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Prognostic and Monitory EEG-Biomarkers for BCI Upper-limb Stroke Rehabilitation

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***Abstract*—With the availability of multiple rehabilitative interventions, identifying the one that elicits the best motor outcome based on the unique neuro-clinical profile of the stroke survivor is a challenging task. Predicting the potential of recovery using biomarkers specific to an intervention hence becomes important. To address this, we investigate intervention-specific prognostic and monitory biomarkers of motor function improvements using quantitative electroencephalography (QEEG) features in 19 chronic stroke patients following two different upper extremity rehabilitative interventions viz. Brain-Computer Interface (BCI) and transcranial Direct Current Stimulation coupled BCI (tDCS-BCI). Brain symmetry index was found to be the best prognostic QEEG for clinical gains following BCI intervention (r = -0.80, p = 0.02), whereas power ratio index (PRI) was observed to be the best predictor for tDCS-BCI (r = -0.96, p = 0.004) intervention. Importantly, statistically significant between-intervention differences observed in the predictive capabilities of these features suggest that intervention-specific biomarkers can be identified. This approach can be further pursued to distinctly predict the expected response of a patient to available interventions. The intervention with the highest predicted gains may then be recommended to the patient, thereby enabling a personalised rehabilitation regime.**

***Index Terms*—Chronic stroke rehabilitation, Biomarkers, BCI, tDCS, qEEG.**

I. Introduction

Approximately 60% of stroke survivors experience motor function impairments and require rehabilitation [1]. Hence, many rehabilitative interventions have been developed for the purpose of motor function restoration [2]–[8]. Although numerous studies have validated the group level clinical benefits of these interventions [9]–[11], at individual level, the extent to which patient respond to them is highly subject-specific[6], [12]. Therefore, it is necessary to identify the most suitable rehabilitative intervention for a patient and to predict the corresponding recovery. In literature, the heterogeneity in the rehabilitation gains has been primarily attributed to the unique neuro-clinical profile of the patient[3], [4], [13]–[18]. Studies have identified that individual factors such as age [19], volume and location of initial infraction [20], extent of injury to corticospinal tract [13], [18], [21], presence of motor evoked potential [12], [13], [22], and other functional and structural neuroimaging factors [3], [16] affect the patient's response to the intervention and the overall potential of recovery. However, while determining patients' response, other than neuro-clinical profile, the type of intervention in itself is another crucial factor, which is often ignored. Many studies have highlighted that different rehabilitative interventions facilitate the recovery of the damaged brain in a unique manner [8], [23]–[28]. A direct consequence of these intervention-specific recovery mechanisms is that patient responds differently to interventions [15]. Hence, the process of rehabilitation should be treated as an interaction between the patient and the given intervention.

The previous approach of prognostication, which is solely based on the neuro-clinical profile of the patient, does not account for this interaction effect. Therefore, considering rehabilitation from an interaction viewpoint, we propose the existence of intervention-specific prognostic biomarkers. We hypothesise that these biomarkers can encapsulate the interactions between the intervention and the patient, and can uniquely predict the clinical efficacy of the given intervention. More importantly, identification of these prognostic biomarkers can be further pursued to distinctly predict the expected response of a patient to all available interventions. The intervention with the highest predicted gains may then be recommended to the patient, thereby enabling a personalised rehabilitation regime. Furthermore, since the mechanisms of neuronal recovery elicited by different interventions are not identical, we hypothesize that these mechanisms can be encapsulated using intervention-specific monitory biomarkers. The change in these biomarkers can then be used to monitor the evolution of neuronal recovery providing a finer scale to monitor patients' progress. To test these hypotheses, this study investigates between-intervention differences in prognostic and monitory biomarkers of post-stroke recovery. For this purpose, we study the data of chronic stroke patients undergoing upper extremity (UE) motor rehabilitation using a brain-computer interface controlled robotic paradigm (BCI group) and transcranial direct current stimulation (tDCS) coupled BCI paradigm (tDCS-BCI group).

