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# Investigating the synergistic neuromodulation effect of bilateral rTMS and VR brain-computer interfaces training in chronic stroke patients

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## Abstract

*Objective.* Stroke is a major cause of adult disability worldwide, resulting in motor impairments. To regain motor function, patients undergo rehabilitation, typically involving repetitive movement training. For those who lack volitional movement, novel technology-based approaches have emerged that directly involve the central nervous system, through neuromodulation techniques such as transcranial magnetic stimulation (TMS), and closed-loop neurofeedback like brain-computer interfaces (BCIs). This, can be augmented through proprioceptive feedback delivered many times by embodied virtual reality (VR). Nonetheless, despite a growing body of research demonstrating the individual efficacy of each technique, there is limited information on their combined effects. *Approach.* In this study, we analyzed the Electroencephalographic (EEG) signals acquired from 10 patients with more than 4 months since stroke during a longitudinal intervention with repetitive TMS followed by VR-BCI training. From the EEG, the event related desynchronization (ERD) and individual alpha frequency (IAF) were extracted, evaluated over time and correlated with clinical outcome. *Main results.* Every patient's clinical outcome improved after treatment, and ERD magnitude increased during simultaneous rTMS and VR-BCI. Additionally, IAF values showed a significant correlation with clinical outcome, nonetheless, no relationship was found between differences in ERD pre- post- intervention with the clinical improvement. *Significance.* This study furnishes empirical evidence supporting the efficacy of the joint action of rTMS and VR-BCI in enhancing patient recovery. It also suggests a relationship between IAF and rehabilitation outcomes, that could potentially serve as a retrievable biomarker for stroke recovery.

## 1. Introduction

Stroke is a cerebrovascular medical condition that disrupts blood flow to the brain, causing brain tissue death, and loss of function. The two main causes are the blockage or rupture of a blood vessel, causing ischemic or hemorrhagic stroke, respectively [1]. This condition may have several consequences such as the loss of movement capability, depression and cardiac damage, and overall, consequences depend on the location size and time since the stroke, especially those related to motor impairment [2]. It is understood that 70%–85% of first strokes are accompanied by hemiplegia, the paralysis of the muscles of the lower face, arm, and leg on one side of the body [3]. In this regard, although the majority of patients slightly

recover the ability to walk, motor control of the arm and hand often remains impaired [4].

Stroke rehabilitation should start as early as possible to benefit from the earlier effects of neuroplasticity, the brain's ability to reorganize itself in response to internal or external stimuli [5]. Concretely, stroke patients' neurological recovery reaches a plateau after 6 months [6], and studies demonstrated that the majority of the recovering process occurs in the first 3 months following stroke onset [7, 8]. Regarding upper limb rehabilitation, as current practice, therapies such as mirror therapy [9] and constraint-induced movement therapy (CIMT) [10] are performed at hospitals and at home to return quality of life to patients. These rely on the repetition of task-oriented exercises to regain motor control and are performed in hospitals and at home during physical and occupational therapy [11].

To improve rehabilitation efficacy and allow treatment of patients with more severe initial paralysis who lack volitional movement, technology-based approaches for directly training the central nervous system (CNS) have been utilized. Specifically, neurofeedback training such as brain-computer interfaces (BCIs) can help patients to self-regulate their brain function, providing a form of non-invasive and unobtrusive neuromodulation. For instance, BCIs can decode brain activity to infer user intent and generate appropriate outputs [12]. Electroencephalography (EEG) is the most common brain activity measurement modality, measuring the combined electrical post-synaptic activity of thousands of neurons with scalp electrodes. EEG is portable, relatively low-cost, and it has good temporal resolution. By using EEG signals, BCI leverage neurofeedback to promote targeted neural states via the mechanism of operant conditioning [13]. Its objective is to facilitate the training and modulation of neural oscillatory patterns to induce enduring alterations, leveraging cerebral neuroplasticity [14]. Moreover, in rehabilitation, the practice of motor imagery (MI) and motor observation (MO) is commonly used in BCI training since it leads to the modulation of the sensorimotor brain rhythms [15]. This brain rhythm modulation is primarily detected during task-based EEG (i.e. when the user is actively moving or imagining movement) [16], and has been shown to correlate with motor recovery [17]. Furthermore, the practice of MI and MO in BCI training can benefit from several techniques to provide proprioceptive feedback such as functional electrical stimulation (FES), robotic support, and virtual reality (VR), in order to close the intention-action-perception loop of the trained movement.

Concretely, VR simulations enable user interaction with objects and events through various sensory channels, such as visual and auditory. Moreover, VR can provide motivation mechanisms composed of many gamification elements, which can increase the adherence of the patient to the treatment [18]. Also, VR leverages ecological validity, or the realism degree to which the design of an evaluation setup is equivalent to a real world scenario [19], to enhance the realistic experiences in the therapy [20], allowing patients to train tasks that are transferable to their daily lives.

Transcranial magnetic stimulation (TMS) represents a non-invasive method of neuromodulation, utilizing electromagnetic induction to elicit neuronal currents. This technique involves the application of a pulsating magnetic field via a coil, thereby inducing electrical currents in subjacent neural structures [21]. TMS can be administered as a single pulse or as a series of pulses, the latter known as repetitive TMS (rTMS). The precise mechanisms underlying rTMS are hypothesized to be modulating neuronal excitability, synaptic plasticity, and neurotransmitter dynamics. In fact, by inducing the formation of repetitive electrical currents in the brain cortex, long term changes occur in the cortical excitability, which last further than the stimulation time [22]. rTMS can be categorized based on frequency: low-frequency rTMS (approximately 1 Hz) is associated with reduced cortical excitability, whereas high-frequency rTMS (approximately 10 Hz) enhances it [23]. Regarding the intensity at which rTMS is delivered, the resting motor threshold (RMT) is frequently the point of reference. This represents the minimum stimulus intensity required to evoke a motor evoked potential (MEP) of more than 50 $\mu$V in a resting muscle of the patient in at least half of the trials [24]. The stimulus is applied to the motor hotspot, corresponding to the scalp location where the greatest amplitude and minimum latency of the MEP are elicited. There is an inter-individual variability on the motor hotspot location and, therefore, TMS is used to find the optimal position for the electrode. Furthermore, a low resting motor threshold is associated with high cortical excitability and vice versa, as this signifies that a small stimulation intensity is sufficient to elicit the desired response [25]. RMT was also correlated with upper limb (UL) function following stroke, and it appears to be an UL motor function predictor for stroke sequelae recovery [26]. Moreover, a single session of subthreshold rTMS (90% of the RMT) to the primary motor cortex (M1) has provided the induction of a long-lasting muscle-specific increase in resting corticospinal excitability [27], defined as the strength of the response of cortical neurons to a given stimulation [28]. In that case it appears that for rTMS applied to M1 at intensities just below RMT, the frequency mainly defines the direction of change in the corticospinal excitability (inhibition of excitation), whereas the magnitude and duration of the

after effects seem to depend mainly on the number of pulses applied [27].

To study the effect of the combination of both therapies, one could use the EEG data, besides taking advantage of clinical scales evaluation. Indeed, some longitudinal BCI articles refer to post-hoc analysis, to discover brain biomarkers of stroke recovery and BCI functioning. The most commonly analysed EEG feature in this regard is the event-related desynchronization (ERD) due to its intuitive nature and physiological connection to MI and stroke rehabilitation [29–33]. ERD is defined as a relative reduction in the frequency power, when compared to a resting state baseline, as a result of motor preparation, execution and imagination. ERD reflects a decrease in rhythmic neural activity associated with an internal or external event, measured as a percentage of power relative to baseline, or the EEG signal just prior to the movement when the patient is resting [34]. This desynchronization occurs primarily in the $\alpha$ (around 8–13 Hz) and $\beta$ (around 13–30 Hz) EEG bands and the topography is fairly localized, most predominantly over the contralateral sensorimotor (centrotemporal area) region during motor preparation, and extending bilaterally symmetrically with movement initiation [35]. Consequently, in the case of MI, imagining left or right movements results in desynchronization of $\alpha$ and $\beta$ rhythms over the contralateral primary motor cortex area [15]. Many studies have demonstrated that stroke patients are able to evoke these features, nevertheless their minimum $\alpha$ ERD is less negative than in healthy subjects [36]. These studies, in addition, refer to ERD as being more predominant in the unaffected hemisphere than in the affected hemisphere, when dealing with hemiplegic stroke patients. Repeated MI training in both healthy and stroke patients has been shown to increase ERD magnitude compared to no training, supporting the use of ERD to evaluate rehabilitation [37]. Thus, increased ERD magnitude can be understood as an increase in corticospinal excitability both in healthy and stroke patients [38].

Finally, while ERD is a common feature to evaluate rehabilitation effects, other features, such as individual alpha frequency (IAF), may provide valuable information about patients' state and the underlying principles of therapy success or failure. IAF is the frequency value corresponding to the maximum power in the EEG frequency spectrum between 8 and 13 Hz, when eyes are closed. Low IAF is associated with slower information processing, reduced memory performance, and lower general intelligence [39]. IAF decreases with age and is associated with cognitive decline in various disorders, including stroke, ADHD, and depression [40]. IAF also demonstrates a correlation with task engagement and preparation [41]. This correlation is modulated by both the subject's baseline neural state and their cognitive investment in the specific task, increasing during the task, when compared to rest [42]. Thus, IAF can be a useful neurophysiological biomarker of brain function. Understanding the impact and variation of IAF within BCI training is important, but there is limited research on IAF variation in stroke patients, making this a novel field to explore. There are various factors which influence the IAF, both intra and interindividual. Concerning interindividual variability, genetic predispositions and age are the most significant determinants. Additionally, intra-individual factors comprise memory performance and the velocity of information processing [43], alongside the presence of neurological pathologies. Notably, IAF values have been observed to increase from childhood to adulthood, followed by a decline commencing around the age of 40 [40]. Furthermore, in a paper by Cecere *et al* (2015) the temporal window of patients could be entrained by stimulating the occipital lobe with tACS at IAF and surrounding frequencies [44], therefore allowing for the hypothesis that the modulation with rTMS in the M1 it could provide an entrainment effect as well.

This paper aims to investigate the synergistic neuromodulation effect of VR-BCI and rTMS, both in terms of clinical outcome of the patient and brain activity. Specifically, it aims to explore the relationship between EEG features such as ERD or IAF and the clinical outcome of patients, and identifying possible brain biomarkers for stroke recovery.

## 2. Methods

### 2.1. Participants

Ten hemiplegic stroke patients (4 female, aged 62.30 $\pm$ 8.33) were recruited at the Brain Damage Unit of Beata María Ana Hospital in Madrid, Spain, and approved by an independent Clinical Research Ethics Committee at Hospital Universitario de Fuenlabrada, with approval reference number: 19/11. The protocol was prospectively registered in clinicaltrials.gov with unique identifier NCT04815486. The inclusion criteria for participant recruitment encompassed individuals aged 18 years and above, diagnosed with ischemic or hemorrhagic stroke by a neurologist through at least one imaging test, and with a minimum duration of 3 months since the onset of the stroke. Additionally, participants were required to demonstrate proficiency in reading and writing, possess cognitive capacity to comprehend and execute tasks (assessed with a Token Test score $>$11), and maintain stable antispastic medication for at least 5 days. Exclusion criteria comprised a history of seizure or brain aneurysm, presence of pacemakers or metal implants on the head, use of medication pumps, as well as abnormal muscle tone in the wrist and hand. Furthermore, individuals with pre-existing neurological conditions, previous strokes resulting in sequelae, aphasia following TMS post-stroke, hemispatial neglect, visual impairments, and

**Table 1.** Patient demographics, sex, age, stroke state, type of stroke and time since stroke.

| Patient | Sex | Age | Affected limb | State | Type | TSS (months) |
|---|---|---|---|---|---|---|
| **P1** | M | 62 | Left | Chronic | Cortical/Ischemic | 18 |
| **P2** | M | 62 | Right | Chronic | Cortical/Ischemic | 13 |
| **P3** | M | 64 | Left | Chronic | Cortical/Hemorrhagic | 37 |
| **P4** | F | 79 | Right | Chronic | Subortical/Ischemic | 11 |
| **P5** | M | 65 | Right | Chronic | Cortical/Hemorrhagic | 8 |
| **P6** | M | 60 | Left | Subacute | Cortical/Ischemic | 6 |
| **P7** | F | 56 | Left | Chronic | Cortical/Ischemic | 46 |
| **P8** | F | 53 | Left | Chronic | Cortical/Ischemic | 121 |
| **P9** | M | 51 | Left | Subacute | Subcortical/Ischemic | 4 |
| **P10** | F | 71 | Right | Chronic | Cortical/Ischemic | 13 |

*Notes:* PX—Patient X, M—Male, F—Female, TSS—Time since stroke.

flaccid paralysis at Brunnstrom's stage = 1 were excluded. The sample exhibited a relatively balanced distribution of paralysis classification, with 4 cases of right limb paralysis and 6 cases of left limb paralysis, and a mean duration since stroke onset of 27.70 ± 35.51 months (table 1).

### 2.2. Clinical assessment

All patients were evaluated clinically in the first session and one week after the conclusion of the treatment period. Specifically, the clinical evaluation involved the Fugl-Meyer Assessment (FMA), the Montreal Cognitive Assessment (MoCA) and the Resting Motor Threshold (RMT) of the contralesional (unaffected) hemisphere.

