A discussion of statistical criteria for assessing awareness with SMR BCI after brain injury

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***Abstract*—This work discusses the implications of selecting particular statistical metrics and thresholds as criteria to diagnose awareness through Brain-Computer Interface (BCI) technology in patients with Disorders of Consciousness (DOC). We report a first analysis of a novel dataset collected to investigate whether a motor attempt electroencephalography (EEG) paradigm coupled with Functional Electrical Stimulation (FES) can detect command following and, therefore, signs of conscious awareness in DOC. We assessed 22 DOC patients admitted to the acute rehabilitation unit after a brain lesion over one or more sessions. We extracted EEG sensorimotor rhythms and performed a standard open-loop BCI pipeline evaluation, classifying motor attempt against resting-state trials. We validate this approach by correlating classification accuracy with the established clinical scale Coma Recovery Scale Revised. We employ a machine learning (ML)-inspired diagnostic criterion based on confidence intervals over chance-level classification accuracy and show that it yields more conservative and, arguably, reliable inference of Cognitive Motor Dissociation (CMD) by means of command-following, neuroimaging-based tools, compared to diagnoses based on clinical assessments or criteria examining the statistical significance of brain features across different mental states.**

***Index Terms*—disorders of consciousness, awareness, brain-computer interface, motor attempt, chance-level**

I. Introduction

Victims of traumatic brain injury or cerebrovascular accidents are prone to neurological disorders, including DOC that affect a patient's awareness of themselves and their environment. Consciousness can be classified through two components; arousal (being alert, awake and attentive) and awareness (perceive, feel and be cognizant of events) [1]. DOC are characterised by disruptions along these two components. Brain injuries may leave the victim in a coma (characterised by no eye opening, or no meaningful interaction with environment), in a so-called Vegetative State (VS), characterised by eye opening, but absence of purposeful responses, or in a Minimally Conscious State (MCS) which comprises a spectrum of conditions characterized by increased, even if minimal, environmental awareness compared to VS [2]. As such, coma can be described as the physical absence of arousal and thus awareness. Whereas VS, nowadays preferably termed Unresponsive Wakefulness Syndrome (UWS), can be defined as the recovery of arousal in the absence of any physical sign of awareness [1].

Diagnosis of these patients is mainly done through clinical instruments such as the Coma Recovery Scale-Revised (CRS-R) and the Glasgow Coma Scale (GCS) [3]. However, these diagnostic tools suffer great limitations [4]–[6]. Most importantly, due to the fact that they are strongly dependent on the patients' ability to elicit motor responses, they are particularly vulnerable to "false negative" (type-II) errors [5]. Literature suggests that up to 37-43% of patients with DOC may be misdiagnosed [3], [7], [8]. Several studies have early postulated that awareness or intentionality may manifest even in the absence of motor functions [9]–[12]. To confirm this hypothesis and improve diagnostic accuracy in DOC, researchers have proposed several techniques relying on neuroimaging. In seminal works, the authors of [10] and [11] showed that functional Magnetic Resonance Imaging (fMRI)-based assessment could reveal cases that had been erroneously categorised as UWS. These and other studies employing functional or electrophysiological brain imaging [6], [13] have provided mounting evidence that covert awareness may be concealed by a patient's inability to produce voluntary motor output spontaneously, or in response to commands and/or stimulation, a situation identified as CMD [14], [15]. Cases of CMD where the afflicted individual is known (or likely) to maintain high-level cognitive function are referred to as (complete or incomplete, depending on whether there is residual motor activity and/or spared communication channels) Locked-in Syndrome (LIS). It naturally follows that, in LIS, assuming intact or nearly intact cognition and vigilance, imaging-based paradigms can be further leveraged to enable independent communication by converting a diagnostic paradigm from open-loop ("offline" brain activity processing, no patient feedback) to closed-loop (real-time, "online" processing with feedback). Effectively, there exists an apparent and recognized affinity between neuroimaging-based diagnostics for DOC and BCI in both formalization and purpose [9], [16], which accounts for a "'de facto' merge of the two fields [6].