Motor-imagery (MI) based BCI is a promising intervention in the field of UE motor rehabilitation [29], and has been reported to be extremely beneficial particularly to patients with moderate to severe impairments, where active voluntary movement is difficult [10], [30], [31]. MI-BCI controlled robotic system, such as the one used in this study, conducts a passive movement of the affected hand upon the detection of MI performed by the patient, thereby bridging the gap between

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movement intention and execution. This time-locked feedback sequence stimulates the neuronal processes associated with the normal closed loop motor activity and promotes recovery of the lesioned brain network based on the principles of the motor learning and Hebbian plasticity [30], [32].

tDCS is another novel intervention proposed to facilitate the recovery of motor functions after stroke [11], [33]. It involves non-invasive stimulation of brain areas by application of weak direct current using anode and cathode placed at the specific location on the scalp [34]. tDCS has been shown to modulate the cortical activations by changing the resting state membrane potentials of the neurons, with anodal stimulation resulting in enhanced activations and cathodal stimulation exerting suppressive effect [33], [34]. In the field of motor recovery, tDCS aims to target reduced ipsilesional primary motor cortex (M1) activations and increased inter-hemispheric inhibition, which are common effects of stroke [35]. Clinical studies have shown that multi-session tDCS with anode placed over ipsilesional M1 and/or cathode over contralesional M1 may promote the recovery of lost motor functions [11], [36]. Apart from the stand-alone effects, by taking advantage of activated state of the brain following tDCS, studies suggest that a combination of tDCS with other therapies could result in synergistic effects achieving better clinical gains [33]. Although, few studies have investigated the clinical benefits of BCI [10] and tDCS-BCI intervention [37] further understanding of neuronal recovery following these interventions is necessary. Hence, we investigate the exact neuronal mechanisms of motor recovery elicited by these interventions in this study.

To quantify the neuronal changes induced by the tDCS-BCI and BCI interventions, and to predict clinical gains, we used quantitative electroencephalographic (Q-EEG) features. Compared to other neuroimaging modalities, EEG is a low cost and versatile technique which provides information about electrodynamic activations of the brain with high temporal resolution. EEG, commonly perceived in rhythmic form, is highly sensitive to the changes in the Cerebral Blood Flow (CBF) that occur in acute stage of the stroke [38]. Consequently, many acute stroke studies have demonstrated the usefulness of QEEG features. The features based on the power spectrum analysis of resting state EEG have been found to be particularly effective for monitoring of stroke progression as well as for prediction of sub-acute motor status[39]–[43], [43]–[46]. Specifically, the relative power in classical EEG frequency bands [38], [40], [44], the ratio of power in slow v/s fast frequency bands (Power Ratio Index: PRI) [43], [45], [46] and delta to alpha power ratio (Delta Alpha Ratio: DAR) [43], [45], [46] have been observed to be informative in acute stage. In these studies, high relative power in slower frequencies and consequently high values of PRI and DAR have been normally associated with bad motor status and poor prognosis. Furthermore, since, stroke most frequently results in inter-hemispheric imbalance of activations, features quantifying this inter-hemispheric brain asymmetry (Brain Symmetry Index: BSI) namely revised BSI, and pairwise derived BSI (pdBSI) have also shown the predictive and monitory capabilities in motor rehabilitation [47]–[49]. Despite their effectiveness in acute and sub-acute stages, very few chronic stroke rehabilitation studies have evaluated the prognostic and monitory value of these QEEG features [27], [50]–[53] and to the best of the authors' knowledge, no study other than our preliminary analysis [54], [55] has explored the neuroplasticity following BCI and tDCS-BCI intervention using QEEG.

To address this gap, this study investigates the prognostic and monitory capability of resting state QEEG features for the same intervention. Moreover, the MI task state activations can be presumed to be more relevant especially in the field of motor rehabilitation and hence they can provide unique information absent in rest state [28]. Therefore, this study also provides comparative insights about the efficacy of using rest and task state QEEG for prediction and monitoring of BCI and tDCS-BCI rehabilitation. Importantly, we investigate the between-intervention differences in the prognostic and monitory capabilities of QEEG features with an aim to identify intervention-specific signature biomarkers.

II. Methods and Materials

A. Ethics Statement

The experimental procedures involving human subjects described in this study were approved by the Domain Specific Review Board of the National Healthcare Group, Singapore and were in accordance with the Code of Ethics of the World Medical Association.