The FMA is a 226-point multi-item Likert scale that evaluates motor function recovery after hemiplegic stroke. The scale is divided into five domains, and the upper extremity section (FMA-UE) in the motor domain is scored on 33 items. Each item is scored from 0 to 2, totaling 66 points, in which higher scores reflect better function [45]. The disparities in scores on the scale between pre-intervention and post-intervention were employed as markers for clinical assessment of upper limb motor recovery. The Minimally Clinically Important Difference (MCID), is the minimal improvement in the score for a given clinical scale, the patient considers worthwhile, after a treatment. For a chronic stroke patient and for the FMA-UE scale, the MCID value lies between 4.25 and 7 [46].

The MoCA is a widely used screening assessment for detecting cognitive impairment. Its scores range from 0 to 30, and a score higher than 26 is considered to be normal. In this case, patients initial MoCA score was an average of 23.40 ± 3.97 points, which reveals mild cognitive impairment [47].

### 2.3. TMS

The TMS procedure started with a single pulse TMS in order to acquire the individual RMT using Magstim Rapid2, a device with an air-cooled 70 mm figure-of-eight magnetic stimulator coil. The coil was placed in the M1 of both hemispheres and the stimulation output intensity was used to reach RMT and calculate the parameters for the stimulation sessions.

In those sessions, the rTMS delivery occurred following a bilateral stimulation paradigm. For the unaffected hemisphere, the intensity was set at 90% of the RMT of the unaffected hemisphere, administered at a frequency of 1 Hz, with a total of 1000 pulses and a 50 s inter-train interval. After a 5-min rest period, stimulation of the affected M1 area took place at 90% of the RMT from the unaffected hemisphere, at a frequency of 10 Hz a total of 1000 pulses, and a 5-second inter-train interval.

### 2.4. EEG acquisition

The EEG recordings were performed using a 64 active electrode system from Brain Products (figure 1(A)), equipped with a low noise bio-signal amplifier and a 24 bit A/D converter at 256 Hz (figure 1(E)). EEG data acquisition and real-time processing was performed through the OpenVibe platform [48].

### 2.5. VR-BCI setup

For the BCI training, NeuRow was used, a VR-BCI training paradigm which provides embodied feedback by rendering a virtual body from a first-person perspective, synchronously with vibro–tactile feedback [33]. The visual feedback was delivered through a head-mounted display (HMD) with 90° horizontal field-of-view (figure 1(B)), and the haptic feedback was delivered through the VR controllers (figure 1(C)). The protocol involved a fixation cross followed an arrow, before initiating the left or right movement of the virtual arm (figure 1(D)). Then, during the VR-BCI sessions, the first part of data acquisition, the training session, was the recovery of EEG data to train a classifier to distinguish between left and right motor imagery of the arm using the NeuRow VR-BCI paradigm, and following the same protocol as a previous pilot study [33].

### 2.6. Experimental protocol

All patients followed a general protocol which lasted for 4 weeks. Specifically, in the first two weeks,

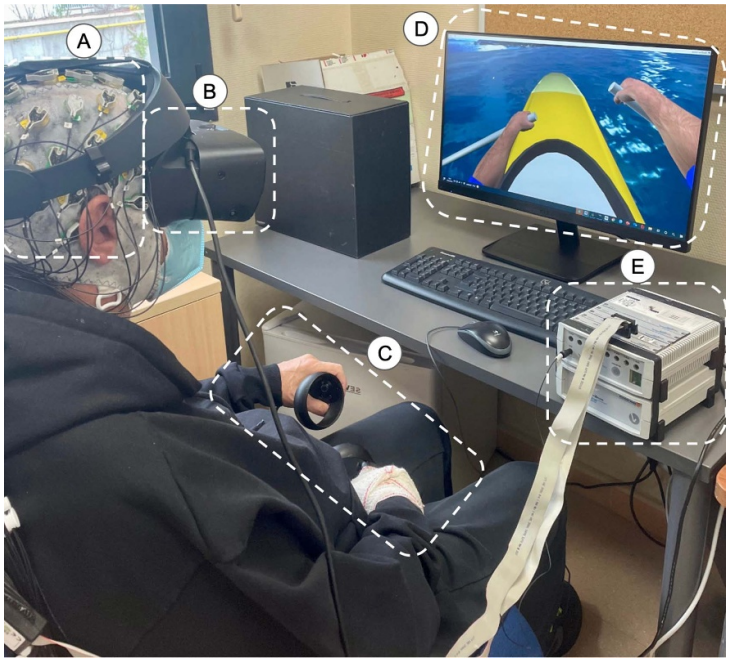



**Figure 1.** VR-BCI Experimental setup: (A) EEG cap with 64 active electrodes; (B) VR Head-Mounted Display; (C) Vibro–tactile feedback; (D) VR Training Task; (E) EEG amplifier.

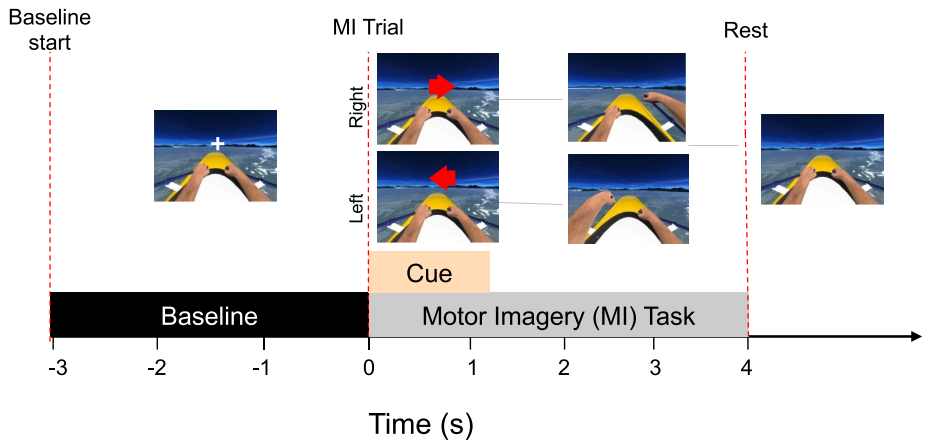



**Figure 2.** Representation of a trial of MI for ERD extraction, with referenced timepoints. At $t = 0$ s, the cue for which movement to imagine was provided to the patient, for 1.25 s. The baseline preceded the trigger for 3 s and then the MI task was performed for 4 s after the trigger.

patients underwent 10 sessions of rTMS (every business day) simultaneously with 6 sessions of VR-BCI (on Monday, Wednesday and Friday). In the last two weeks, subjects only underwent 6 sessions of VR-BCI. Regarding the timing of delivery of sessions, rTMS was delivered firstly, and the sessions took around 40 min. Before each VR-BCI session, resting state data were acquired in the beginning of the first and last sessions, a 2 min eyes-open eyes closed. Moreover, each patient was firstly told to perform the rowing movement with both upper limbs, and helped in the paretic side, as a motor priming strategy for augmenting further the MI training efficacy during VR-BCI [49] (figure 2). Given the exploratory aim of this study, a control group was not included. The primary focus was to evaluate the feasibility and immediate effects of TMS on BCI task performance. Future investigations will incorporate control groups for robust validation and extension of the present findings. The study employed consecutive sessions to optimize participant recruitment and minimize potential performance confounds introduced by extended breaks or external interruptions. This approach, while acknowledging limitations, facilitates a controlled comparison within a consistent time frame.

### 2.7. EEG preprocessing pipeline

EEG signals were processed in MATLAB (R2022b; The MathWorks, Inc. Natick, MA, USA), using

the EEGLAB toolbox[4] (v2022.0; Swartz Center for Computational Neuroscience, San Diego, CA, USA). Initially, the EEG signals were downsampled to 128 Hz and filtered with a bandpass filter between 1 and 40 Hz. Then, to remove artifacts from the EEG signals, the Artifact Subspace Reconstruction (ASR) algorithm was used, followed by the Independent Component Analysis (ICA). Next, using the ICLabel tool [50], the artifactual components obtained from ICA were labeled and removed. Further, the signal was re-referenced using the Common Average Reference (CAR). Finally, the signal was segmented into epochs between −3 and 4 s, where the first 3 s were deemed the baseline. The time-frequency plots and time domain of each signal were inspected and, if any glaring artifact was present, it was removed manually.

### 2.8. ERD extraction

We calculated the event-related synchronization/desynchronization (ERS/ERD) across the $\alpha$ band (8–12 Hz) as the percentage decrease in power relative to the baseline by using the following equation (2), where $P_{MI}$ and $P_{BL}$ represent the power of a given frequency band during the MI and during the baseline, respectively based on [51].

$$\text{ERS/ERD} = \frac{P_{MI} - P_{BL}}{P_{BL}} \times 100\%. \quad (1)$$

In order to obtain the ERD values, firstly, an ERSP (Event Related Spectral Perturbation) matrix was obtained from the time domain EEG signal using the *newtimef* function from EEGLAB. This function automatically computes the relative power in decibels for each time point in relation to the average power of the whole defined baseline, for each frequency at 0.5 Hz steps. The baseline is different for each frequency and, in this case, starts 3 s before the trigger/cue and finishes at $t = 0$ s.

The function automatically presents the final ERSP values for each frequency and time point as an average of the relative power of all 21 epochs recorded during the training period, and the baseline as the average power of each time point of all 21 epochs, as well. Afterwards, an ERD matrix (as percentages of baseline power) was computed from the ERSP matrix (in decibels) according to the following equation:

$$\text{ERD}(\%) = \left(10^{\text{ERSP}/10} - 1\right) \times 100\%. \quad (2)$$

The resulting matrix's lines were averaged in the frequencies corresponding to 8 to 12 Hz (the alpha band) resulting in a vector of ERD for the alpha band, per time. This vector was then averaged from 0.5 s since the trigger ($t = 0$ s), until the 4 s mark, in order to account for reaction time and prolonged ERD. According to Klimesch *et al* (2007), ERD has a late onset at about 0.2 s post stimulus and a peak (maximal ERD) close to 0.35 to 0.6 s [52]. Having in mind the involved individuals are stroke patients, the ERD onset was considered to be slightly later. These values were extracted from the C3 and C4 electrodes if the imagined movement was corresponding to right or left hand, respectively, because the ERD is present in the primary motor cortex contralateral to the motor imagery performed. This is a fixed and uniform approach to the to the computation of ERD, which is less precise than computing ERD individually for each patient and session, nonetheless, it provides a comparable approach to processing performed in literature.

Furthermore, for each patient, the $\Delta$ERD was also extracted, by subtracting the final session's ERD with the first session's. Due to missing sessions, for patients 5 and 7, session 12 was replaced by session 11, and for patient 9, session 1 was replaced by session 4.

Finally, to obtain the vector of the ERD per time stamp, besides averaging the values in the alpha band in the ERD matrix, the vector was subjected to a sliding window of length of 86 samples, which corresponds to the number of samples in the baseline. This method, will result in the value of the ERD becoming 0% at $t = 0$ s due to it resulting of the average of the 86 points prior, which is always 0. The reason for using a sliding window was due to the noisy nature of the EEG, which was masking the real and theoretical time profile of ERD, not only due to the hospital setting but also due to the cortical integrity of patients being damaged.

### 2.9. IAF extraction

To extract IAF, the EEG signal was analysed from the resting state EEG acquired before the first and last sessions. This data was pre-processed as the training data, except for the ICA and epoching steps, to remove the majority of noise. Then, the algorithm developed by Sousa (2019) [53] was run through, which employs *findPeak* function from the *restingIAF* MATLAB toolbox[5] from Andrew W. Corcoran. The goal of this function is to find the peak in the $\alpha$ frequency band power spectrum.

In general, the IAF is extracted from parietal and occipital regions of the brain and, in this case, it was extracted from Pz, P1/2, POz, PO3/4, Oz, O1/2 electrodes. Afterwards, the IAF values obtained for each patient from each of these electrodes were averaged, and the resulting value was assumed to be the patient's IAF at that stage.

### 2.10. Statistical analysis

In order to ensure the statistical validity of the results, the Lilliefors-corrected Kolmogorov-Smirnov

[4] github.com/sccn/eeglab.

[5] github.com/corcorana/restingIAF.

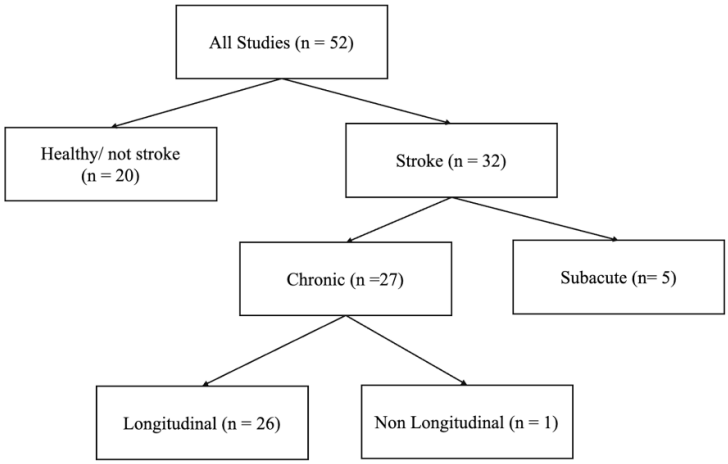



**Figure 3.** Guideline scheme for the choice of literature articles to which this study was compared.

test [54] was applied to look for non-Gaussian distribution ($p < 0.05$). Following the confirmation of a non-Gaussian distribution, Spearman Correlation [55] was used to perform correlations in the results. Furthermore, when deemed necessary, to further illustrate the correlation in a visual form, in addition to the Spearman Correlation test, a linear regression was performed in the same set of data, using the *polyfit* function from MATLAB, for an order 1 polynomial. Also, the Mann–Whitney U Test [56] was utilized to check for statistical significant difference between two independent groups, and Wilcoxon [57] between two dependent groups, such as the same patients in different treatment time points (both statistical tests with the threshold being $p < 0.05$). Furthermore, each statistical comparison only involved pairwise comparisons between two distributions simultaneously and, therefore, multiple comparison corrections were not required for the analysis.