Functional imaging has offered the first breakthrough in this research line [10], denoting that an–assumed–VS patient was observed to be aware via the use of fMRI, since areas of the motor cortex were determined to be active when the patient was instructed to execute motor tasks [10]. fMRI has dominated and is still widely in use in this domain [17]–[20], as it is still broadly accepted that high resolution imaging (including Positron Emission Tomography (PET) [21]) offers greater possibilities for discerning even the slightest evidence of awareness of people with DOC. However, EEG is gradually emerging as the method-of-choice, offering similar results with fMRI [22] while being less expensive, always non-invasive and less obtrusive, portable and more practical [6], [23]–[27]. Certain studies have obtained comparable results in overlapping patient samples employing both fMRI and EEG [20]. Hybrid neurological methods [28] and more invasive electrophysiological techniques [29] have also been used to detect consciousness in DOC patients.

Another important distinction in the typology of imaging paradigms for DOC is whether the protocol targets some kind of passive brain process in response to stimulation that may correlate with awareness [5], [30], [31], or more actively seeks to assess the ability of the patient to engage into command-following or, in general, tasks requiring higher-level cognitive processing, like in a typical BCI. The former approaches have the advantage of exerting lesser demands on the subject, and thus may be less sensitive to a patient's current vigilance and cognitive capacity; on the other hand, demonstrated command-following ability of an assumed DOC patient is rightfully considered as a more definite marker of this person's awareness. As recently surveyed in [6], not only are EEG-based DOC diagnostics gaining ground , but more recently, the paradigms and ML architecture of the neighboring BCI field are adopted, which has naturally led to the assimilation of evaluation metrics regularly used in BCI: predominantly, classification accuracy between samples/trials of different mental tasks.

Neuroimaging-based diagnosis for DOC entails a fundamental caveat: a profound lack of ground truth. In other words, there is no diagnostic metric that can be considered as golden standard and which can serve as the absolute measure of evaluating novel approaches. Established clinical scales like CRS-R and GCS are still the most reliable and accepted, but the aforementioned suspected tendency of Type-II errors is what has motivated the search for alternative approaches in the first place. New clinical instruments like the Motor Behaviour Tool (MBT) [32] have also been introduced to address this fallacy, but they require themselves validation by independent, reliable methodologies. Effectively, in the absence of any universally acceptable standard, researchers seek "weak" validation by showing that a new method tends to agree with the outcomes where an ensemble of other methods seem to also converge to. For this reason, most literature (as also this work) reports findings contrasted to CRS-R, GCS and different imaging methods simultaneously. In that respect, a major projected advantage of command-following neurodiagnostics for DOC is that, by being extensible to closed-loop control BCI systems [6], [33], [34], they offer a possible communication channel to "unlock" conscious/aware LIS/CMD patients, who can then self-confirm a CMD diagnosis and, thus, progressively the validity of the overall approach.

Still, the lack of unquestionable ground truth renders the problem of neuroimaging-based DOC diagnosis to essentially be a "game of thresholds". More specifically, one can identify two main avenues for identifying awareness with brain imaging, command-following paradigms: either statistical testing is performed on brain features quantifying whether these are "'significantly different' between an active/target and a control/non-target mental task or response [11], [15]; or, an ML model is employed to classify brain patterns into the corresponding categories, and the classification accuracy is thresholded to assess whether a patient is identified as CMD or unaware/DOC. In the latter case, the expected accuracy value of a random classifier $1/N_c$, where N_c the number of classes present in the classification task may be used as threshold [33], with a variety of other classification-based decision rules proposed, among which thresholds corresponding to some confidence level that the denoted accuracy is not generated by a random classifier is a popular choice [27], [35]–[38].

The present work offers two distinct contributions to the literature. First, we report on the preliminary analysis of a novel dataset of 22 DOC patients assessing command-following with a standard EEG, Sensorimotor Rhythms (SMR), BCI-based processing loop, with the additional novelty of coupling movement commands with rich, somatosensory afferent feedback through FES, conjectured to increase patient vigilance and potentially also enhance awareness through feedback training. Second, we compare the inference output obtained on our data through different criteria including clinical scores, classification accuracy with chance-level control and per-feature significant differences with/without correction, and discuss the implications of these choices in the reliability of inferences over the different aspects of DOC diagnosis.