B. Patients

The clinical trial was designed as a participant and outcomes assessor blinded (double blinded), Randomized Controlled Trial (RCT) with parallel assignment and was conducted from January 2011 to January 2014 at National University Hospital, Singapore. The trial is registered with U.S. National Institutes of Health and detailed protocol is available at clinicaltrials.gov with Clinical Trial Registration Unique Identifier: NCT01897025 (date of registration: July 8, 2013). The sample size was determined by our preliminary results and other studies that used similar endpoints. The study targeted patients with moderate to severe unilateral UE motor impairments who had fewer other therapeutic options available owing to their greater difficulty in movement execution. The pre-intervention degree of impairments was assessed with UE motor part of Fugl-Meyer assessment (FMA) [56], and patients aged between 21 to 70 who had their first ever-stroke unilateral at least 9 months before enrolment with FMA score between 11 to 45 were considered for the study. 42 patients showed interest in this RCT and were assessed with the inclusion criteria and BCI performance criteria [37]. 16 patients were excluded because they did not meet the criteria and another 7 declined to participate. The remaining 19 eligible patients provided written informed consent and participated in the intervention.

C. tDCS-BCI and BCI intervention

The recruited 19 patients were randomly assigned to the tDCS-BCI (n=10) or BCI (n=9) interventions All the recruited patients received BCI rehabilitation for two weeks, which consisted of ten sessions lasting one hour each. The BCI

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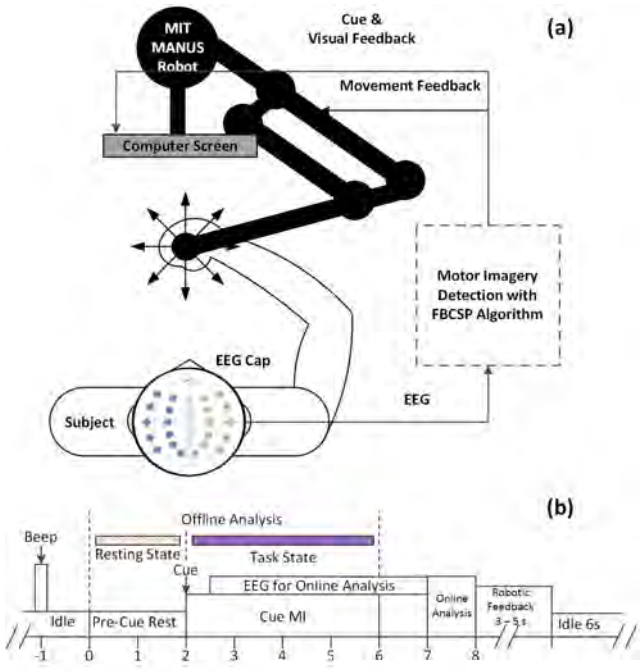

Fig. 1. Rehabilitation system, and protocol. **a.** Setup of Brain Computer Interface (BCI) system for upper extremity rehabilitation. In a trial based setting patients were instructed to perform imagination of moving their affected arm. This motor imagery (MI) was detected in real-time by a patient specific Filter Bank Common Special Patterns (FBCSP) [57] algorithm using the EEG data. The robot performed passive movement of the strapped hand upon the successful detection of MI and this was accompanied with the visual Feedback. **b.** The timeline of BCI rehabilitation trial. Every run started with preparation cue. The MI cue was presented 2s after the preparation cue and following MI cue patients performed MI for 4s. The EEG data collected during 0.5 to 4.5 seconds form the MI cue was processed online to detect MI. In this offline study, the 0s to 2s pre-cue resting state data and 2s to 6s MI task state data have been analysed.

rehabilitation involved BCI triggered robotic movement of the paretic hand upon the detection of motor imagery (MI). In a trial-based setting, patients performed MI of the reaching task with the paretic hand; which was identified online using EEG and successful detection of MI was rewarded by immediate passive movement of the paretic hand using the Inmotion MIT-Manus robot. Each rehabilitation session involved four therapy runs with 40 such trials in each run constituting, in total, 160 repetitions. The design of the trial is presented in Fig. 1 **a,b**. Detailed description of BCI rehabilitation protocol is presented in [37]. In addition to the BCI rehabilitation, the patients in tDCS-BCI group received 20 minutes of 1 mA bi-hemispheric tDCS (the anode over the ipsilesional M1 and the cathode over the contralesional M1) before the start of every session. The M1 positions for tDCS electrodes were approximately determined as locations of the C3 and C4 electrodes in the international 10-20 EEG montage. To ensure the randomized blinding, the BCI group also received a similar but sham-tDCS where the current was applied only for the first 30s.