Additionally, besides the Spearman correlation, the ERD data for all sessions was modelled using a two-stage linear modelling. Given the necessity of averaging epochs to achieve reliable ERD estimation (as per Pfurtscheller et Da Silva 1999, [51]), our dataset effectively has a single ERD measure per session for each patient, limiting the application of mixed effects models at the epoch level. In that regard, mixed effects models were applied at the session level, to account for between-subject and within-subject variability across sessions. The protocol chosen was derived from studies encountered, such as Ray *et al* (2020) [58]. The first step was modeling the data, the mean ERD across time, for the 10 patients using a mixed effects model, assuming the general interception (initial ERD) and the general slope (ERD progression) are fixed effects, whereas the individual ERD dynamics (initial value and ERD evolution across training) were introduced random effects of the model. In that case, the model provided these two coefficients per patient, the individual model slope as the ERD progression and the individual model intercept as the particular initial ERD. Then, extracting the individual dynamics, there were fed into a linear regression model, to predict the $\Delta$ FMA-UE from each of the initial ERD values and ERD evolution across time, as well as the interaction between these two ERD dynamics. Finally, to validate the significance of the model, the F-test was performed [59].

### 2.11. State of the art

To evaluate how this paper positioned itself in terms of state of the art, focusing on comparing the standard recovery degree of improvement for stroke patients undergoing BCI training, a literature review was conducted using Google Scholar and PubMed databases. The goal was to identify longitudinal studies using BCI therapy to treat chronic stroke patients, and the diagram for the line of thought is represented in figure 3. Although this paper focuses on NeuRow, which uses the VR feedback modality, all feedback options were considered viable due to the lack of studies specifically investigating VR feedback. From the 26 studies which followed the keywords 'longitudinal', 'chronic' and 'stroke patients', the ones which made reference to the FMA-UE scale as a clinical evaluation metric were organized, and the results were compiled, to compare to this experiment. Given these studies are characterized by different sample sizes and inclusion criteria, although focusing in similar experiment longevity and similar stroke patients, this analysis should be taken with caution.

## 3. Results

Results are divided into three parts. First, presenting the impact of the intervention in terms of clinical scales, next the impact in EEG activity, and lastly, the relationship between clinical outcome and EEG features.

**Table 2.** Clinical scales scores for FMA-UE, MoCA and RMT.

| Patient | FMA-UE Pre | FMA-UE Post | ΔFMA-UE | MoCA Pre | ΔMoCA | RMT Pre | ΔRMT |
|---|---|---|---|---|---|---|---|
| **P1** | 31 | 61 | 30 | 29 | −1 | 75 | −13 |
| **P2** | 9 | 21 | 12 | 18 | 4 | 55 | 3 |
| **P3** | 8 | 16 | 8 | 21 | 2 | 51 | 6 |
| **P4** | 26 | 53 | 27 | 24 | 0 | 65 | −2 |
| **P5** | 30 | 62 | 32 | 26 | 2 | 66 | −5 |
| **P6** | 32 | 55 | 23 | 26 | 1 | 66 | −3 |
| **P7** | 14 | 24 | 10 | 29 | 1 | 61 | 14 |
| **P8** | 25 | 34 | 9 | 21 | 5 | 75 | 0 |
| **P9** | 47 | 64 | 17 | 21 | 4 | 55 | 68 |
| **P10** | 23 | 35 | 12 | 19 | 8 | 68 | −2 |

### 3.1. Clinical impact

The first measure of improvement is the evaluation of patients using clinical scales. The results for FMA-UE, MoCA and RMT on the contralesional hemisphere can be found in table 2. On average, patients improved 18 ± 9.21 points on the FMA-UE scale which is significantly above the MCID, using the Mann–Whitney test ($p$ <0.01, $U = 0$). The difference between the scores before and after the treatment was also deemed statistically significant, **according to the Wilcoxon test ($p = 0.020$, $W = 55$,** $Mdn_pre = 25.5 and Mdn_post = 44$) (figure 4).

This clinical improvement distribution was further compared with longitudinal chronic stroke rehabilitation studies in the literature, which only encompassed BCI training across a variety of feedback paradigms (figure 5). The studies were compared using the Mann-Whitney test, for independent groups of data, where a p-value lower than 0.05 corresponded to a significant difference. Furthermore, only studies in which all the individual patients' scores were specified were considered for this analysis (and not when only median or mean were provided), to ensure more statistical validity. The results point to a significantly higher improvement in the FMA-UE score for this study, when compared to those experiments, regardless of the feedback option.

Finally, to illustrate the relationship between an improvement in a motor function scale and cortical excitability, the difference in values of FMA-UE scores and RMT before and after the treatment were correlated and a significant correlation was found between these two variables, using the Spearman Correlation test($r = -0.83$, $p < 0.05$). Indeed, a larger clinical improvement was correlated with a larger decrease in the RMT value (figure 6). Although the Spearman correlation does not translate into a direct linear correlation, a linear regression was performed which fitted the ensemble of points and is also shown in the figure, as a trend line.

### 3.2. EEG impact

#### *3.2.1. Patients' ability to modulate their sensorimotor rhythms*

To understand how ERD values were overall varying across sessions, the temporal evolution of the relative $\alpha$ frequency band power was extracted from all sessions (figure 7). Each session is visualized by a mean line, reflecting the average ERD across all patients and epochs for that specific session at each time point. Additionally, the shaded region surrounding the mean line depicts the standard deviation of the individual patient ERD trajectories. From figure 7, it is possible to infer ERD time patterns are similar to those found in literature [60]. Furthermore, to illustrate the period in which rTMS is present or absent, sessions 6 and 12 from figure 7 were chosen for a deeper analysis in terms of the ERD sustained period and the ERD slope, because patients in these sessions have already undergone all protocol sections with and without rTMS, respectively. These results were obtained by visual inspection of the ERD time patterns and choice of 3 main points, the start of the ERD for that session (at 500 ms), the starting time of the sustained ERD period, when ERD stopped becoming more negative at a faster pace, and, finally, the finishing of the sustained ERD period, where ERD seemed to have a trend of becoming more positive consistently. These points are represented in figure 8. When rTMS is present, the mean line exhibits a more negative slope ($slope$ = *-5.43* $\times 10^{-3}$ %/ms) than when rTMS is not applied ($slope$ = *-2.60* $\times 10^{-3}$ %/ ms). Also, the ERD is more sustained ($t$ = *1171.84* ms) when patients are undergoing rTMS, than when not ($t$ = *749.98* ms). This trend repeats itself for the majority of sessions of the two protocols.

Then, to further enhance the clarity of how ERD is changing throughout the treatment, the ERD per channel was displayed topographically in the EEG channel locations for the first session with both techniques, the first session recorded without rTMS and the last session recorded of the therapy protocol

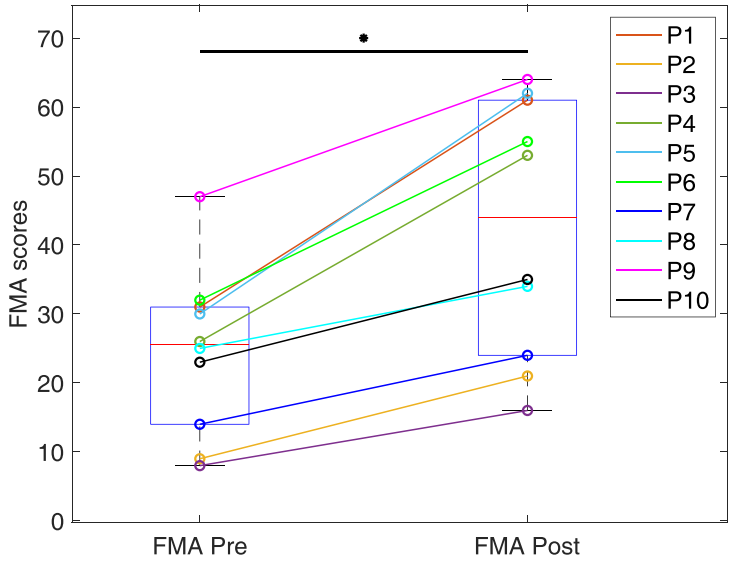



**Figure 4.** FMA-UE score distribution for each patient (P1-P10), with statistically significant differences pre- and post-intervention ($p < 0.05$).

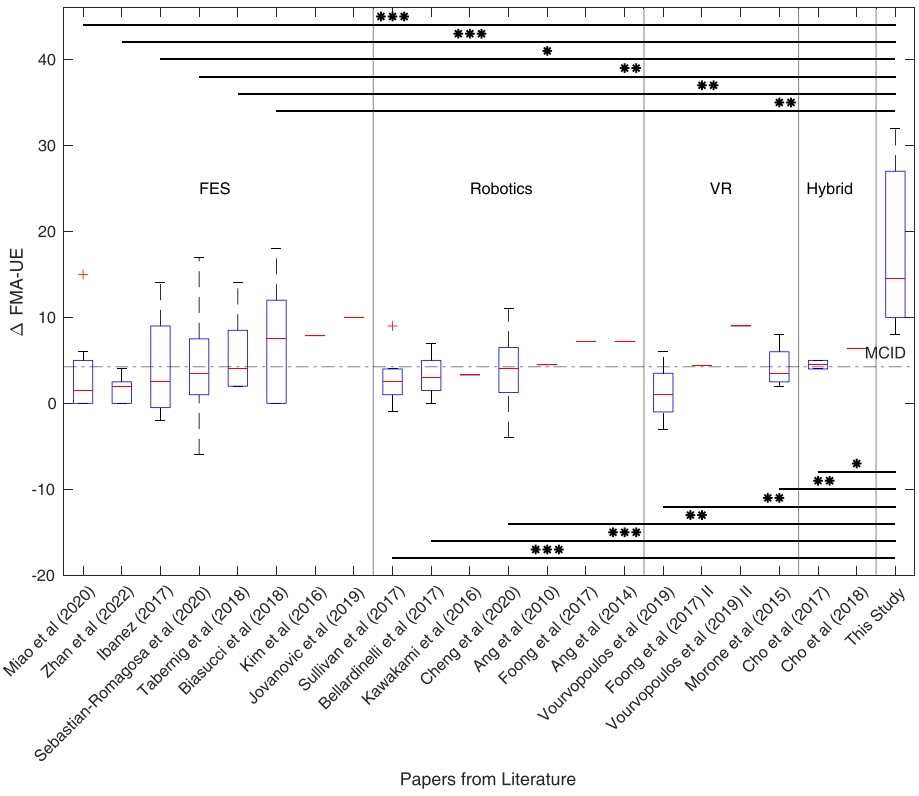



**Figure 5.** ΔFMA-UE scores for different studies in the literature using rehabilitation with BCI with various feedback options. All distributions of values in the literature are significantly different when compared to the ΔFMA-UE values obtained in this study ($p < 0.05$). The same occurs for the MCID value.

(figure 9). Ideally and for most cases, this corresponded to sessions 1, 7 and 12, nonetheless, when these sessions were not available, sessions 4 (for patient 9), 8 (for patients 1, 5 and 6) and 11 (for patients 5 and 7) were analyzed, respectively.

To further elaborate on the ERD patterns when all 10 patients undergo rTMS sessions, ERD on the contralateral side of the affected MI was acquired and the results per patient and per session can be observed in figure 10. In figure 10, there is no trend for how

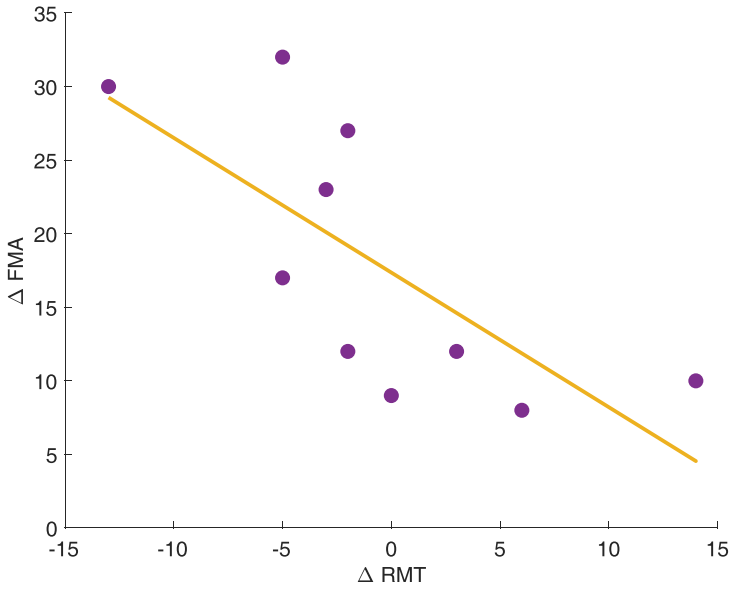



**Figure 6.** Scatter plot depicting the relationship between ΔRMT and ΔFMA-UE for all patients. A significant correlation was identified between these variables ($p < 0.05$). The yellow line represents the trend line of this correlation.

