85, Warning common extensor of the fingers 75
"071"	60	f	HG	5/5	4/5	biceps mep decrease, 11:40:05, Trial 94	Warning Short abductor of the thumb 53,120, Warning biceps 87,135
"053"	56	f	HG	4/5	4/5	No	No
"009"	75	f	HG	5/5	4/5	No	Warning biceps 21, warning common extensor of the fingers 21
"018"	18	m	HG	5/5	5/5	No	No
"019"	48	f	HG	5/5	5/5	No	No
"045"	36	m	HG	5/5	5/5	No	No, Warning biceps 21
"010"	54	F	HG	5/5	5/5	No	No
"014"	56	f	HG	5/5	4+/5	No	Warning Short abductor of the thumb 18
"015"	57	f	HG	2/5	2/5	Left upper limb, 11:22:45, Trial 94	Warning Short abductor of the thumb 64,90
"030"	73	m	HG	5/5	5/5	No	No
"076"	74	m	HG	5/5	5/5	No	No
"037"	72	m	HG	5/5	1/5	Mep decrease, 11:20:47, Trial 339	Warning abductor digiti minimi 74—297, Warning biceps 297—345, Warning common extensor of the fingers 427—434
"065"	67	f	HG	5/5	5/5	Short abductor of the thumb (left), common extensor of the fingers, 17:16:01	Multiple Warning Short abductor of the thumb
"004"	70	m	MTS	5/5	5/5	No	No
"069"	83	m	HG	5/5	5-/5	No	No
"032"	31	f	LG	5/5	1/5	lower limbs mep variability12:34:21, Trial 319	Warning short abductor of the thumb 43—365, Warning common extensor of the fingers 370,380
"086"	51	f	HG	5/5	5/5	No	No
"082"	31	m	LG	5/5	5/5	No	No
"020"	58	m	HG	5/5	5/5	No	No
"061"	64	m	HG	5/5	2/5	No	No
"072"	55	m	HG	5/5	5/5	No	Warning short abductor of the thumb 145—251
"035"	69	f	HG	5/5	5/5	No	Warning abductor digiti minimi 201—301, Warning biceps 298—315, Warning common extensor of the fingers 79—263
"025"	77	m	HG	5/5	5/5	No	Warning abductor digiti minimi 12, Warning biceps 11

Patient's code, age, sex, histologic grade of insular lesion (HG = high grade, LG = low grade, MTS = metastasis, sec WHO 2021[17]), Medical Research Council Scale (MRC) for muscle power assessment (0 = no contraction, 1 = flicker or trace contraction., 2 = active movement, with gravity eliminated, 3 = active movement against gravity, 4 = active movement against gravity and resistance 5 = normal power) and warning signs, analyzed for each patient included in the study.

MEPs Signal Representation

A representation of the Baseline and Trials MEPs was then obtained using the Fourier transform (FT).[19] This is a mathematical method to analyze functions and signals by converting them from the time (or spatial) domain to the frequency domain.[20] This transformation enables the decomposition of a signal into its

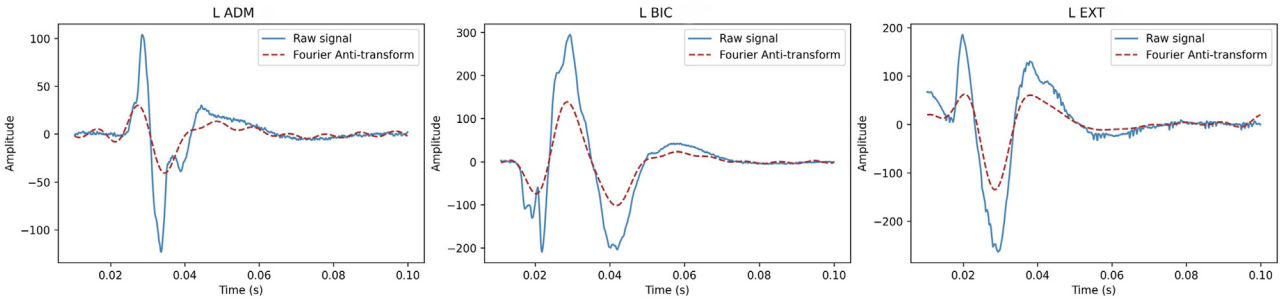

Figure 3. Example of the representation of MEPs by means of the Fourier antitransform for extensor digitorum, abductor pollicis brevis, and biceps brachii muscles.

constituent sine waves, characterized by specific amplitudes and phases, thus providing insights into the frequency components of a signal and their respective contributions.

Mathematically, the FT of a time-domain function f(t) is defined as:

$$F(w) = \int_{-\infty}^{+\infty} f(t)e^{-iwt}dt$$

where F(w) is the frequency-domain representation, w is the angular frequency and is the imaginary unit.