II. Materials and Methods

A. Patients and data

We assessed 22 patients (6 female, age 20 to 75), admitted to the Acute Neurorehabilitation Unit of the Lausanne University Hospital (CHUV), Switzerland. Written consent to participate in the study was acquired from the relatives. The experimental protocol (No 142/09) was approved by the ethical committee of the Canton of Vaud, Switzerland and adheres to the principles of the declaration of Helsinki. Data of another 10 enrolled patients were discarded due to presence of strong artifacts on the EEG signal. In total we report on 131 runs/blocks over 47 recording sessions by 22 DOC patients. All patients underwent repeated behavioral CRS-R scoring during their hospitalisation by medical doctors. MBT evaluation was done at admission.

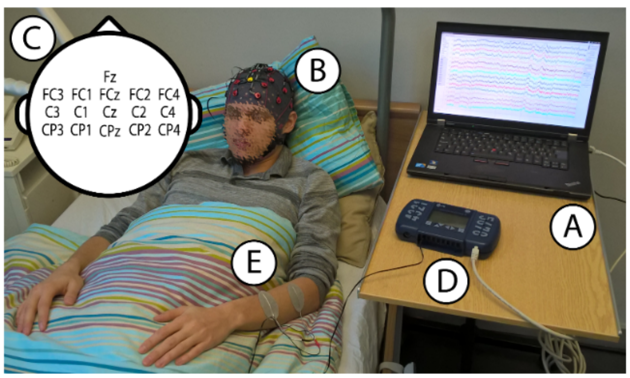


Fig. 1: Experimental setup: (a) Protocol presentation/recording computer, (b) EEG cap and g.Nautiulus amplifier, (c) EEG layout, (d) FES device, (e) FES electrodes.

B. Experimental setup

During an EEG session, patients were lying in their beds. EEG signals were recorded with a 16-channel active electrode montage in the standard 10-20 positions covering the motor cortex (see Fig. 1). The amplifiers used were a g.USBamp sampling at 512 Hz, and a g.Nautilus wireless amplifier sampling at 500 Hz (g.tec, Schiedlberg, Austria). Biphasic FES was implemented with one bipolar channel through a Motionstim 8 device (MEDEL, Hamburg, Germany). The FES train was delivered at 35 Hz, lasted 2 s and consisted of a 1 s ramp with linearly increasing pulse width from 10 to 500 μs, followed by 1 s of continuous stimulation.

C. Experimental protocol

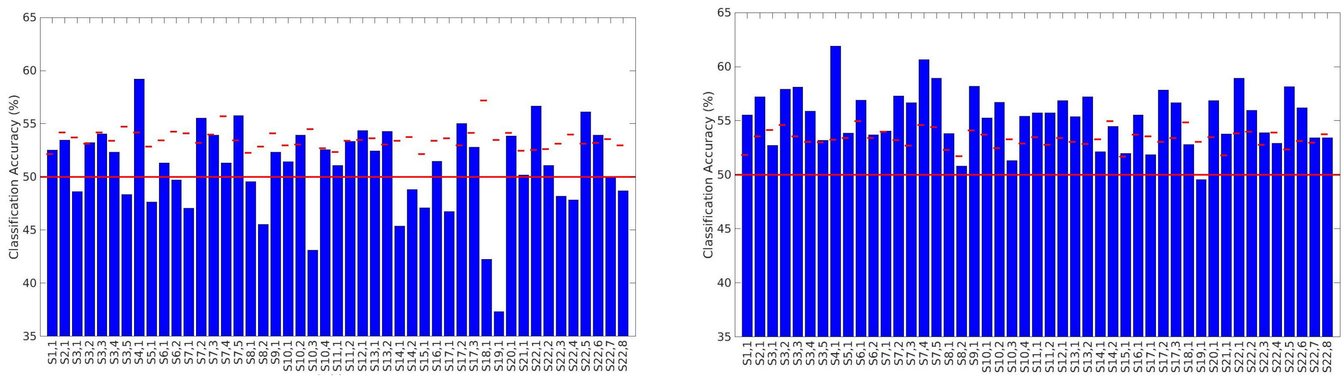
Each patient participated in 1 to 8 sessions (average 2.2), which comprised 1 to 5 runs (average 3). Each run was about 6 minutes long and consisted of 15 motor attempt trials randomly interleaved with 15 rest trials. Before each session, patients were woken up and given verbal instructions to either attempt unilateral hand movement on the (most) affected side, or rest following the corresponding auditory cues. Two FES electrodes were placed on the extensor digitorum communis of the same-side arm forming a single bipolar channel and the FES amplitude was adjusted so as to achieve a full hand extension movement. FES amplitudes varied between 8 and 15 mA. Each trial lasted 5 seconds and started with an auditory cue played via in-ear headphones, which prompted (in French) the patient to either move (”bougez”) or to not move (”ne bougez pas”). Only motor trial offsets were followed by FES.