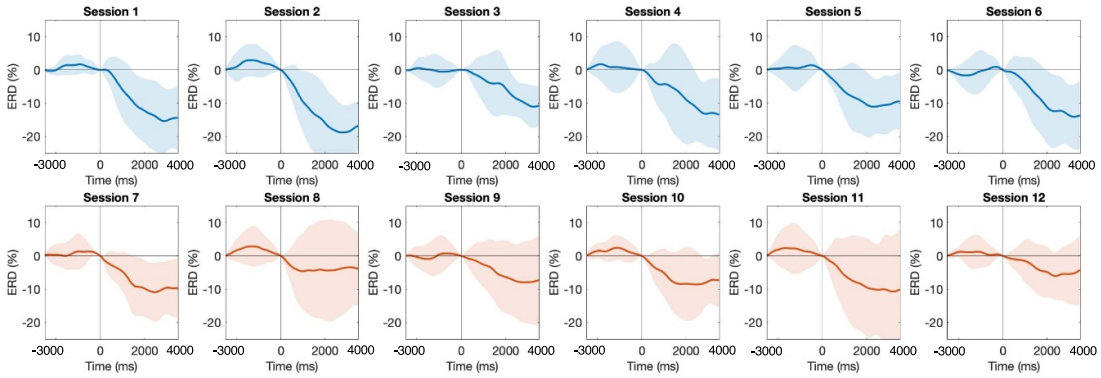



**Figure 7.** ERD time patterns for all 12 sessions, for all patients and respective sessions. The blue and orange lines correspond to the mean profile of all patients' time plots of $\alpha$ frequency power for the sessions with VR-BCI + rTMS and with only VR-BCI, respectively. The shaded area corresponds to the standard deviation for all patients.

patients' ERD varies across sessions, as ERD values fluctuate. Nevertheless, almost all sessions, except for sessions 9 and 12, are statistically significant when compared to no ERD (0%), employing the Mann–Whitney test. Patients with more positive or negative ERD values tended to maintain this characteristic across sessions. Patient 7 (dark blue) consistently had less negative ERD values than the median, while Patient 1 had a very positive ERD outlier in session 1 but has otherwise more negative ERD than the median. Other extreme outliers included Patients 7 and 4 in sessions 8 and 11, respectively. The median ERD was lower when TMS was present, nonetheless this difference is not significant.

To understand if the presence of rTMS was significant, the medians' distributions were compared and were not found statistically different, according to the Wilcoxon test with $p = 0.094$ and $W = 2$ ($Mdn = -12.03\%$ for the rTMS, and $Mdn = -6.67\%$ for the non-rTMS). Sessions 6 and 7 were compared to see immediate effects of the removal of rTMS and, although the median increases, the increase is not significant ($p = 0.84$ and $W = 9$).

### 3.2.2. rTMS effects per severity group

The next step resided in finding clusters of patients which could react differently to the treatment. The cluster chosen was the initial clinical state of the patients (given by the FMA-UE scale), as this has a correlation with the clinical improvement of patients ($r = 0.699$, $p < 0.05$). The clusters chosen were those referred to in Hijikata *et al* (2020): Severe: FMA-UE < 30, Moderate: 30 < FMA-UE < 45, and Mild: FMA-UE > 45 [61]. Nevertheless, as only one patient was

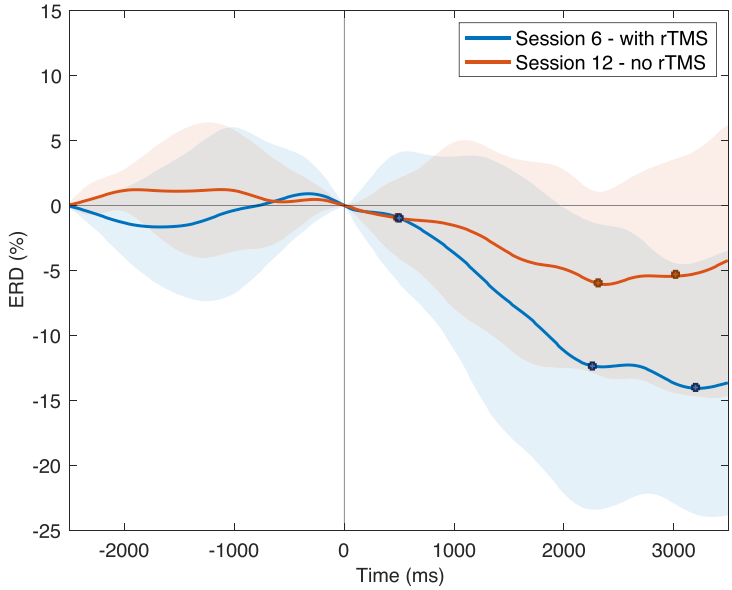



**Figure 8.** ERD time patterns for sessions 6 and 12 in blue and orange, respectively. There are 3 points illustrated in the figure. The one closer to 500 ms corresponds to what was considered the beginning of ERD. The last two points correspond, respectively, to the beginning and end of the ERD sustained period, used to compute how long the ERD was sustained for.

**Table 3.** Clusters FMA-UE scores according to Hijikata *et al* (2020) [61].

| | Patients |
|---|---|
| Moderate FMA-UE | P1, P5, P6 and P9 |
| Severe FMA-UE | P2, P3, P4, P7, P8 and P10 |

in the mild category, and due to low sample size, the patient was moved to the moderate category. The distribution of patients per cluster is defined in table 3.

For severe patients, the median ERD was reduced when rTMS was removed, from $Mdn = -10.98\%$ to $Mdn = -8.22\%$ ($\Delta\ Mdn = 2.76\%$). Nevertheless, this increase was not significant**, conforming to the Wilcoxon test**($p = 0.219$, $W = 4$). Then, in the case of moderate patients, the ERD also reduced when rTMS was withdrawn, from $Mdn = -17.03\%$ to $Mdn = -10.02\%$ ($\Delta\ Mdn = 7.01\%$). Although the difference is more noticeable than in the severe cluster, with $p = 0.125$ and $W = 0$, it is still not statistically significant, in consonance with the Wilcoxon test.

Finally, for both therapy paradigms, the moderate patients were characterized by lower ERD than severe patients, although no difference was statistically significant, $p = 0.114$ and $U = 4$ for rTMS and $p = 0.476$ and $U = 8$ for the absence of rTMS (figure 11), using the Mann-Whitney test.

To further investigate potential confounds within the moderate group, a subgroup analysis was conducted. This analysis stratified the moderate group ($n = 4$) by disease chronicity (chronic vs. subacute) to account for the potential heterogeneity within this category. The distribution of the outcome variable (period with and without rTMS) between these subgroups was subsequently visualized using a boxplot (figure 12).

Overall the results point to different tendencies in how contralateral ERD evolves across treatment with the presence and absence of rTMS: chronic patients seem to maintain the ERD magnitude ($median\ \Delta ERD = -1.53\ \%\ ,\ p = 1.0,\ W = 2$), nonetheless subacute patients seem to decrease the magnitude of ERD ($median\ \Delta ERD = 8.04\%,\ p = 0.5,\ W = 0$), both differences analysed using the Wilcoxon test. Even between the two groups the differences are not significant with $p = 0.67$ and $U = 1$ for the period in which there was rTMS present and $p = 0.33$ and $U = 0$ for the period where patients were only performing VR-BCI training, according to the Mann–Whitney U-Test.

### 3.2.3. rTMS effects per hand

To evaluate the results for the MI of the unaffected hand, since rTMS was delivered bilaterally, ERD for the MI of the affected and unaffected movements was compared. In the case of figure 13(a), for the severe patients during the rTMS period, the ERD for the unaffected movement appeared to be less negative ($Mdn = -6.26\%$) than that of the affected movement ($Mdn = -10.44\%$), even though it was not significant, $p = 0.093$ and$U = 7$, based on the Mann–Whitney U-test. When rTMS was removed, the ERD for the affected movement remained less negative ($Mdn = -7.75\%$) than that of the affected movement ($Mdn = -9.62\%$). This difference is not statistically significant, $p = 0.699$ and $U = 15$.

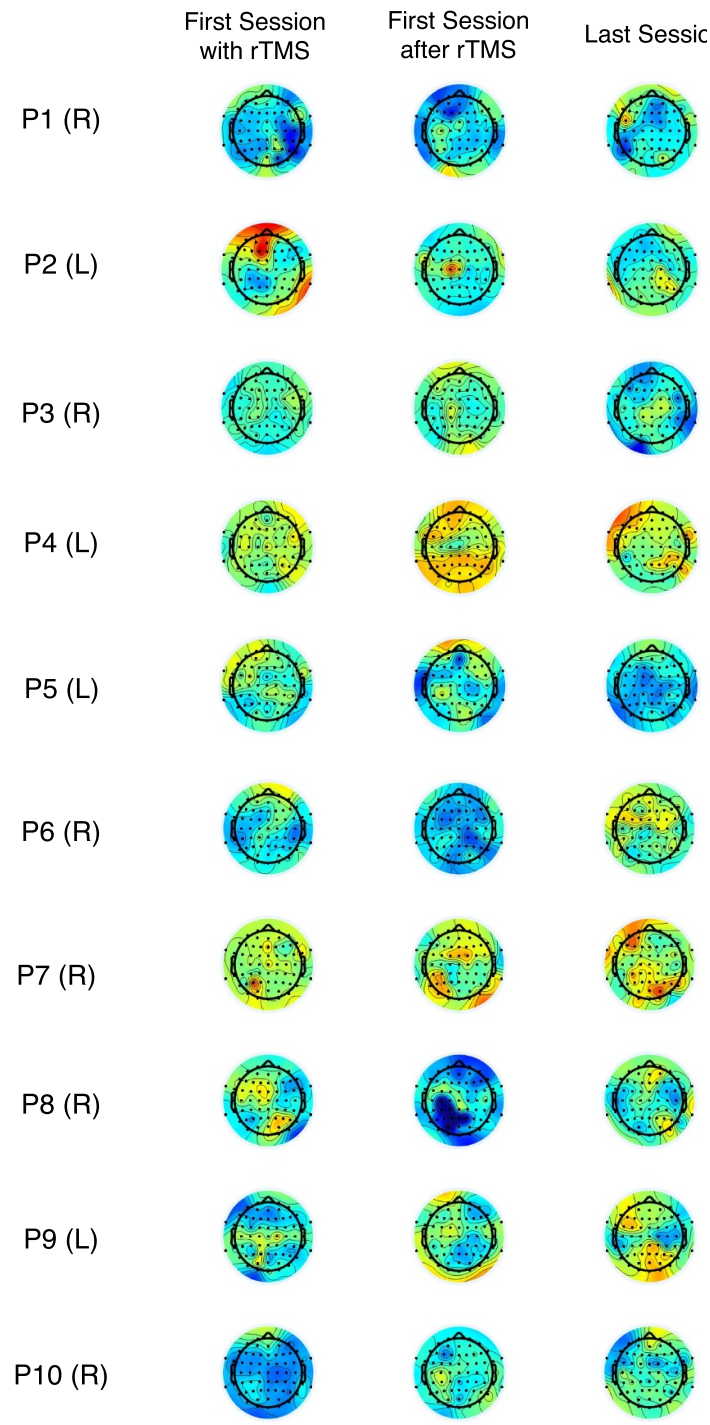



**Figure 9.** Topographical representations of ERD for the first session with rTMS, the first session without rTMS and last session recorded, per patient during MI of the affected movement, represented as a letter next to the patient's number, as L—Left or R—Right. All topographical representations have the same scale, ranging from −50% to 50%.

Between therapies, however, the ERD for both movements reacted differently. In the case of the unaffected movement, the ERD became slightly more negative (from $Mdn = -6.26\%$ to $Mdn = -7.75\%$) when rTMS was removed, even though it is not significant($p = 0.844$, $W = 12$). In the case of the affected movement, ERD became less negative (from $Mdn = -10.44\%$ to $Mdn = -9.62\%$), despite this increase not being significant, $p = 0.219$ and $W = 4$. Both analysis were perfomed in accordance with the Wilcoxon test.