The inverse FT is used to reconstruct the original time-domain signal f(t) from its frequency-domain representation F(ω). It is given by:

$$f(t) = \int_{-\infty}^{+\infty} F(w)e^{iwt}dw$$

In our study, the FT was applied to both the baseline and trials signals. To reconstruct the signal, we used only the first ten Fourier coefficients, which represent the most significant low-frequency components. Higher-frequency components, which

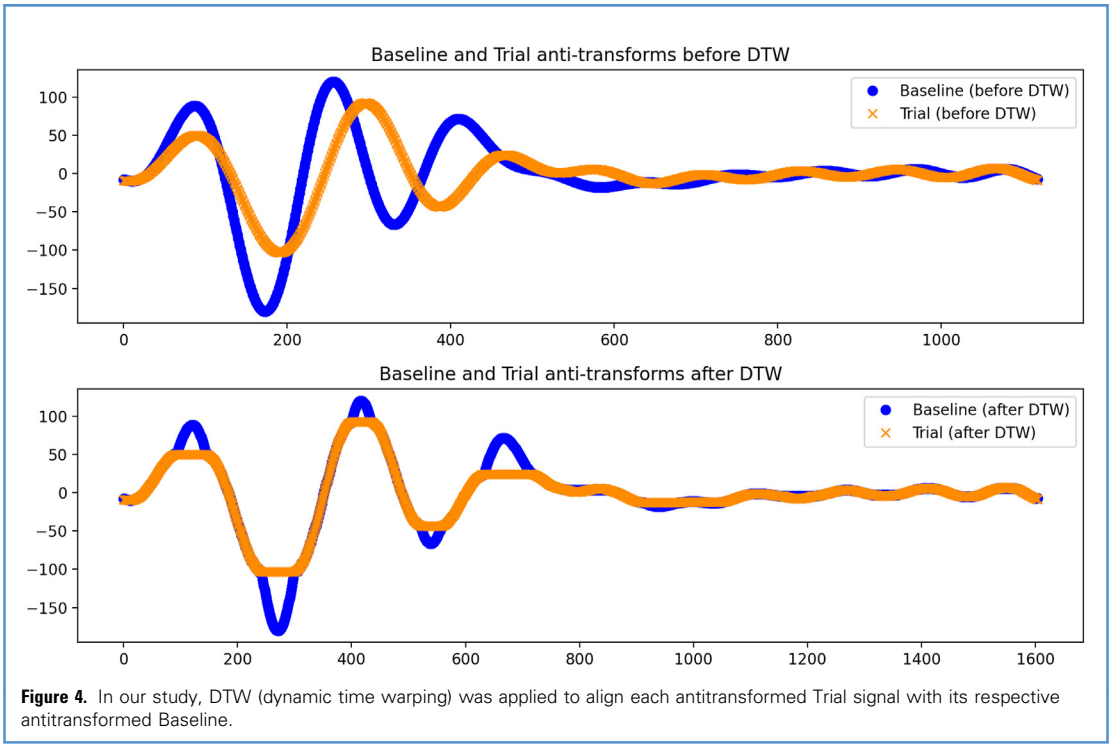

Figure 4. In our study, DTW (dynamic time warping) was applied to align each antitransformed Trial signal with its respective antitransformed Baseline.

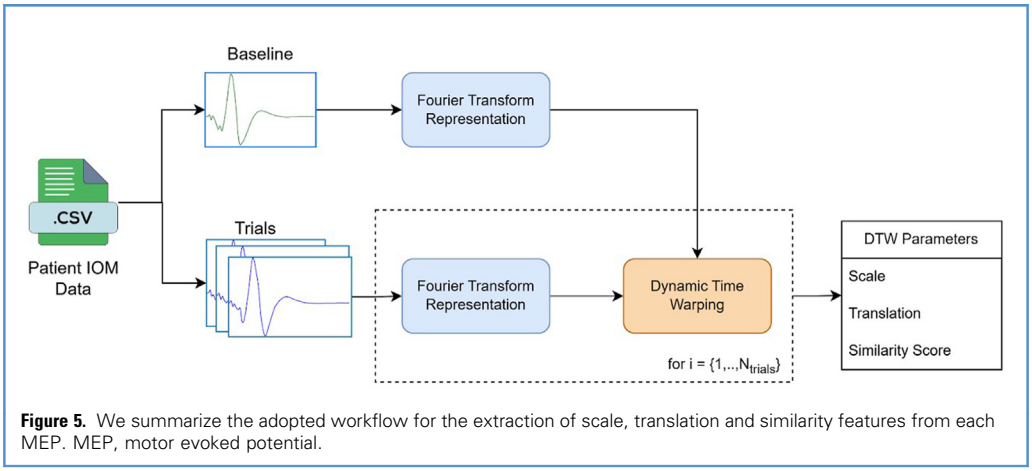

Figure 5. We summarize the adopted workflow for the extraction of scale, translation and similarity features from each MEP. MEP, motor evoked potential.

may include noise or rapid fluctuations, were excluded, thus resulting in a smoother representation of the signal.