D. Data analysis and evaluation

Data analysis was applied separately for each session. EEG signals were treated with FORCe artifact removal [39], DC removal and cross-Laplacian spatial filtering. Power Spectral Density (PSD) of all channels was computed over 1 s sliding windows with 62.5 (g.USBamp) or 100 ms (g.Nautilus) shift in the band [4-48] Hz with 2 Hz resolution. For each session, the 5 best features (pairs of channels/bands) were selected after Fisher score ranking, excluding candidate features on (vulnerable to artifacts) channel Fz and bands outside the physiologically relevant μ (8-12 Hz) and β (18-24 Hz) bands. Classification accuracy was computed with leave-one-trial-out cross validation employing Quadratic Discriminant Analysis (QDA) decoders. The distribution of random classification (chance) accuracy is estimated with 100 repetitions of classification with random label permutation. A patient was considered as CMD/DOC if accuracy in the session exceeded/fell-short-of a chance-level criterion derived as the 99.9% percentile of the corresponding session-wise random accuracy distribution. Exceeding this threshold substantiates adequate SMR modulation during motor attempt trials to significantly (in the statistical sense) differ from resting trials, thus implying that the patient was consciously reacting to the instruction to move. This criterion reflects a p-value threshold of $p = 0.001$ for extracting statistical significance of classification accuracy (i.e., the probability that this accuracy level can be derived by an ignorant classifier is less than 0.001). We compare inferences acquired with this method (termed CVA) with CRS-R- and MBT-based assessment, as well as with a “feature significance”-based method (termed FS) similar to the one described in [15]. Specifically, we subject each candidate PSD feature to an unpaired, two-sided Wilcoxon rank-sum test. We compare different versions of this approach with Bonferroni ($FS - BF - N$), False Discovery Rate (FDR) (($FS - FDR - N$)) and without correction ($FS - NC - N$), and demanding either a single or N consecutive bands ($N = 1, 3, 7$ reported) on at least one channel to be significant (corrected/uncorrected $p = 0.05$) in order to infer CMD. The Methods are further elaborated in [40].

III. Results

Fig. 2 presents the main, classification accuracy results. As illustrated in Fig. 2a for the proposed CVA approach, out of 47 sessions and 22 subjects, 12 (25.5%) sessions belonging to 9 (40.9%) different subjects would lead to a CMD diagnosis,

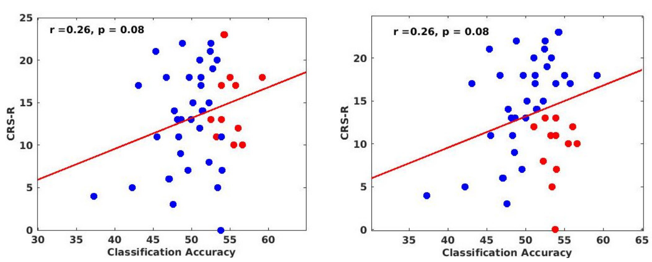


(a) Leave-one-trial-out cross validation accuracy with chance-level.

(b) Leave-one-sample-out cross validation accuracy with chance-level.