Having this said, for the moderate cluster in figure 13(b), when TMS was present, ERD was more negative during the simulation of the affected movement ($Mdn = -15.98\%$) than in the simulation of the unaffected movement ($Mdn = -14.20\%$), being

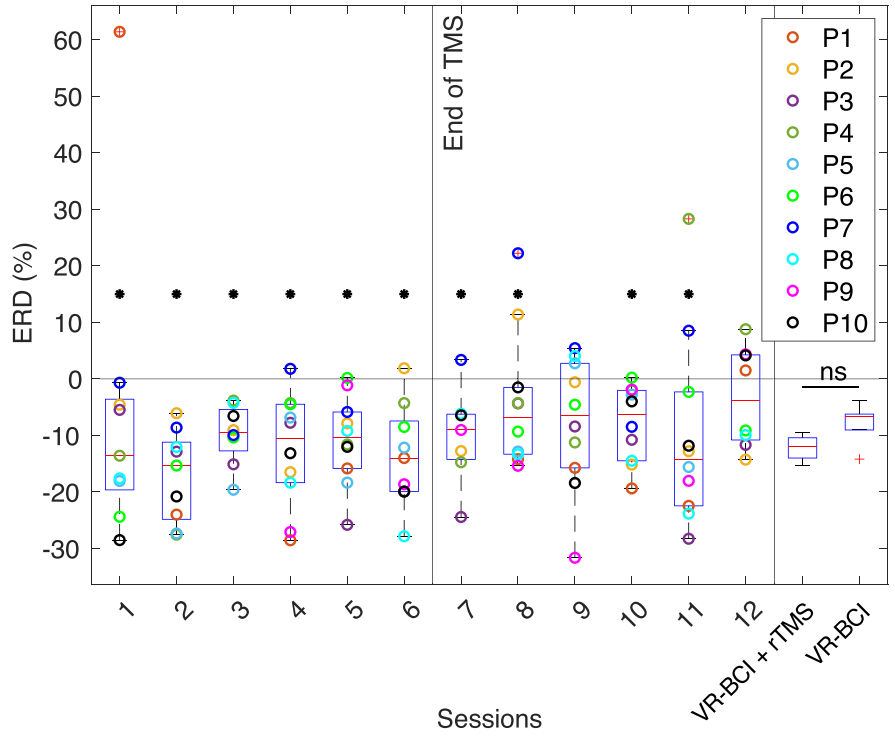



**Figure 10.** Distributions of ERD values for the contralateral electrode to the side of the affected movement per patient per session. Each patient is represented with a different colour.

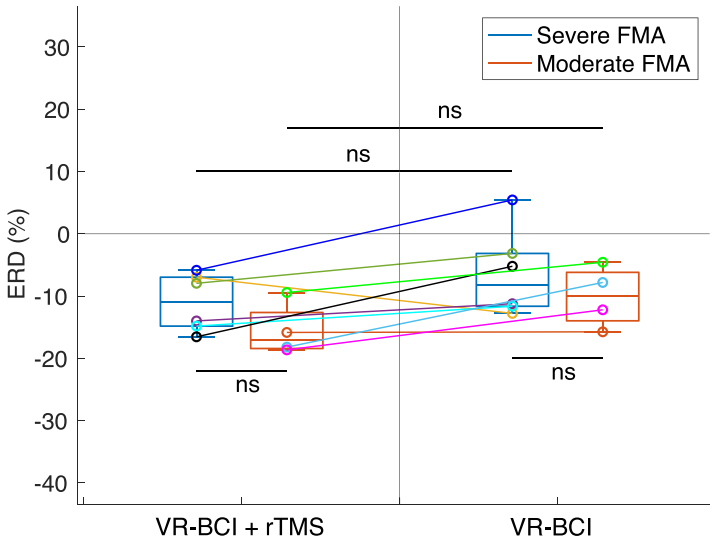



**Figure 11.** ERD on the contralateral electrode during MI of the affected arm, clustered by severity according to FMA-UE score. Each line corresponds to a patient, and each data point corresponds to the average of all sessions from a protocol for one patient. Overall, patients appear to increase their ERD, except for outliers P1 and P2.

non-significant nonetheless, $p = 0.394$ and $U = 12$, using the Mann–Whitney U-test. When patients were not undergoing rTMS, ERD remained more negative when patients were simulating the affected movement ($Mdn = -9.60\%$) than when they were imagining the unaffected movement ($Mdn = -9.01\%$). This difference is, nonetheless, not significant, $p = 0.699$ and $U = 15$.

Between protocols, in the case of moderate, both the unaffected and affected movement's ERD became less negative, with $\Delta\ Mdn = 5.19\%$ and $\Delta\ Mdn = 6.38\%$, respectively. These differences are, nevertheless, non-significant with $p = 0.688$ and $W = 8$ for the simulation of the unaffected movement, and $p = 0.094$ and $W = 2$ for the affected movement, both based on the application of the Wilcoxon test.

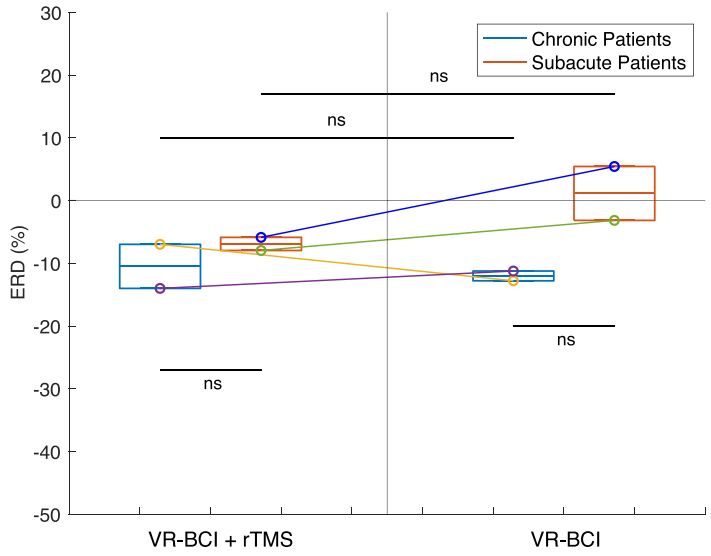
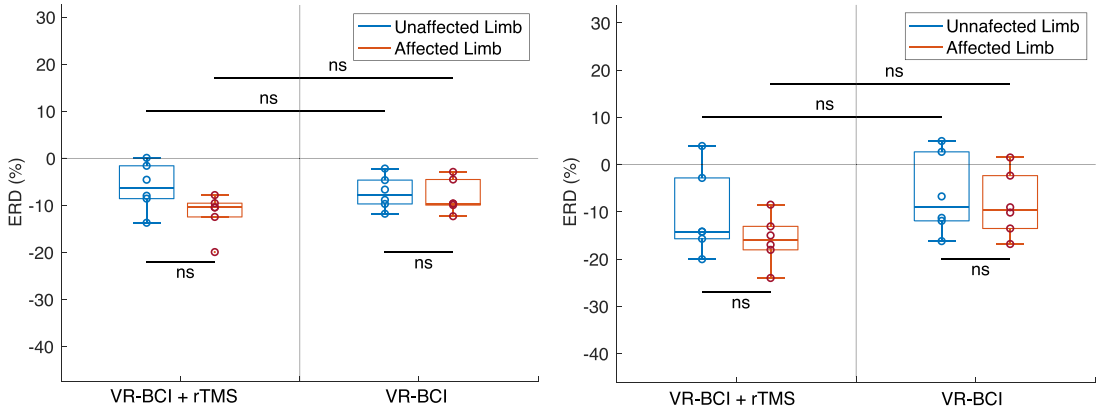



**Figure 12.** ERD on the contralateral electrode during MI of the affected movement, clustered by chronicity of the stroke for the patients, within the moderate cluster, defined according to FMA-UE initial score. Each line corresponds to a patient, and each data point corresponds to the average of all sessions from a protocol for one patient.




(a) Severe patients. (b) Moderate patients.

**Figure 13.** ERD on the brain area contralateral to the paralysed and the unaffected arm, clustered by severity of FMA-UE. Each data point is an average of all patients for a single session, for each category of functional loss severity.

### 3.3. Relationship between EEG features and clinical outcome

*3.3.1. ΔERD and clinical outcome*

In an attempt to find a relationship between brain changes and functional outcome, ΔERD was correlated with the ΔFMA-UE (figure 14), despite clinical measures only being recovered before and after the whole treatment. Overall, no correlation was found when all patients were considered and the Spearman correlation test was employed ($r = -0.018$, $p = 0.960$). Nevertheless, when separating by clusters, two different trends appeared. On one hand, the severe patients presented a correlation between a more positive ΔERD and a higher clinical outcome ($r = 0.464$, $p = 0.372$). On the other, moderate patients developed a non-significant correlation between a more negative ΔERD with a higher ΔFMA-UE ($r = -0.800$,$p = 0.333$). When separating by clusters, to visually illustrate the difference in trend, a linear regression was fitted to each set of samples and represented in a plot as a trend line.

In addition, to correlate these two variables, a two-stage mixed-effects linear model was developed to predict changes in FMA-UE scores across training, taking advantage of individual contralateral ERD dynamics, initial ERD values, and ERD progression during training. The F-test analysis yielded an F-statistic of 4.81 with a p-value of 0.048, indicating significance at the 5% and an $r^2 = 0.59$. The linear term (intercept and slope) produced an F-statistic of 0.071

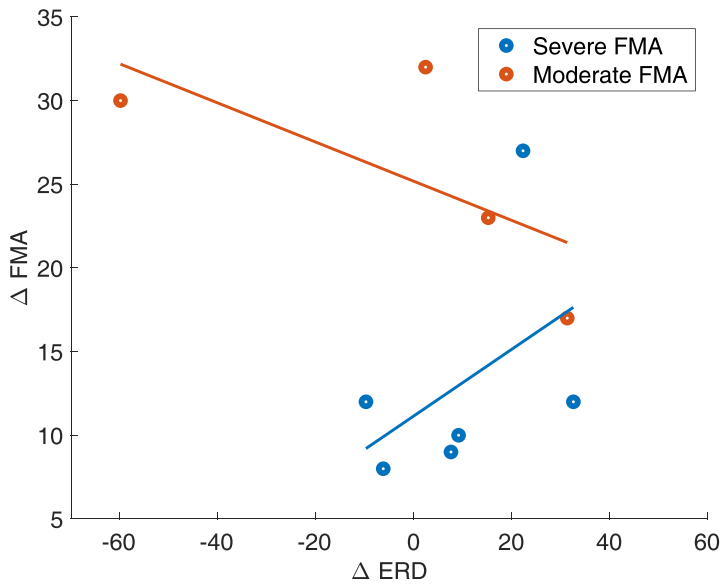



**Figure 14.** Scatter plots of ΔERD vs ΔFMA-UE with trending lines. The blue corresponds to severe patients and the red to moderate patients.

with a p-value of 0.797, while the non-linear term resulted in a significant F-statistic of 9.553 with a p-value of 0.018.

To visualize model behavior, the median individual intercept ($m = -0.279$) was used to divide patients into two groups: those with weaker initial ERD (more positive than the median) and those with stronger initial ERD (more negative than the median). The initial ERD was fixed at various values, more positive or negative than the median intercept, and the ERD progression was varied to model the different ΔFMA-UE values. Figure 15 shows the resulting variation in ΔFMA-UE for the two groups.

The overall trend observed indicates that for patients with weaker initial ERD, a larger clinical improvement is correlated with a more positive ERD progression. Conversely, for patients with stronger initial ERD, a higher clinical improvement is correlated with a more negative ERD progression.

*3.3.2. IAF and clinical outcome*

It is possible to infer that the differences between the initial and final IAF values are non significant, based on the Wilcoxon test ($p = 0.322$, $W = 38$), even if the values decrease slightly (figure 16). In fact, although the median IAF per period decreases from $Mdn = 9.43$ Hz to $Mdn = 8.90$ Hz, there is no clear trend on whether patients vary their IAF values. In both situations, the maximum value for the IAF is around 10.5 Hz.

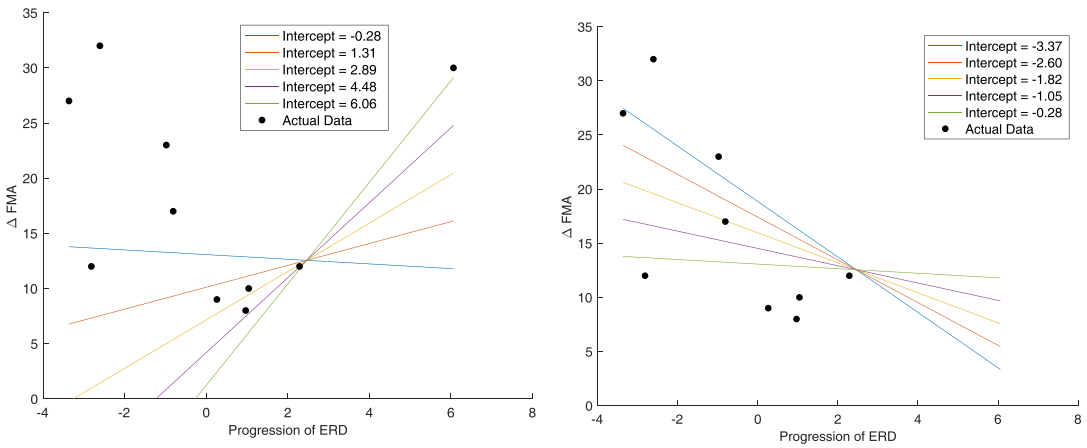
Then, regarding correlations between IAF and other clinical scales, three clinical scores demonstrated relationships with this feature: unaffected hemisphere RMT, MoCA and FMA-UE. In the following figures, the clusters are merely for additional information, as the correlation was performed for all patients simultaneously. Also, all correlations were performed using the Spearman Correlation test and, in addition to such test being applied, a linear regression was fitted to each of the data points, to further illustrate the overall trend of the data. Beginning with the relationship between the initial IAF and the difference in RMT, a relationship was found between a lower IAF and a higher decrease in the RMT value ($r = 0.6098$, $p = 0.061$). Then, regarding the final IAF, a relationship seemed to appear for the majority of patients, where a lower final IAF corresponded to a lower RMT value ($r = 0.5915$, $p = 0.0717$). Both correlations can be observed in figure 17.