Figure 3 shows an example of the representation of MEPs by means of the Fourier antitransform for extensor digitorum, abductor pollicis brevis, biceps brachii muscles.

DTW

After obtaining the representation of each MEP by means of the FT, the degree of similarity of each Trial signal to the associated Baseline was calculated using the DTW technique.

DTW is an algorithm designed to measure the distance between two sequences that may have differences in velocity or nonlinear variations over time.[21] The process involves the construction of a matrix in which each cell represents the distance between the points of 2 sequences. The algorithm provides a measure of similarity by exploring the possible combinations to find the optimal pathway that minimizes the total distance and guarantees the optimal alignment between sequences.

DTW is widely used in a variety of fields, including speech recognition and finance, but is also employed in the classification and analysis of biosignals, such as for the detection of heart rate variations, electrocardiogram segmentation and classification, and the comparison of genomic sequences.[22,23] In our study, DTW was applied to align each antitransformed Trial signal with its respective anti-ransformed Baseline[24] (Figure 4).

Three specific parameters were computed to characterize the degree of similarity between the two signals: scale and translation and similarity score. They were calculated based on the aligned signals obtained from DTW, with scale and translation specifically estimated using a linear regression approach.

- **Scale:** represents the proportional factor by which the Trial signal differs in magnitude from the Baseline. It was derived as the slope of the best-fit line in a linear regression model applied to the aligned Trial signal (x) and Baseline signal (y) [$y = \text{scale} \cdot x + \text{translation}$]. A scale value > 1 indicates that the Trial signal is smaller in magnitude than the Baseline, while < 1 indicates that it is larger.
- **Translation:** Represents the vertical shift required to align the Trial signal with the Baseline. It corresponds to the intercept of the linear regression equation above. A positive translation indicates that the Trial signal lies below the Baseline on average, while a negative value indicates that it lies above.
- **Similarity:** Quantifies the overall similarity between the two signals after alignment. It was calculated as the normalized DTW distance, divided by the length of the optimal warping path, providing a measure that accounts for differences in length and alignment between the signals. Lower similarity scores indicate greater resemblance between the two signals. Figure 5 summarizes the adopted workflow for the extraction of scale, translation, and similarity features from each MEP.

MEPs Classification

Subsequently, a Machine Learning method was developed to classify each Trial MEP into 2 classes: "no alarm" = class 0, "possible alarm" = class 1. As a classifier, we employed the well-known logistic regression model.[25] logistic regression uses the logit function, which is a sigmoid function, to model the relationship between the independent variables and the probability of the event of interest. Using this function, logistic regression maps a weighted linear combination of characteristics to real values between 0 and 1.The model produces as output a probability between 0 and 1, which can then be converted into a class (e.g. using a threshold of 0.5 to distinguish between the 2 categories). To train the model, we used a supervised learning approach, using the 50% decrease in amplitude as the reference label for each Trial MEP. Scale, translation, and similarity parameters obtained from DTW were used as input features for the classifier.

To ensure robust evaluation of the model, we implemented 5-fold cross-validation (Table 2). This approach involves partitioning the dataset into 5 subsets, or "folds." Specifically, the cross-validation was performed using a grouped splitting approach, where the split was based on the subject identifier. This ensures that all trials from the same subject are either in the training set or in the test set, but not in both. Such a strategy is

considered a best practice in cases where data points from the same group (e.g., subject) are likely to be correlated, as it prevents data leakage and provides a more realistic evaluation of the model's generalizability to new subjects. For each fold, the model was trained on 4 groups and tested on the remaining group, iterating this process 5 times such that each fold is used once as the test set. This method helps to reduce over fitting, i.e. when the model over fits training data and does not generalize well on new data and provides a more accurate estimate of model performance as it is based on multiple test samples. During each iteration, the accuracy, precision and recall of the model were computed. Finally, the average of the metrics across the five folds was calculated as a summary measure of the model's performance. Following the cross-validation, the predictions for each trial were extracted and analyzed to identify warning patterns. Specifically, we hypothesized that isolated positive predictions for the "possible alarm" (class 1) might not reliably indicate a meaningful clinical event, as they could reflect transient fluctuations or noise in the data. Conversely, a consistent pattern of consecutive class 1 predictions over time is more likely to represent a clinically significant event. Based on this assumption, a threshold was established such that a warning is flagged only if 5 consecutive predictions indicate a possible alarm.