Fig. 2: Classification accuracy across all subjects and sessions. Chance-level in session-wise red limit lines.

as the session-wise accuracy (blue bar height) exceeds the permutation-based chance-level for $p = 0.001$ (bar-wise red lines). Importantly, patients $S5, S20$ for whom both CRS-R and MBT agree are in coma and thus act as controls in our dataset, are indeed found to be DOC (non-CMD) with CVA. Fig. 2b shows the equivalent results with conventional, leave-one-sample-out cross-validation. The large PSD window overlapping imposed here leads to large dependence of consecutive feature values, resulting in dependent samples present in both training and testing folds. This yields seemingly over-optimistic results, where in 37/47 (78.7%) sessions and 19/22 patients (including coma patients $S5, S20$ and excluding $S14, S18, S19$ for whom the correct CVA evaluation yields the same outcome) a CMD diagnosis would be obtained.



(a) Above-chance accuracy.

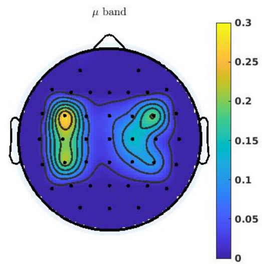
(b) Accuracy>50%, CRS-R<12

Fig. 3: Correlation of classification accuracy with CRS-R.

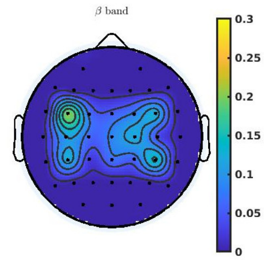
Fig. 3 shows an emerging (marginally non-significant) correlation between classification accuracy and CRS-R ($r = 0.25693$, $p = 0.081268$). In Fig. 3a we mark in red, sessions found to be CMD with CVA and in 3b sessions with above-average accuracy and below-average CRS-R (13.8, hence, the possible "false negatives"). This seems to further validate the outlined approach, since a fairly strong CRS-R vs accuracy correlation indicates both metrics capture the same main trends of awareness in a patient population, but the known Type-II error shortcoming of CRS-R prevents this correlation from being stronger and statistically significant.

Fig. 4, provides favourable evidence for the soundness of this analysis, confirming by example that patient sessions resulting in CMD diagnosis and exhibiting high classification accuracy will also show the anticipated, neurophysiologically relevant SMR patterns of activity, similar to those manifesting in able-bodied BCI users performing motor attempt or imagery [40]. Specifically, "textbook" strong, lateral Event-Related Synchronization/Desynchronization (ERD/ERS) activation (Fisher score feature discriminancy between motor attempt and resting trials) manifests in the μ (8-12 Hz) and β bands (14-28 Hz) (mostly contralateral, with a weaker ipsilateral component) of CMD patients $S4, 1$ and $S7, 2$. On the contrary, coma patient $S5$ and the participant exhibiting low accuracy, show no signs of relevant SMR modulation, and are classified as DOC with our CVA method.

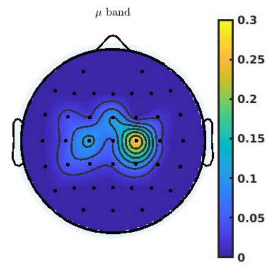
Fig. 5 shows that the MBT assessment classifies all, but two ($S5, S20$) patients as CMD, suggesting that this tool may be over-sensitive and prone to Type-I, false positive errors. It is confirmed that CRS-R fails to identify potential CMD cases at admission (of note, the % illustrated in these first two–pre-EEG evaluation–bars refer to the 22 subjects, not the 47 sessions referred to by the rest of the bars in the figure). CRS-R seems to misdiagnose CMD even as some of the patients seem to gradually emerge from UWS/MCS, since only $S17$ is determined by CRS-R to be CMD both at admission and after 3 EEG sessions. This subject is confirmed to be CMD by CVA along with another 8 subjects (having at least one above-chance session each, 12/47 in total): $S1, S3, S4, S7, S10, S12, S13, S17, S22$. These 9 subjects were considered as either MCS or even UWS by CRS-R. Overall, CVA seems to be able to reveal several latent CMD and potential LIS cases missed by CRS-R, while being more conservative than the MBT. On the contrary, all variations of the method relying on per-feature extraction of statistical significance, even when using conservative Bonferroni–as opposed to FDR–correction and cluster-based analysis requiring larger band ranges to be consistent, seem to be over-optimistic in diagnosing awareness. Of note, even the most conservative versions $FS-BF-7$ and $FS-FDR-7$ consider coma patient $S5$ as being CMD, contradicting all other tools (CRS-R, MBT and CVA).