D. Clinical evaluation

The UE motor part of FMA (range 0-66) was used to assess the clinical recovery of the motor functions, and it was conducted at three time points: 1. Pre-intervention (FMA_{T0}), 2. Post-intervention: immediately after the intervention (FMA_{T2}), and 3: Follow-up: at a two weeks follow-up after the intervention (FMA_{T4}). The intervention gain $\Delta FMA(0,2)$ was calculated as the difference between pre-intervention and post-intervention FMA (FMA_{T2} - FMA_{T0}). Also, 'intervention + follow-up' gain $\Delta FMA(0,4)$ was calculated as the difference between pre-intervention and follow-up FMA (FMA_{T4} - FMA_{T0}).

E. EEG data acquisition, preprocessing and feature extraction

During all the rehabilitation sessions, BCI system continuously captured the brain activity using the Neuroscan Nuamps EEG amplifier with 27 unipolar channels with a sampling frequency of 250Hz [37]. With impedance kept below 5kΩ, the electrodes were positioned according to the international 10/20 system and were referenced to the ear electrode. For the offline analysis, as done in the previous study [55], the continuous EEG data was cleaned for the line noise and zero-phase FIR filtering with hamming window function was performed to bandpass filter the data between 0.5 - 45Hz. The first six seconds of single trial data was extracted from this filtered data and an expert user discarded noisy trials and channels (along with their homologous channels) with the help of PREP [58] and FASTER [59] toolbox. Following this, the common average referencing was performed and eye blink and muscle-related artefacts were removed using Independent Component Analysis (ICA). Expert user removed artefactual components with the help of SASICA [60] toolbox. Finally, from this clean data, a 2s pre-cue resting state EEG and 4s post-cue task state MI data were separately extracted from each trial for the analysis.

From the above data, the single trial Power Spectral Density (PSD) was computed using Welch's periodogram for every channel. This single trial PSD was averaged over all the trials and was summed across 1.0-4.0 Hz, 4.0-7.5 Hz, 7.5-12.5 Hz, and 12.5-30.0 Hz bands to obtain absolute band power in delta (δ), theta (θ), alpha (α), and beta (β) power bands respectively. Moreover, the relative band power was calculated by dividing the absolute band power in each band with the total power in 1-30Hz. This relative power at each channel was then averaged over the scalp to obtain global relative power features: $r\delta$, $r\theta$, $r\alpha$, and $r\beta$. The absolute band power at all the channels was also averaged over the scalp to obtain a global absolute band power in δ, θ, α, and β power bands and it was used to calculate the five global power ratio based features:

$$\text{Power Ratio Index, PRI} = \frac{\delta+\theta}{\alpha+\beta} \quad (1)$$

$$\text{Delta Alpha Ratio, DAR} = \frac{\delta}{\alpha} \quad (2)$$

$$\text{Theta Beta Ratio, TBR} = \frac{\theta}{\beta} \quad (3)$$

$$\text{Theta Alpha Ratio, TAR} = \frac{\theta}{\alpha} \quad (4)$$

$$\text{Theta Beta Alpha Ratio, TBAR} = \frac{\theta}{\alpha+\beta} \quad (5)$$

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Finally, the trial averaged absolute PSD at all channels was used to compute pairwise-derived Brain Symmetry Index (pdBSI) [48] and revised Brain Symmetry Index (rBSI)[61]. Using the averaged activations over two hemispheres, rBSI encapsulates the global inter-hemispheric asymmetry whereas pdBSI is a more localized measure of asymmetry and quantifies the activation imbalance between the homologous channels pairs (left v/s right). As done in the previous studies [27], the rBSI and pdBSI between 1-25Hz were calculated as:

$$rBSI = \frac{1}{N}\sum_{i=1}^{N}\left|\frac{R_i - L_i}{R_i + L_i}\right| \quad , \quad R_i = \frac{1}{M}\sum_{j=1}^{M} r_{ij} \tag{6}$$

$$pdBSI = \frac{1}{MN}\sum_{j=1}^{M}\sum_{i=1}^{N}\left|\frac{r_{ij} - l_{ij}}{r_{ij} + l_{ij}}\right| \tag{7}$$

Here, r_{ij} and l_{ij} represent the trial averaged PSD from right and left homologous channel pairs (at channel pairs *j= 1,2,...,M)* at frequency *i= 1,2,...,N*. R_i and L_i (similarly calculated) are the average power over all the channels on the right and left hemispheres at frequency *i*.