RESULTS

Between January 2023 to September 2024, we identified a final cohort of n = 30 patients with insular lesions and interpretable MEPs tracings:18 patients were females and 12 males; 29 had primitive intra-axial lesions (25 high-grade gliomas, 4 low-grade) and 1 with metastases from pulmonary adenocarcinoma. Four had motor deficits pre-operatively, 7 developed motor impairment postoperatively (Table 1 with patients' characteristics). Histological diagnoses were based on the WHO 2021 Classification.[17,26,27]

Based on the previously defined parameters, the accuracy of our classifier was 91.45%. In addition to the MEP signal amplitude parameter, the 3 components of the DTW were also assessed to identify a possible prewarning sign (scaling, transition, similarity). Notably, in our case series, 76.7% (23/30) patients did not present motor deficits in the postoperative period, while 23.3% (7/30) reported transient deficits.

Table 2. Accuracy of Classifier

	Fold0	Fold1	Fold2	Fold3	Fold4	Average
Precision no alarm	0.99	0.92	0.92	0.86	0.92	0.92
Precision possible alarm	0.93	0.90	0.91	0.98	0.59	0.86
Accuracy	0.99	0.91	0.92	0.89	0.86	**0.91**

We performed a cross-validation to ensure that all patients could be used as test_files. The accuracy of our classifier was found to be 91.45%. To give the warning signal, we decided to put a threshold, i.e. after 5 trials of possible alarms, an early warning signal/prewarning signal (PWS) is created. Finally, we visualized the trend of the parameters in relation to the presence of a warning signal (WS).

Bold values represent the accuracy and the values of precision for each fold, with a final accuracy for the test classifier of 0.91: 91% (precise value: 91.45%).

Prewarning Signalling (PWS) versus Warning Signalling (WS)to Predict MEPs Drop

Among 30 analyzed traces, 15 patients were found to have WS-/PWS- (of which one patient had postoperative deficits), 9 patients had WS-/PWS+ (of which two had motor deficits), 5 patients had WS+/PWS+ (of which three had motor deficits), and one had WS+/PWS- (with motor deficits) (Figure 6A and B). Considering PWS versus WS, we calculated: Sensitivity 83.3%; Specificity 62.5%; positive predictive value (PPV) = 35.7%; negative predictive value (NPV) = 93.8% (Figure 6A). NPV resulted as the highest value, meaning that if PWS was not detected by our model, no WS was identified in the MEPs traces analyzed.

Sensitivity (83.3%): good value, indicating that most patients with postoperative deficits were correctly identified. Specificity (62.5%): less high; this means that there are false positives, and that some patients without deficits have been incorrectly classified as being at risk. PPV (35.7%): indicates that only 35.7% of patients with a positive prewarning showed a deficit, suggesting a rather high rate of false positives.

NPV (93.8%): very high, suggesting that if a patient has no prewarning, it is very likely that this patient will not show WS and postop motor deficit.

Predicted Postoperative Outcome with PWS versus WS

Considering the clinical outcome, we then calculated the same parameters evaluating PWS and clinical outcome: Sensitivity = 83.3%, Specificity = 62.5%; PPV = 35.7%; NPV = 93.8% (Figure 6B) Importantly, the NPV is superimposable, and reports very high values. This may suggest that PWS and clinical outcome have a significant correlation: no pre-warning signals during surgery can relate with a favorable clinical outcome.

We reported a significant example where PWS and WS were identified: (Figure 7):

Patient P037 (WS+/PWS+) reported postoperative deficits. There was a decline in amplitude in Trial 339, i.e. where the neurophysiologists reported the Warning (red vertical line), i.e. MEPs drop>50%, while the green vertical line (Trial 286) indicates our prediction [PWS at Trial 286, WS at Trial 339]. We highlight that PWS was able to anticipate the WS by at least 50 trials ahead of the drop in MEPs>50%, this latter was not recovered at the end of the intervention. The patient developed postoperative paresis in the right hemisoma, for which was progressively rehabilitated with physiotherapy and 7-days-cycles of neuronavigated transcranial magnetic stimulation (nTMS), so that one month after surgery the deficit was recovered. In addition to the amplitude parameter, the DTW parameters were also represented: considering these parameters, in addition to the "classic" amplitude parameter, made it possible to identify the prewarning sign. This is a retrospectively assessed case, so the pre-warning sign information did not lead to any change in the surgical strategy. However, the drop in MEPs >50 % likely led to a change in the surgical strategy with irrigation of the surgical field and use of papaverine for prevention of suspected arterial vasospasm. Analyzing the IOM trace, again changes in the trend of the parameters at the time of the alarm can be identified.