Due to its documented relationship with cognitive state of a patient, initial IAF was correlated with the initial MoCA scores. In that regard, a significant correlation was found between these two variables, which can be observed in figure 17 ($r = -0.821$, $p = 0.004$), where a higher initial MoCA score was correlated with a lower initial IAF value.

Finally, as was performed with the ERD, the values of IAF were correlated with the functional outcome, more specifically the ΔFMA-UE. Unlike ΔERD, the initial IAF has a significant correlation with clinical improvement of patients, $r = -0.748$ and $p < 0.05$ (figure 18). This means there is a correlation between a lower initial IAF and a higher difference in FMA-UE between the beginning and end of the treatment.

## 4. Discussion

Current results indicate significant enhancements in patients' voluntary motor skills. This suggests the effectiveness of the synergistic neuromodulation effect of rTMS and VR-BCI employed. Although no direct correlation was observed between clinical




(a) $ERD_i \geq$ -0.279 (b) $ERD_i <$ -0.279

**Figure 15.** Linear mixed effects model representation, by fixing initial contralateral ERD values (linear model intercepts) and varying the ERD progression, to predict ΔFMA-UE values. Separated into two groups, according to the median individual intercept value, one with weaker initial ERD and one with stronger initial ERD.

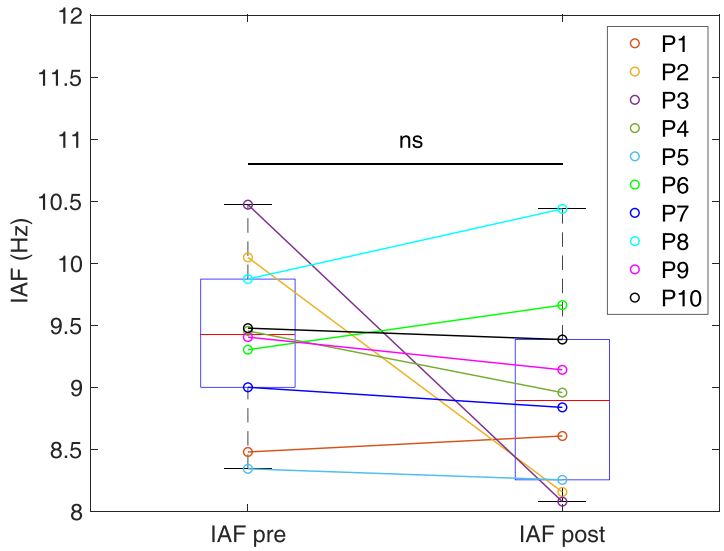


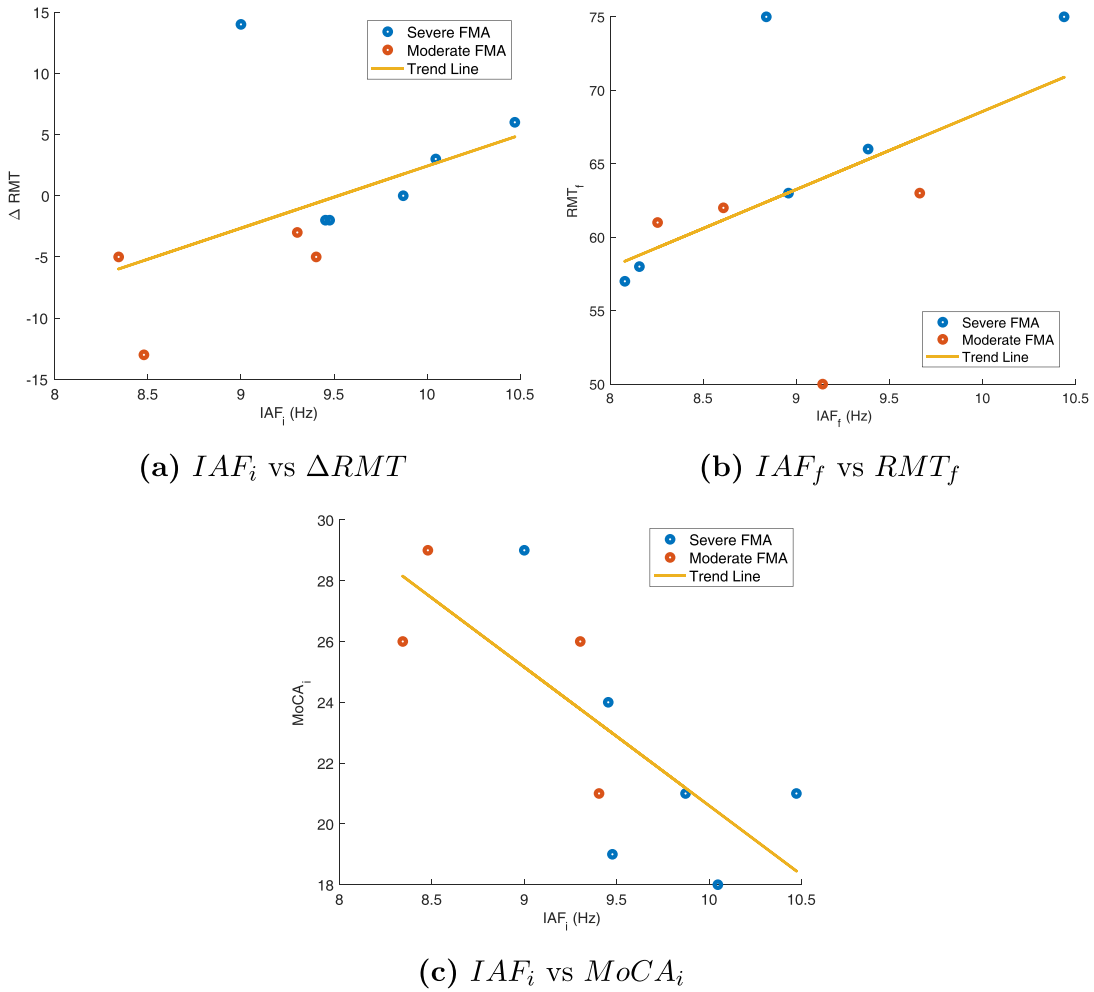

**Figure 16.** IAF distributions of all patients, pre- and post- intervention.

improvement and ERD, a potential new stroke recovery indicator was identified in IAF.

### 4.1. Clinical impact

In respect to the clinical improvement of patients, values of FMA-UE were significantly altered between the beginning and end of the treatment, both when comparing between the patients and with other similar publications. An improvement stemming from the addition of rTMS compared to its absence was expected taking into account previous literature where the introduction of rTMS in other rehabilitation techniques, such as physical or occupational therapy, provided greater functional improvements in patients [62]. Although a high ΔFMA-UE was obtained for these patients, it could be due to a few outlier patients improving much more than the MCID. Even so, the combination of exogenous (rTMS) and endogenous (VR-BCI) neuromodulation techniques holds a promise for enhancing motor performance through cortical activation reinforcement. In general, the improvement in FMA-UE likely stems from a subtle overall enhancement in various components in the brain of the patient that collectively impact functionality, and future studies should aim to characterize this effect with greater precision.

One of those components is neuronal excitability, as measured by the RMT. In literature, increased bilateral activation resulting from elevated contralesional activation was correlated with poorer motor recovery [63], and, therefore, neuromodulation techniques such as bilateral rTMS and VR-BCI can be




(a) $IAF_i$ vs $\Delta RMT$

(b) $IAF_f$ vs $RMT_f$

(c) $IAF_i$ vs $MoCA_i$

**Figure 17.** Scatter plots of IAF and RMT at different time points of the treatment, as well as initial IAF (in Hz) vs initial MoCA score. The yellow line represents the trend line.

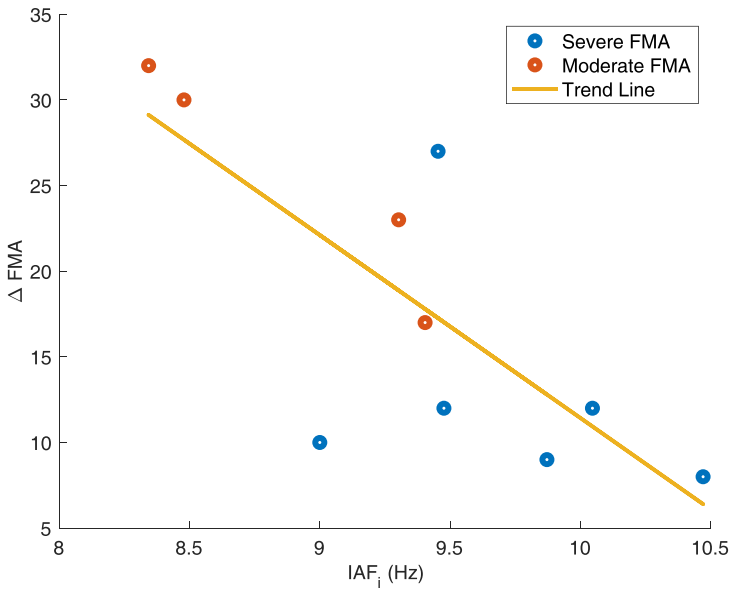



**Figure 18.** Scatter plot of initial IAF (in Hz) vs ΔFMA-UE score, with trending line.

used to regain hemispheric balance. As a result, in the ipsi-lesional hemisphere, the corticospinal excitability was expected to increase as training progressed and patients regain their motor function [64]. Nonetheless, for the contralesional hemisphere, although some papers refer to contralesional hemisphere excitability of better recovered patients to decrease as time progresses, others have disclosed that more severe patients increase corticospinal excitability in contra-lesional M1, as a result of the training [65]. In this particular experiment, when comparing the RMT values with the functional outcome of the treatment, a significant correlation was found between a higher motor improvement and a higher decrease in the contra-lesional RMT value. The reasons for this could be a transition of the brain activity to the contra-lesional side, as we are dealing with severe patients and, due to the training being bilateral in the VR-BCI modality, although the bilateral rTMS is compensating improvements in the healthy side, we could be training also the healthy hemisphere, causing the excitability to increase and the RMT values to decrease. As lower RMT value translates into higher cortical excitability [25] and this influences BCI performance due to its relationship with ERD magnitude [38], rTMS had an influence on how patients were training and, therefore, improving.

### 4.2. Patients' ability to modulate their ERD

Generally, patients' ERD was significant when compared to no ERD (0%), indicating that they could modulate their sensorimotor rhythms and were performing the training correctly. Moreover, both non-significant ERD sessions occurred in the protocol without rTMS.

In literature, a decrease in the ERD during a treatment has been associated with clinical recovery [37]. So, when comparing the presence and the absence of the rTMS, the lower medians indicate that rTMS had an influence in how patients evoked their SMR. This could be a result of the fact that rTMS was performed only 30 min prior to BCI training and studies have demonstrated that cortical excitability, which is in turn correlated with ERD magnitude [38], increases for at least 30 min following a single high frequency rTMS delivery [27]. Although rTMS has been shown to have long term potentiating effects in the brain [22], the immediate increased cortical excitability proved to have more intensive effects in the ERD of patients, hence the higher ERD magnitudes in the rTMS delivery period of the treatment. Nonetheless, as rTMS sessions and non-rTMS sessions were conducted consecutively, any observed changes could be attributed to the learning of the BCI task or other temporal factors. An alternating or randomly interleaved protocol would better isolate the effects of rTMS, as the current setup may confound short-term impacts of rTMS with task familiarity or other time-related influences.

Furthermore, it was expected that throughout the therapy, the magnitude of the ERD would increase, or it would become more negative. Nevertheless, as soon as rTMS was removed, the ERD was less negative than in the first part of the therapy, although not significant. Thus, rTMS appears to have at least a short term effect in how patients evoke ERD. Several factors could explain the lack of trend in ERD response across patients. The noisy hospital setting, brain lesions, and impaired cortical integrity may have weakened the ERD response. In addition, motivation may have also played a role. This is highlighted by patient 7, who was not the worst patient clinically or in terms of age, but was consistently unmotivated, according to the physician. This lack of motivation was reflected in their ERD, as they were one of the few patients with ERD values mostly above the median. Another important factor is the initial ERD modulation ability. Ray *et al* (2020) observed that stroke patients who could elicit a stronger (or more negative) ERD at the beginning of BCI training, were able to learn to control the machine better, when compared to patients who had a weaker ERD [58].

As occurred with the overall magnitude of ERD, the time variation of ERD in sessions in the period with or without rTMS may be due to the timing schedules and the effects of a single high frequency rTMS session [27]. These effects may be a result of the frequency stimulation of rTMS [23].