Considering these two brain symmetry features and nine band power features, in total eleven QEEG features were extracted for each subject from the first (pre-intervention: EEG_{T0}) and the last (post-intervention: EEG_{T2}) rehabilitation session from both the rest and task state EEG data.

F. Group-level correlation analysis and statistical tests

The usefulness of above-mentioned EEG features as rehabilitation biomarkers was investigated by examining their correlation with the FMA scores. Owing to the non-normal distribution of the data, a non-parametric statistical analysis was performed, and hence the relationship between EEG features and the clinical outcome was assessed using Spearman's rank correlation. The correlation was computed for the following combination of times points.

- Prognostication: Pre-intervention values of biomarkers (EEG_{T0}) vs. two- and four-week change in the FMA score (EEG_{T0} vs. ΔFMA(0,2), EEG_{T0} vs. ΔFMA(0,4)). These correlations indicate whether the EEG-features can predict the functional outcomes and aid in intervention prognosis.
- Monitoring: FMA score vs. values of biomarkers at pre and post-intervention time points (EEG_{T0} vs. FMA_{T0}, EEG_{T2} vs. FMA_{T2}), as well as intervention-induced change in biomarkers vs. change in FMA ($\Delta EEG(0,2)$ vs. ΔFMA(0,2)). These regressions represent the utility of biomarkers for evaluation of recovery and may aid in monitoring the patients' progress.

The small sample size of the study and performing multiple correlations simultaneously increases the likelihood of overestimation of statistical significance and chance of false discoveries. Hence, for the proper estimation of statistical significance of correlations, as done in the previous studies [28], the method of non-parametric permutation testing was employed [62]. Permutation testing involves repeated shuffling of labels across subjects and recalculation of correlation coefficient (ρ) for each arrangement. Random shuffling destroys any relation between two variables, and hence these calculated ρ values represent a distribution of the null hypothesis that there is no relationship between the two variables. The distribution can be approximated to the normal distribution and using it the statistical significance of the original observed correlation is calculated by two-tailed z-test, testing the hypothesis that the observed ρ lies at extreme tails of this distribution [62]. In our analysis, clinical parameters in the correlation (FMA_{T0}/ FMA_{T2}/ $\Delta FMA(0,2)$/ $\Delta FMA(0,4)$) were randomly shuffled 5000 times to obtain null distribution. This procedure provides a robust estimation of statistical significance reducing the Type-I errors, at the same time preserves the power of the study limiting Type-II errors. Finally, assuming Spearman's rank correlation coefficient of 0.6, the sample size of the study was just enough (n≥9) to achieve a statistical power of 80% with a significance level of α = 0.05.

To investigate the possibility of intervention-specific biomarkers, the inter-intervention difference in the strength of relation between any EEG biomarker and FMA feature was examined by statistical comparison of their correlation coefficients (CC) using Fisher Z-transformation [63]. This method allows statistical testing of whether a particular EEG feature has a rather strong relationship with the clinical features in one particular group and no/weak relationship with the other group, making that feature an intervention-specific biomarker of recovery. In addition, we analysed the differences in the relationship of pre-intervention EEG features with two vs. four week clinical gains using Dunn's z-test [64]. This analysis was performed to understand the effect of prediction duration on the prognostic capabilities of EEG features. Moreover, to encapsulate the mechanism of recovery, the change in EEG features during the intervention was assessed using Wilcoxon signed-rank test. Finally, the inter-intervention differences in the features were tested using Wilcoxon rank sum test.