To sum up: The FT allowed us to model all the signals of the selected muscles, rather than using a specific model for each muscle. New parameters of the DTW were used (scaling, transition, similarity). This algorithm allowed the anticipation of the warning value (WS) thanks to a PWS: we demonstrated the

A	Warning +	Warning -
Pre-warning +	5 (3 deficit)	9 (2 deficit)
Pre-warning -	1 (1 deficit)	15 (1 deficit)

Se=83.3%
Sp=62.5%
PPV=35.7%
NPV=93.8%

B	Post operative motor deficit+	Post operative motor deficit -
Pre-warning +	5	9 (3 mild deficit)
Pre-warning -	1	15 (2 mild deficit)

Se=83.33%
Sp=62.50%
PPV=35.71%
NPV =93.8%

Figure 6. (**A**): Distribution of Patients according to PWS/WS (presence of prewarning/warning signs) Warning Negative/Pre-Warning Negative (15 patients): only 1 showed a postoperative deficit. Warning Negative/Pre-Warning Positive (9 patients): 2 patients with deficits are noted Warning Positive/Pre-Warning Positive (5 patients): 3 patients showed deficits, suggesting the presence of both warnings may have a significant association with clinical outcome. Warning Positive/Pre-Warning Negative (1 patient): this last patient showed no deficits Total numbers of true positive and negatives, Total numbers of false positive and negatives Final values of Se, Sp, PPV, NPV. **B**: Distribution of Patients according to PWS/clinical outcome (presence of postoperative motor deficits). Total numbers of true positive and negatives, Total numbers of false positive and negatives. Final values of Se, Sp, PPV, NPV. Sensitivity and NPV value are the same obtained considering the Distribution of Patients according to PWS/WS. Se, sensitivity; Sp, specificity; PPv, positive predictive value; NPV, negative predictive value.

superiority of PWS in identifying a possible MEPs drop and predicting the clinical outcome.

DISCUSSION

We know that MEPs monitoring is helpful to predict postoperative motor deficits in insular glioma patients.[28] Our work proposed an innovative model of IOM interpretation with anticipation of MEPs drop during insular surgery. Analyzing MEPs of the upper limb, with a selection of specific muscles, we found encouraging results, with a prewarning alert that can be provided, anticipating the clinical warning, normally set up at MEPs amplitude drop >50%. The real neurosurgical challenge is represented by the onco-functional balance, considering the "connectome-guided" surgical era.[1,2,29,30] IOM represents a valid tool to facilitate this aim.

Although MEP alarm criteria may have an important impact on the preservation of motor function in supratentorial neurosurgical procedures, no consensus exists regarding the optimal cut-off values and interpretation of MEP signal changes.[14] Therefore, we tried to give our contribution to this blurry and debated issue.

IOM – MEPs: Transcranial Cortico-Spinal Motor Evoked Potentials

MEPs are muscle-detectable responses after direct or transcranial electrical stimulation of motor pathways. Recording of m-MEPs using a stimulus train (or D-wave directly from the epidural space) can be used.[13,14,31,32]

Stimulus train technique (m-MEPs): a train of high-frequency, high-intensity stimuli is added to depolarize the spinal motor neurons and thus enable the recording of muscular responses. The inhibitory effects of anesthetics on the alpha motor neuron can be overcome by the temporal summation of excitatory postsynaptic potentials, elicited by the train of descending stimuli, activated by stimulation of the motor cortex. The m-MEPs allow the motor system to be monitored from the cortical motor neuron to the neuro-muscle junction. They also allow the assessment of damage lateralization and provide real-time data. However, they have limitations: they are abolished by curatives and volatile anesthetics; they cause movements that may interfere with surgery, and their disappearance is often disruptive.

As well known, reversible changes in MEPs do not mathematically correspond to postprocedural motor deficits, and irreversible changes in MEPs are correlated with a higher number of permanent rather than transient deficits, as reported in a review published in 2021.[14] In the available literature, MEPs drop correlation with clinical outcome showed values of Specificity and NPV high, while Sensitivity and PPV are low.[14] This is comparable to our preliminary results, since PWS demonstrated to be more reliable to anticipate MEPs drop and correlate with clinical outcome with higher Se and NPV. PWS has especially a high NPV, so if no PWS is detected, most likely no motor impairment occurs after surgery [NPV 93.8%].