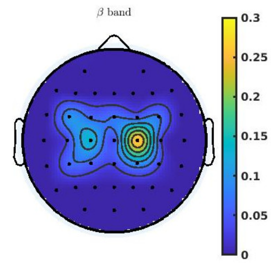
(a) μ band for Subject $S_{4,1}$



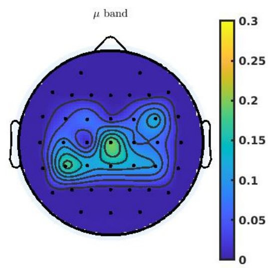
(b) β band for Subject $S_{4,1}$



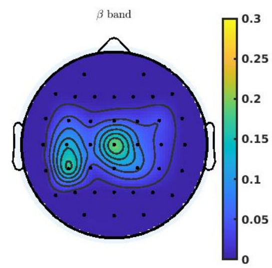
(c) μ band for Subject $S_{7,2}$



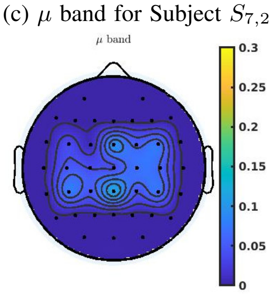
(d) β band for Subject $S_{7,2}$



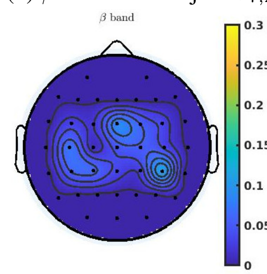
(e) μ band for Subject $S_{5,1}$



(f) β band for Subject $S_{5,1}$



(g) μ band for Subject $S_{19,1}$



(h) β band for Subject $S_{19,1}$

Fig. 4: Topographic SMR distribution for CMD ($S_{4,1}$, $S_{7,2}$), coma ($S_{5,1}$) and UWS ($S_{19,1}$) subject/sessions.

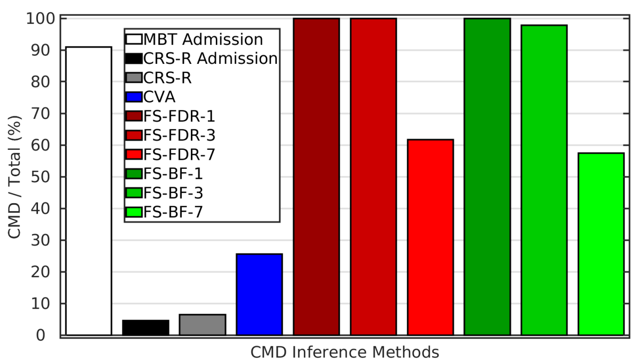


Fig. 5: Comparison of DOC diganosis with clinical, feature-based and chance-level accuracy-based methods.

IV. Discussion

Our analysis of a new DOC dataset verifies the literature regarding the potential of EEG paradigms, in particular those based on open-loop SMR BCI processing, to detect CMD in populations considered DOC with conventional clinical assessment. Although further analysis will be needed to support such a claim, it could be that the novelty of including the FES as feedback modality may account for the larger percentage of CMD misdiagnosis uncovered here compared with some of the similar works in the state-of-the-art [35], [37].

This work underlines several potential red flags on the statistical analysis often employed for evaluating DOC with neuroimaging. First, we have shown how subtle mistakes like violating fold-independence in cross-validation can cause the diagnostic capacity of an otherwise sound method to collapse. Most importantly, our results suggest that criteria relying on solid measures of confidence intervals around chance-level ML-based classification accuracy extraction will tend to be more conservative than those based on extracting statistically significant differences of individual features, even when the latter are subjected to the strictest correction. These results seem to be confirmed by the majority of literature which tends to be more (potentially, extremely) optimistic when adopting the latter approaches [15] compared to the former [27], [35]–[38]. Last but not least, we confirm all these works that already pinpointed the need to define and employ chance-level bounds as opposed to merely using the expected accuracy value as threshold [33].

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