### 4.3. rTMS effects per severity group

From current results, it is noticeable that ERD becomes less negative when rTMS is removed from both groups, which could indicate that the neuronal and time effects of rTMS are the same regardless of the motor severity of the patient. Even so, moderate patients demonstrated a higher difference between the ERD during the period with rTMS and without rTMS, which could indicate a larger effect in these patients. Despite the non-uniform distribution of the sample across clusters, the clustering strategy was based on established literature demonstrating significant correlations between initial FMA-UE scores and ERD variations [61]. This approach should ensure a representative patient set for ERD extraction and subsequent comparisons. This is inline with prior research, where one of the most important indicators for clinical recovery was deemed the initial functional state of the patient [6, 66].

Furthermore, when performing an analysis within the moderate group, two non-significant trends appeared in the plots. On one hand, chronic patients' contralateral ERD seemed to react similarly to the period with and without rTMS, whereas subacute patients appeared to decrease the contralateral ERD magnitude, having less pronounced ERD during the period where patients were only undergoing VR-BCI. All of these differences were deemed, nonetheless, non-significant which is not worrisome,

as the sample size in evaluation (2 patients per subgroup) is very small to draw significant conclusions, and more patients would be necessary to infer in the progression of ERD when rTMS is removed from training protocol.

### 4.4. rTMS effects per hand

The more negative ERD in the ipsi-lesional hemisphere during MI of the affected movement, although not significant, is in accordance with the rationale for the use of rTMS: high-frequency rTMS to the ipsi-lesional hemisphere increases neuronal excitability, while low-frequency rTMS to the contra-lesional inhibits new neural connections [23]. This also is in agreement with the importance of bilateral stimulation, as stimulating only the affected hemisphere could perpetuate the disparity between the healthy and affected limbs.

On the other hand, the fact that the more negative ERD in the ipsi-lesional hemisphere during the affected movement, maintained itself when rTMS was removed, despite the lack of significance, could also be attributed to the lasting effects of rTMS on brain remodeling, as observed previously in literature [22]. Indeed, the fact that ERD becomes more negative on the severe patients but not on the moderate patients, when rTMS is no longer applied, could indicate that moderate patients will suffer more lasting effects on this therapy than severe.

The presence of two subacute patients in the moderate group may explain why they were more affected by rTMS than the severe group. As time since stroke onset is a major factor in brain reorganization, this disparity is a limitation of the study and should be addressed in future research.

### 4.5. Relationship between ΔERD and clinical outcome

Despite the expected correlation between ΔERD and ΔFMA-UE [60], no correlation was found in this experiment. This could be due to the small sample size, the lack of a control group, the heterogeneity of stroke patients (e.g. demographic characteristics, lesion location, time since stroke onset, previous rehabilitation, motivation), or other unknown factors. In addition, the fact that the mean ERD per patient per session had fluctuations, could indicate that the ERD may suffer slight alterations during the use of BCI as result of fatigue, motivation, concentration and acquisition equipment malfunction. Thus, ΔERD values are affected by these fluctuations and the overall correlation might be affected.

When separating into the clusters, the results are coherent with rTMS affecting more positively the moderate patients than the more severe patients, with patients improving more when ERD values become more negative in this case. One other limitation is that ΔERD represents the whole protocol, encompassing both parts with and without rTMS because no FMA-UE was measured between paradigms. This could cause inaccuracies in the correlations, since it has been shown that removing the rTMS changes the ERD. By measuring FMA-UE between therapy protocols, it would be easier to understand the effect of rTMS in scales and correlate it with the brain shifts. Also, due to the small sample size, and even further reduction by separation into groups, a large variation in an individual ERD could influence the overall correlation and should be accounted for in future developments of this experiment.

Nonetheless, a significant method for predicting the clinical outcome using the contralateral ERD was obtained when modelling a linear mixed effects model. Indeed, the fact that the F-statistic was associated with a p-value lower than 0.05, signifies that at least one of the predictors, or the interaction term between them, contributes significantly to predict Δ FMA. By observing the F-statistic of each of these terms, the one for the linear term (with p-value higher than 0.05) suggests that the linear relationship between the predictors and the response variable is not strong. On the other hand, the F-statistic for the nonlinear term having a p-value of 0.018, which is lower than 0.05, indicates that the nonlinear term (the interaction between intercept and slope) is statistically significant at the 5% level, suggesting that the relationship between the predictors and the outcome is more complex than a simple linear relationship. This suggests there is a significant interaction effect between the intercept and slope in predicting the Δ FMA.

Then, regarding the visualization of the model behaviour, the results obtained were similar to those found in Ray *et al* (2020) [58]: when initial ERD was higher (more positive), the more positive the ERD becomes throughout the therapy (more positive slope), the higher the clinical recovery, according to the FMA-UE. When the initial ERD was more negative, the more negative the ERD becomes throughout the therapy, the higher the clinical recovery, according to the FMA-UE scale. As the classifier behind the BCI machine relies indirectly on the individual ERD patterns and how well the affected and the unaffected MI are distinguishable, patients with more pronounced ERD in the lesioned hemisphere (contralateral to the affected movement) will, most probably, benefit more from the machine form the earliest sessions, when compared to patients with less pronounced initial ERD and, therefore, will improve more and provoke the ERD to become even progressively more negative. Those with 'weaker' initial ERD, perhaps modelled the brain to increase activity in the ipsilateral hemisphere, and should be evaluated also in future studies.

All in all, this model presented itself as a more robust and significant alternative to the Spearman correlation, to predict clinical recovery for the small sample size of 10 patients, nonetheless the sample size

and variability in the lesion site and degree should also be considered a limiting factor to the significance of this model.

### 4.6. IAF and clinical outcome

Few studies have investigated IAF in stroke rehabilitation with rTMS or motor imagery, likely due to the variability in affected areas in hemiplegia, rTMS stimulation sites, and stimulation frequencies across studies. Furthermore, the lack of standardization of IAF recording electrodes further complicates comparisons between studies. Despite these limitations, due to its relation with task alertness (critical for MI-BCI use) [39], cognitive state [41] and also to its ease of recovery, IAF was selected as a potential stroke state and recovery biomarker. In the context of this experiment, the lack of significant IAF changes is positive, as IAF was not a therapeutic target. This suggests that this feature is a robust and reliable biomarker of stroke recovery.

In the context of correlating with clinical scales, the observed correlations between IAF and the resting motor threshold, despite not achieving statistical significance ($p > 0.05$), may provide insight into patient improvement. Despite the distinction between the sources of these measures—RMT derived from the unaffected motor cortex and the IAF derived from the occipital lobe—there is potential for IAF to be linked to variations in cortical excitability, given its association with reaction time and patient training regimens. Moreover, research suggests that rTMS has the capacity to modulate occipital alpha activity and influence IAF [67], indicating the possibility of similar effects within the motor cortex. This suggests the potential for rTMS to impact the alpha band in the motor cortex, affecting cortical excitability. Given the interconnectedness between the motor cortex and supplementary motor structures in the occipital lobe [68], there may exist a close relationship between IAF and cortical excitability as assessed by RMT. Nevertheless, further investigation is warranted to elucidate the precise nature of this relationship in the context of treatment efficacy.

Furthermore, regarding the MoCA correlation, a significant relationship was found between a higher initial MoCA score and a lower initial IAF. This is contradictory to the evidence found in literature, where a lower IAF is associated with a lower cognition [41]. Nonetheless, as IAF is controlled by many factors such as age and cortical integrity and dependent on EEG noise reduction, future studies will be necessary to further test this relationship and eliminate the other factor's presence.

Despite these disadvantages, a strong correlation was found between a lower initial IAF at the beginning of the treatment and a higher clinical recovery, as measured by the Fugl-Meyer Assessment. This correlation being statistically significant is very important when discussing the possible use of IAF as a quantitative inclusion criteria for future studies. Indeed, this feature is easily recovered, only requiring a 2-min resting state EEG, it is robust to BCI training, could predict if this treatment is adequate for a patient or another approach should be investigated and if all patients were considered optimal for the treatment, could allow for the investigation of the underlying mechanisms of recovery.

All in all, although rTMS was applied to the primary motor cortex rather than the occipital lobe, where IAF is extracted, IAF may influence therapy outcomes due to its relationship with attention, task preparedness, and supplementary motor structures in the occipital lobe that contribute to posture and voluntary movement [68].

## 5. Conclusions

The main goal of this paper resided in understanding the neuromodulation effect of rTMS when joined with VR-BCI training, in the EEG rhythms and clinical outcomes of stroke patients.

Overall, findings suggest that rTMS had a positive effect on chronic stroke patients recovery with BCI and conventional therapy. Patients showed significantly greater clinical improvement at the end of the treatment when compared to literature, and their ERD values were lower during the period when they were receiving rTMS. The effects of rTMS were more pronounced in patients with moderate lesions, but they were also present in patients with severe lesions.

No correlation was found between clinical outcome and variation in ERD when all patients were considered, which may be due to the clinical setting, some sessions missing from the dataset or due to cortical deterioration and between-patient variability. Nonetheless, when modeling the contralateral ERD data, a significant linear mixed effects model was derived to predict the clinical improvement of patients based on the initial measure of ERD and the progression of this feature throughout treatment.

It was also found a relationship between IAF and clinical outcome, as measured by the FMA-UE scale. Patients with lower initial IAF had a higher recovery on the FMA-UE scale. Also, the initial and final IAF values showed interesting relationships with RMT values, suggesting a possible relationship between these two measures and a mechanism for stroke recovery. Besides, although contradictory with literature, IAF was negatively correlated with the MoCA score and this relationship should be investigated in the future.

## 6. Limitations

Nonetheless, a set of limitations were identified. Firstly, $N = 10$ patients is a small sample size to derive stable and irrefutable conclusions. This is even

more relevant when the disease in study is stroke, a multifactorial medical condition. In this case, there is a lot of intra–patient variability, due to factors such as the side and size of lesion, initial clinical and motor function, brain areas affected and time since stroke onset. This variability influences how patients recover and, thus, the findings in experiments. Not only this, but also therapies were performed differently for patients, which can also influence several confounds. Another limitation resided in the timing of clinical state measurements. Patients were assessed with clinical scales, such as the FMA-UE, before and after the 4-week intervention, which included both rTMS and non–rTMS protocols. This caused complications when correlating brain features before and after the treatment, because when computing the $\Delta$ERD, the initial session included rTMS and the final one did not. In fact, rTMS influences ERD, thus performing a correlation disregarding this effect led to inconclusive results. Regarding the experimental protocol, we acknowledge limitations inherent to the experimental design, including potential learning confounds and the absence of a control group. These factors may impact the generalizability of the findings to broader populations. Future studies will mitigate these limitations by employing more rigorous experimental designs incorporating appropriate control conditions.

Furthermore, it is necessary to refer to the noise in the data. Indeed, the fact that this EEG was recorded in a hospital setting, despite being positive to enrich this field of study with a closer experience to the real world, means that acquisitions were contaminated with unpredictable factors. In fact, the data could have such strong artifacts that not even more robust methods are able to remove it. The nature of the data also offered its set of challenges and, in order to compare this experiment to different studies already present in the literature, the ERD extracted was uniformly extracted for all patients and sessions. As different patients elicit ERD in different forms, both in terms of time and frequency domain, and due to the weak nature of this feature, computing ERD in a fixed form, could induce a less precise analysis of the ERD per patient. This should be further researched in a future study, comparing a fixed to an individualized ERD extraction. Finally, as this technique is quite patient-dependent, the motivation, fatigue or even cortical damage comprise limitations which are quite relevant, even though are outside the control scope of this paper.

Regarding future work, three main areas arose when discussing the findings of this study. Initially, as a relationship was found between IAF and the clinical outcome, and due to this feature not being widely studied, it would be interesting to explore this connection. When understanding the ease of recovery of this brain feature, this future work direction becomes more pertinent. In fact, IAF can be extracted from a resting state EEG of 2 min, and could be used as inclusion criteria for rehabilitation studies and when evaluating if a certain treatment is the most adequate, given this relationship between IAF and clinical outcome when using BCI and rTMS is proved. Next, throughout the literature, many studies were performing brain network analysis, such as Functional Connectivity or Lateralization Indices between hemispheres. This analysis is important in order to understand how these networks communicate and reorganize after stroke, which is crucial for developing effective rehabilitation strategies. Finally, given the impact that the cortical integrity has on the induced ERD after a stroke lesion, and due to the intra–patient variability, the extraction of personalized EEG features is necessary. This could include the utilization of multimodal neuroimaging, and specifically the use of simultaneous EEG-fMRI recordings. This way, more personalized and fMRI-informed EEG features can be extracted and modeled.

## Data availability statement

The data cannot be made publicly available upon publication because they contain sensitive personal information. The data that support the findings of this study are available upon reasonable request from the authors.