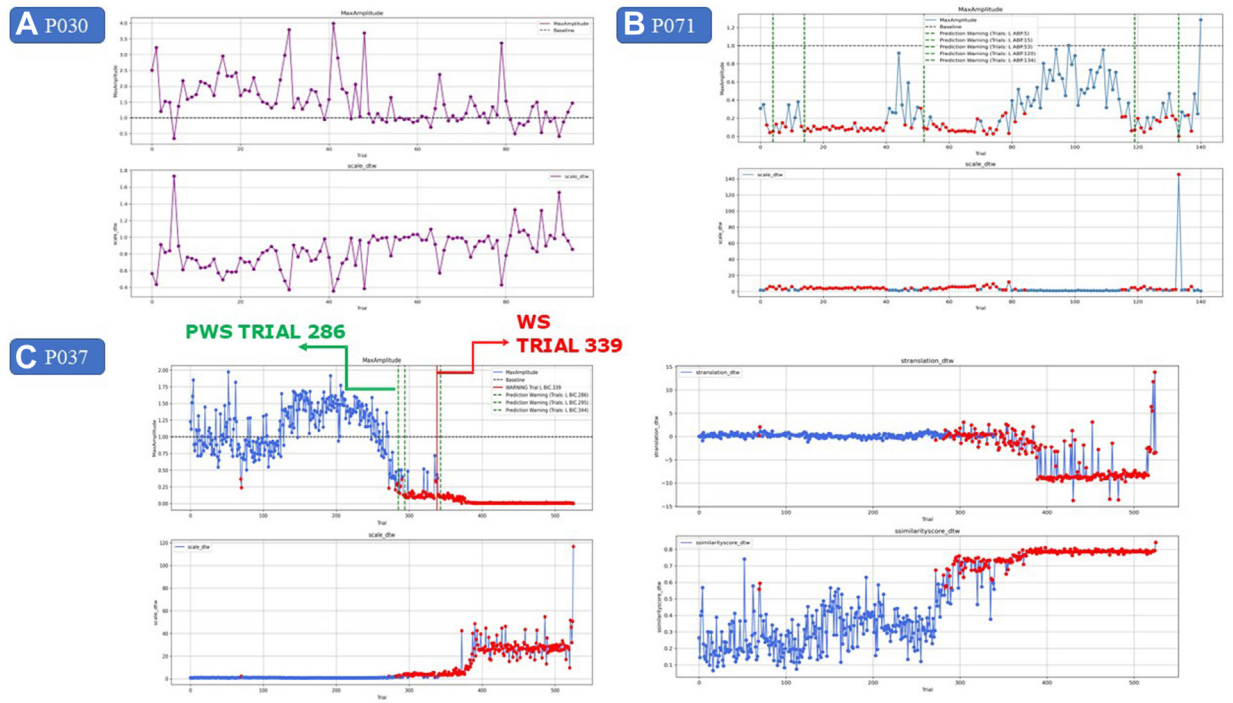

Figure 7. An illustrative case of the proposed PWS model P037 (WS+/PWS+): this patient reported postoperative deficits. During MEPs recordings, there was a decline in amplitude in Trial 339, i.e. where the neurophysiologists reported the Warning (*red vertical line*), i.e. MEPs drop >50%, while the green vertical line (Trial 286) indicates our prediction. It should be noted that PWS was able to anticipate the WS by at least 50 trials ahead of the >50% drop in MEPs (Trial 286 vs. 339). MEPs drop was not recovered at the end of the intervention. The patient developed postoperative paresis in the right hemisoma, for which was progressively rehabilitated with physiotherapy and cycles of neuronavigated transcranial magnetic stimulation (nTMS), so that one month after surgery the deficit was recovered. In addition to the amplitude parameter, the DTW parameters were also represented: considering these parameters, in addition to the "classic" amplitude parameter, made it possible to identify the prewarning sign. This is a retrospectively assessed case, so the pre-warning sign information did not lead to any change in the surgical strategy. However, the drop in MEPs >50 % likely led to a change in the surgical strategy with irrigation of the surgical field and use of papaverine for prevention of suspected arterial vasospasm. Analyzing the IOM trace, again it can be seen that there were changes in the trend of the parameters at the time of the alarm. MEPs, motor evoked potentials; DTW, dynamic time warping; IOM, intraoperative monitoring; PWS/WS, prewarning signal/warning signal.

It is important to highlight that, being polysynaptic, muscle MEPs are sensitive to anesthesia and neuromuscular blockade, and fade (gradually falling amplitudes and rising thresholds over the hours of surgery).[13,15,33] They are also nonlinear, so that disproportionately large decrements can result from small reductions of the number of conducting corticospinal axons or of LMN excitability, resulting in high sensitivity to central motors compromised particularly in the spinal cord. Finally, they are unstable, exhibiting substantial trial-to-trial variability.[15] These properties obviously challenge warning criteria and make muscle MEPs more sensitive than other commonly monitored evoked potentials.[13] Therefore, having new and more reliable alarm criteria for PEMs would be of extreme interest in intraoperative monitoring of the corticospinal pathway.

Surgical Strategies

Insular surgery is complex because of multiple neuro-vascular and functional characteristics of this anatomical area.[34-36] Diffusion tensor imaging (magnetic resonance imaging) and subcortical stimulation represent useful mapping tools to identify deep motor pathways, whose cortical mapping can be performed with nTMS,[37,38] when approaching the medial and dorsal borders of insular gliomas to establish functional boundaries for resection.[9] nTMS-based diffusion tensor imaging tractography enables somatotopic tract visualization and provides a valuable tool for preoperative planning, intraoperative orientation, and individual risk stratification.[39] While low-grade intrinsic insular and anaplastic tumors typically grow within the medial boundaries of the dislocated and compressed basal ganglia and external/extreme capsule, the demarcation is less evident in the dorsal-apical aspect of the tumor. Here, subcortical stimulation may prove particularly useful in detecting and preserving the motor fibres of the corona radiata and the apical internal capsule. However, direct trauma to the motor pathways seems to be an exception in insular tumor surgery. The main risk arises from the unavoidable exposure and manipulation of the lateral perforating arteries (LSAs) and the deep posterior M3 perforating arteries.[4,9,12,40,41]

Trauma and mechanical vascular spasm can be induced in the LSAs during dissection along the medial part of the tumor, starting immediately from their front-basal entry zone in the anterior perforating substance, while the deep M3 perforating arteries are involved during resection of the dorsal-apical component of the tumor. Trans-Sylvian dissection, if necessary, may also involve both the large M2 and M3 segments and the smaller insular perforating vessels[5,9]: in particular, LSAs, long insular arteries, and long medullary arteries (LMAs) that supply the pyramidal tract could be damaged in case of insular glioma.[42,43] The most critical vessels are the long insular artery and medullary arteries because of (i) the caliber, (ii) surgically unavoidable, and more susceptible to damage during tumor resection. However, the purpose of this preliminary work was to retrospectively analyze MEPs traces of purely insular lesions, to technically develop an algorithm aimed at identifying a reliable prewarning sign to anticipate MEPs drop in amplitude over 50%. The fact that the study is retrospective does not allow us to consider any specific role of the vascular preservation/cauterization and as a predictive element of postoperative outcome. In the next future, this element will be evaluated prospectively.

The loss of function after insular tumor surgery has typically been attributed to ischemic lesions in the corona radiata/internal capsule.[5-7,9,10,34,44-46] Direct lesions of the motor tract are much rare (mechanical surgical disruption or white matter fiber tracts infiltration). Any reduction in local motor tract perfusion (caused by perforating arteries or impaired local microcirculation due to traction/compression) would lead to transient oedema undetected on postoperative imaging or mild traction-related axonal damage and could thus be the cause of reversible MEPs deterioration. Local motor mapping by direct subcortical stimulation is not always able to detect such events, which may be induced by remote manipulation along the course of the above-mentioned vessels or by retraction. Even if the resection has progressed sufficiently to allow useful stimulation of the motor tract, the site of ischemia may still be proximal to the point of stimulation, which may then lead to false-negative results. In addition, surgical manipulation may induce vascular dynamics leading to motor tract ischemia later. Intermittent stimulation (mapping) could therefore miss adverse events, even though it is frequently performed during critical phases of the procedure. It appears that the near-continuous monitoring of motor pathway functions provided by MEPs recordings is particularly well suited to detect ischemia throughout the motor tract, even if it occurs far from the actual dissection site or with some delay. In insular lesions; therefore, transient deterioration of the MEPs is often related to the exposure of perforating vessels during dissection, whereas irreversible loss of the MEPs may be related to a deep stroke, which may occur even at a time when the critical resection has already been completed. So, the motor pathway ischemia sometimes becomes manifest when the causative mechanism is no longer completely reversible.[47]

At the same time, some authors report that there are more cases in which MEPs deterioration occurs early enough for the surgeon to change strategy and prevent a deficit. Monitoring MEPs; however, allows us to detect even transient alarm signals. This also implies a disadvantage of the method, as the cessation of surgery in critical areas could be prematurely induced by unstable MEPs responses.[47]

On the contrary, a sudden decrease or disappearance of motor potentials may be associated with damage, whether ischemic or mechanically direct, that is no longer modifiable, and the suspension or cessation of resection, irrigation or the application of papaverine, leads in any case to a postprocedural neurological deficit.

MEPs Prewarning Signalling

For this reason, the detection of PWS, by identifying early patterns of MEPs alterations, may be crucial to optimize surgical strategy and postoperative results.

In the currently available scientific literature, as far as we know, there are no works that have investigated MEPs changes to identify PWS in cranial surgery.