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## References

[1] Feigin V L, Brainin M, Norrving B, Martins S, Sacco R L, Hacke W, Fisher M, Pandian J and Lindsay P 2022 World stroke organization (wso): global stroke fact sheet 2022 *Int. J. Stroke* **17** 18–29
[2] Wenning G K, Kiechl S, Seppi K, Müller J, Högl B, Saletu M, Rungger G, Gasperi A, Willeit J and Poewe W 2005 Prevalence of movement disorders in men and women aged 50-89 years (Bruneck Study cohort): a population-based study *Lancet Neurol.* **4** 815–20
[3] Cioni G, Sgandurra G, Muzzini S, Paolicelli P B and Ferrari A 2010 *Forms of Hemiplegia.* (Springer Milan) pp 331–56

[4] Bonita R and Beaglehole R 1988 Recovery of motor function after stroke *Stroke* **19** 1497–500
[5] Mateos-Aparicio P and Rodríguez-Moreno A 2019 The impact of studying brain plasticity *Front. Cell. Neurosci.* **13** 66
[6] Kwakkel G, Kollen B and Twisk J 2006 Impact of time on improvement of outcome after stroke *Stroke* **37** 2348–53
[7] Wade D T, Langton-Hewer R, Wood V A, Skilbeck C E and Ismail H M 1983 The hemiplegic arm after stroke: measurement and recovery *J. Neur. Neurosurg. Psychiatry* **46** 521–4
[8] Kwakkel G, Kollen B J, van der Grond J and Prevo A J H 2003 Probability of regaining dexterity in the flaccid upper limb *Stroke* **34** 2181–6
[9] Thieme H, Morkisch N, Mehrholz J, Pohl M, Behrens J, Borgetto B and Dohle C 2018 Mirror therapy for improving motor function after stroke *Cochrane Database Systematic Rev.* **2018**
[10] Taub E, Uswatte G and Elbert T 2002 New treatments in neurorehabiliation founded on basic research *Nat. Rev. Neurosci.* **3** 228–36
[11] Dobkin B H 2004 Strategies for stroke rehabilitation *Lancet Neurol.* **3** 528
[12] Wolpaw J R, Birbaumer N, McFarland D J, Pfurtscheller G and Vaughan T M 2002 Brain–computer interfaces for communication and Control *Clin. Neurophys.* **113** 767–91
[13] Loriette C, Ziane C and Ben Hamed S 2021 Neurofeedback for cognitive enhancement and intervention and brain plasticity *Rev. Neuro.* **177** 1133–44
[14] Hammond D C 2011 What is neurofeedback: an update *J. Neurotherapy* **15** 305–36
[15] Neuper C, Scherer R, Wriessnegger S and Pfurtscheller G 2009 Motor imagery and action observation: modulation of sensorimotor brain rhythms during mental control of a brain–computer interface *Clin. Neurophys.* **120** 239–47
[16] Wriessnegger S, Leeb R, Kaiser V, Neuper C and Müller-Putz G 2013 Watching object related movements modulates mirror-like activity in parietal brain regions *Clin. Neurophys.* **124** 1596–604
[17] McFarland D J, Sarnacki W A and Wolpaw J R 2015 Effects of training pre-movement sensorimotor rhythms on behavioral performance *J. Neural Eng.* **12** 066021
[18] Bermúdez i Badia S, Fluet G G, Llorens R and Deutsch J E 2016 Virtual reality for sensorimotor rehabilitation post stroke: design principles and evidence *Neurorehabilitation Technology* (Springer) pp 573–603
[19] Hartson R and Pyla P S 2012 Rigorous empirical evaluation: preparation *The UX Book* ed R Hartson and P S Pyla (Morgan Kaufmann) ch 14, pp 503–36
[20] Pandita S and Stevenson Won A 2020 Clinical applications of virtual reality in patient-centered care *Technology and Health* ed J Kim and H Song (Academic) ch 7, pp 129–48
[21] Rizvi S and Khan A M 2019 Use of transcranial magnetic stimulation for depression *Cureus* **11**
[22] Adeyemo B O, Simis M, Macea D D and Fregni F 2012 Systematic review of parameters of stimulation, clinical trial design characteristics and motor outcomes in non-invasive brain stimulation in stroke *Front. Psychiatry* **3** 88
[23] Frey J, Najib U, Lilly C and Adcock A 2020 Novel TMS for stroke and depression (NoTSAD): accelerated repetitive transcranial magnetic stimulation as a safe and effective treatment for post-stroke depression *Front. Neurol.* **11** 788
[24] Karabanov A N, Raffin E and Siebner H R 2015 The resting motor threshold – restless or resting? a repeated threshold hunting technique to track dynamic changes in resting motor threshold *Brain Stimul.* **8** 1191–4
[25] Veldema J, Nowak D A and Gharabaghi A 2021 Resting motor threshold in the course of hand motor recovery after stroke: a systematic review *J. Neuroeng. Rehabil.* **18** 1–28
[26] Rosso C and Lamy J C 2018 Does resting motor threshold predict motor hand recovery after stroke? *Front. Neurol.* **9** 1020
[27] Peinemann A, Reimer B, Löer C, Quartarone A, Münchau A, Conrad B and Roman Siebner H 2004 Long-lasting increase in corticospinal excitability after 1800 pulses of subthreshold 5 Hz repetitive TMS to the primary motor cortex *Clin. Neurophys.* **115** 1519–26
[28] Ly J Q M *et al* 2016 Circadian regulation of human cortical excitability *Nat. Commun.* **7** 11828
[29] Ang K K, Guan C, Phua K S, Wang C, Zhou L, Tang K Y, Ephraim Joseph G J, Kuah C W K Chua K S G *et al* 2014 Brain-Computer interface-based robotic end effector system for wrist and hand rehabilitation: results of a three-armed randomized controlled trial for chronic stroke *Front. Neuroeng.* **7** 30
[30] Carino-Escobar R I, Carrillo-Mora P, Valdés-Cristerna R, Rodriguez-Barragan M A, Hernandez-Arenas C, Quinzaños-Fresnedo J, Galicia-Alvarado M A and Cantillo-Negrete J 2019 Longitudinal analysis of stroke patients' brain rhythms during an intervention with a brain-computer interface *Neural Plast.* **2019** 1–11
[31] Kawakami M *et al* 2016 A new therapeutic application of brain-machine interface (BMI) training followed by hybrid assistive neuromuscular dynamic stimulation (hands) therapy for patients with severe hemiparetic stroke: a proof of concept study *Restorative Neuro. Neurosci.* **34** 789–97
[32] Ibáñez J, Monge-Pereira E, Molina-Rueda F, Serrano J I, del Castillo M D and Cuesta-Gómez A 2017 Low latency estimation of motor intentions to assist reaching movements along multiple sessions in chronic stroke patients: a feasibility study *Front. Neurosci.* **11** 126
[33] Vourvopoulos A, Jorge C, Abreu R, Figueiredo P, Fernandes J C and Bermúdez i Badia S 2019 Efficacy and brain imaging correlates of an immersive motor imagery BCI-driven VR system for upper limb motor rehabilitation: a clinical case report *Front Hum Neurosci.* **13** 244
[34] Pfurtscheller G and Aranibar A 1977 Event-related cortical desynchronization detected by power measurements of SCALP EEG *Electroencephalogr. Clin. Neurophysiol.* **42** 817–26
[35] Formaggio E, Storti S, Boscolo Galazzo I, Gandolfi M, Geroin C, Smania N, Fiaschi A and Manganotti P 2014 Time–frequency modulation of ERD and EEG coherence in robot-assisted hand performance *Brain Topography.* **28** 352–63
[36] Daly J J and Cavusoglu M C 2006 Assessment of EEG event-related desynchronization in stroke survivors performing shoulder-elbow movements *Proc. 2006 IEEE Int. Conf. Robotics and Automation, 2006 ICRA 2006*
[37] Tangwiriyasakul C, Verhagen R, Rutten W L C and van Putten M J A M 2014 Temporal evolution of event-related desynchronization in acute stroke: a pilot study *Clin. Neurophys.* **125** 1112–20
[38] Aono K, Miyashita S, Fujiwara Y, Kodama M, Hanayama K, Masakado Y and Ushiba J 2013 Relationship between event-related desynchronization and cortical excitability in healthy subjects and stroke patients *Tokai J. Exp. Clin. Med.* **38** 123–8
[39] Noachtar S 2004 A glossary of terms most commonly used by clinical electroencephalographers and proposal for the report form for the EEG findings *Klinische Neurophysiol.* **35** 5–21
[40] Christie S 2017 Individual alpha peak frequency in ice hockey shooting performance *Front. Psychol.* **8** 762
[41] Bazanova O 2012 Comments for current interpretation EEG alpha activity: a review and analysis *J Behav. Brain Sci.* **02** 239–48
[42] Gray M J and Emmanouil T A 2019 Individual alpha frequency increases during a task but is unchanged by alpha-band flicker *Psychophysiology* **57** e13480
[43] Klimesch W 1999 Eeg Alpha and theta oscillations reflect cognitive and memory performance: a review and analysis *Brain Res. Rev.* **29** 169–95
[44] Cecere R, Rees G and Romei V 2015 Individual differences in alpha frequency drive crossmodal illusory perception *Curr. Biol.* **25** 231–5
[45] Gladstone D J, Danells C J and Black S E 2002 The fugl-meyer assessment of motor recovery after stroke: a

critical review of its measurement properties *Neurorehabil Neural Repair* **16** 232–40
[46] Page S J, Fulk G D and Boyne P 2012 Clinically important differences for the upper-extremity fugl-meyer scale in people with minimal to moderate impairment due to chronic stroke *Phys. Ther.* **92** 791–8
[47] Nasreddine Z S, Phillips N A, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings J L and Chertkow H 2005 The montreal cognitive assessment, MOCA: a brief screening tool for mild cognitive impairment *J. Am. Geriatrics Soc.* **53** 695–9
[48] Renard Y, Lotte F, Gibert G, Congedo M, Maby E, Delannoy V, Bertrand O and Lécuyer A 2010 Openvibe: an open-source software platform to design, test and use brain–computer interfaces in real and virtual environments *Presence* **19** 35–53
[49] Vourvopoulos A and Bermúdez i Badia S 2016 Motor priming in virtual reality can augment motor-imagery training efficacy in restorative brain-computer interaction: a within-subject analysis *J. Neuroeng. Rehabil.* **13** 1–14
[50] Pion-Tonachini L, Kreutz-Delgado K and Makeig S 2019 ICLabel: an automated electroencephalographic independent component classifier, dataset and website *NeuroImage* **198** 181–97
[51] Pfurtscheller G and Da Silva F L 1999 Event-related EEG/MEG synchronization and desynchronization: basic principles *Clin. Neurophysiol.* **110** 1842–57
[52] Klimesch W, Sauseng P and Hanslmayr S 2007 EEG alpha oscillations: the inhibition–timing hypothesis *Brain Res. Rev.* **53** 63–88
[53] Sousa JCV 2019 Study of a neurofeedback methodology for treatment of chronic pain in clinical context *Master's Thesis*
[54] Lilliefors H W 1967 On the kolmogorov-smirnov test for normality with mean and variance unknown *J. Am. Stat. Assoc.* **62** 399–402
[55] Spearman C 1904 The proof and measurement of association between two things *Am. J. Psychol.* **15** 72
[56] Scheff S W 2016 Nonparametric statistics *Fundam. Stat. Princ. Neurobiol.* 2016 157–82
[57] Wilcoxon F 1945 Individual comparisons by ranking methods *Biometrics Bull.* **1** 80
[58] Ray A M, Figueiredo T D, López-Larraz E, Birbaumer N and Ramos-Murguialday A 2020 Brain oscillatory activity as a biomarker of motor recovery in chronic stroke *Human Brain Mapp.* **41** 1296–308
[59] Kissell R and Poserina J 2017 Chapter 2 - regression models *Optimal Sports Math, Statistics and Fantasy* ed R Kissell and J Poserina (Academic) pp 39–67
[60] Vinding M C, Tsitsi P, Piitulainen H, Waldthaler J, Jousmäki V, Ingvar M, Svenningsson P and Lundqvist D 2019 Attenuated beta rebound to proprioceptive afferent feedback in parkinson's disease *Sci. Rep.* **9** 2604
[61] Hijikata N, Kawakami M, Ishii R, Tsuzuki K, Nakamura T, Okuyama K and Liu M 2020 Item difficulty of fugl-meyer assessment for upper extremity in persons with chronic stroke with moderate-to-severe upper limb impairment *Front. Neurol. 11* 577855
[62] Hatem S M, Saussez G, della Faille M, Prist V, Zhang X, Dispa D and Bleyenheuft Y 2016 Rehabilitation of motor function after stroke: a multiple systematic review focused on techniques to stimulate upper extremity recovery *Front. Hum. Neurosci.* **10** 442
[63] Loubinoux I, Carel C, Pariente J, Dechaumont S, Albucher J-F, Marque P, Manelfe C and Chollet F 2003 Correlation between cerebral reorganization and motor recovery after subcortical infarcts *NeuroImage* **20** 2166–80
[64] Stinear C M, Petoe M A and Byblow W D 2015 Primary motor cortex excitability during recovery after stroke: Implications for neuromodulation *Brain Stimul.* **8** 1183–90
[65] Stinear C M, Barber P A, Coxon J P, Fleming M K and Byblow W D 2008 Priming the motor system enhances the effects of upper limb therapy in chronic stroke *Brain* **131** 1381–90
[66] Coupar F, Pollock A, Rowe P, Weir C and Langhorne P 2011 Predictors of upper limb recovery after stroke: a systematic review and meta-analysis *Clin. Rehabil.* **26** 291–313
[67] Lin Y J, Shukla L, Dugué L, Valero-Cabré A and Carrasco M 2021 Transcranial magnetic stimulation entrains alpha oscillatory activity in occipital cortex *Sci. Rep.* **11** 18562
[68] Rieck N W 1959 Motor responses from the macaque occipital lobe *J. Comparative Neurol.* **112** 203–29