- In our work, the FT and DTW for analyzing muscle signals allowed a detailed evaluation of muscle responses, facilitating the identification of significant changes, introducing new parameters for evaluating MEPS (accuracy = 91.45%).
- In the analysis of the patients' distribution, we observed different categories according to the results of warning and prewarning. Finally, one patient with a positive warning and negative prewarning showed no deficit. (**Figure 6A** and **B**).
- Thus, considering PWS versus WS, we obtained a sensitivity of 83.3%, which indicates that a good proportion of patients with postoperative deficits were correctly identified by PWS. Particularly interesting is the NPV = 93.8%: this suggests that in the absence of the prewarning signal, very likely the patient does not present motor deficits.
- Considering prewarning in relation to the clinical outcome, the sensitivity and NPV values remained high, and specificity and PPV comparable. Interestingly, both considering PWS and WS in relation to the clinical outcome, the NPV remains superimposable with very high values. This may suggest a significant correlation between prewarning and clinical outcome.

Finally, our results are preliminary but encouraging data, which could have a significant clinical impact: PWS could anticipate the drop of MEPs >50% in several trials, having a high predictive value to predict the clinical outcome in a highly accurate model (accuracy: 91.45%).

Regarding intraoperative real-time applicability, we acknowledge that our current analysis was performed off-line on retrospectively collected data. However, in a prospective context, the system could be adapted to real-time conditions by applying the Fourier transform and DTW for feature extraction on each newly recorded MEP signal, followed by classification using a pre-trained model. The feasibility of this implementation depends on the processing time required, which seems compatible with surgical procedures where MEP monitoring is performed at longer intervals. In insular surgery, where stimulation may occur every 3–5 seconds, further evaluation is required to ensure that the method can meet these time constraints. However, preliminary estimates

suggest potential for real-time use, particularly in cases with longer stimulation intervals.

Limitations

- The small sample size
- The retrospective nature of the analyses
- Lower limb MEPs were excluded due to the low number of interpretable traces in the cohort
- All our analyses have been performed off-line, with a specific analysis of the MEPs traces by our Biomedical Engineering who were aware of the presence of a clinical warning sign, but worked on the traces to find any pre-wanting signal, relying on the created model. The future step is aimed at validating this model on a larger cohort and bringing it in the operate theatre, to use it online and detect a possible MEPs reduction that could lead to a postoperative motor deficit.
- The algorithm still needs to be refined to establish which specific MEPs parameters are associated with the prewarning signal.
- The off-line analyses performed on MEPs tracks.

CONCLUSIONS

Our retrospective single-center work was performed on 30 patients with insular lesions and homogeneously interpretable MEPs traces. We used signal modelling of the MEPs of the upper limb muscles by means of the FT and DTW to anticipate the WS (MEP drop >50%). Based on our preliminary data, we identified a reliable PWS to predict clinical outcome, and more accurate than WS to identify IOM variations. NPV and Sensitivity of PWS and WS are superimposable and reports very high values. This may suggest that PWS and clinical outcome have a significant correlation: no prewarning signals during surgery can relate with a favorable clinical outcome.

Further analyses are needed to validate our preliminary results. Finally, the study of the lower limb is necessary to validate our model and apply it prospectively.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Camilla Bonaudo: Conceptualization, Data curation, Formal analysis, Methodology, Validation, Writing — original draft, Writing — review & editing. **Sara Lombardi:** Conceptualization, Data curation, Formal analysis, Methodology, Validation, Writing — original draft, Writing — review & editing. **Giulia Sorbi:** Data curation, Formal analysis, Validation, Writing — original draft. **Eleonora Visocchi:** Data curation, Methodology. **Manuel Camelia:** Data curation, Methodology. **Anastasia Galletti:** Data curation, Formal analysis, Methodology. **Alice Esposito:** Data curation, Resources, Validation. **Agnese Pedone:** Data curation, Formal analysis, Validation. **Fabrizio Baldanzi:** Data curation, Methodology. **Simone Troiano:** Data curation, Methodology. **Cristiana Martinelli:** Data curation, Methodology. **Riccardo Carrai:** Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation, Visualization, Writing — original draft, Writing — review & editing. **Francesca Battista:** Data curation, Methodology. **Giovanni Muscas:** Data curation, Formal analysis, Methodology. **Simone Orlandini:** Investigation, Methodology. **Luca Campagnaro:** Data curation, Formal analysis. **Andrea Boschi:** Data curation, Methodology. **Serena Tola:** Data curation, Methodology. **Antonello Grippo:** Data curation, Methodology, Supervision, Validation, Visualization, Writing — review & editing. **Leonardo Bocchi:** Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Supervision, Validation, Writing — review & editing. **Alessandro Della Puppa:** Conceptualization, Data curation, Project administration, Resources, Supervision, Validation, Visualization, Writing — review & editing.

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