III. Results

A. Clinical outcomes

The demographic and clinical details of the patients are listed in Table I. No significant difference was observed between tDCS-BCI and BCI group in terms of age (p = 0.508), post-stroke time (p = 0.720), and baseline FMA (p = 0.6475). Both the groups showed improvements in the FMA scores immediately after the training (tDCS group: 0.9±3, BCI group: 2.8±4) as well as at follow-up assessment (tDCS group: 5±4.4, BCI group: 5.4±5.7). However, only the improvement till the follow-up assessment was statistically significant (tDCS-BCI group: p = 0.006, BCI group: p = 0.021). Importantly, no significant inter-intervention difference was observed in the clinical improvements at any time-point (T2: p = 0.250, T4: p = 0.793). Furthermore, both in the tDCS-BCI and BCI group, the 2 and 4 week clinical improvements did not display any significant correlation with the pre-intervention FMA, age, and post-stroke time (all p>0.4). Therefore, demographic variables did not present any prognostic value. Finally, the correlation between $\Delta FMA(0,2)$ and $\Delta FMA(0,4)$ was significant in BCI group (p = 0.018) but was not significant in tDCS-BCI group (p = 0.059) indicating better sustenance of recovery in the BCI group.

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TABLE I
CLINICAL AND DEMOGRAPHIC DETAILS OF THE PATIENTS. (MEAN ± STD)

Patient	Sex	Age	Lesion side	Type	Nature	Post stroke time (months)	FMA Score		
							FMA_{T0}	FMA_{T2}	FMA_{T4}
tDCS-BCI group									
P1	M	29	R	I	SC	45.2	51	50	51
P2	M	54	L	I	SC	23.3	29	34	42
P3	F	38	R	H	SC	24.3	38	41	42
P4	F	60	R	H	SC	50.1	26	22	31
P5	F	48	L	H	SC	49.1	39	42	46
P6	M	59	L	I	SC	16.0	31	28	31
P7	M	65	L	I	SC	29.5	41	45	48
P8	F	57	L	H	SC	12.9	40	40	44
P9	M	47	R	I	C	11.0	30	31	40
P10	M	64	R	I	SC	89.6	28	29	28
	6M/4F	52.1±11.6	5R/5L	4H/6I	1C/9SC	35.1±24.1	35.3±7.8	36.2±8.8	40.3±7.8
BCI group									
P12	M	51	R	I	SC	41.9	33	42	45
P13	M	39	L	I	SC	22.7	36	42	39
P14	M	59	R	H	SC	51.8	41	46	57
P15	F	70	R	I	SC	19.6	23	25	26
P16	M	59	R	I	SC	51.8	29	24	28
P17	M	58	L	I	SC	30.7	28	32	37
P18	M	47	L	I	SC	10.4	40	40	40
P19	M	58	R	H	SC	27.0	20	22	24
P20	M	66	R	I	SC	50.6	43	45	46
	8M/1F	56.3±9.5	6L/3L	2H/7I	9SC	34±15.5	32.6±8.1	35.3±9.6	38±10.7

B. BCI training parameters

The subject-specific FBCSP model used for the BCI training may have a potential influence on patients' clinical and neurological evolution. Therefore, inter-group differences in spectral and spatial features selected by the FBCSP algorithm were investigated. Spectral analysis indicated that there was no significant difference in the selected filter bands between the two groups (Fisher's exact test, p = 0.523). Moreover, qualitative analysis of selected CSP filters displayed no between-group difference in the spatial features. MI detection accuracy during rehabilitation runs was also not different between the two groups (tDCS-BCI = 83.7%, BCI = 86.3%, p = 0.523).

C. Prognostication

Many pre-intervention rest and task state QEEG features presented significant prognostic capabilities and Table II presents these results. In the tDCS-BCI group, the two weeks FMA gains ($\Delta FMA(0,2)$) showed significant negative correlation with relative delta power ($r\delta_{T0}$, p = 0.028), PRI (PRI_{T0}, p = 0.004), and TAR (TAR_{T0}, p = 0.049) in the resting state. The task state relative delta power ($r\delta_{T0}$, p = 0.063) as well as TAR (TAR_{T0}, p = 0.077) also displayed similar correlations but only the negative correlation of $\Delta FMA(0,2)$ with task state PRI (PRI_{T0}, p = 0.001) was significant. In a similar manner, significant negative correlation was found between four weeks FMA gains ($\Delta FMA(0,4)$) and relative delta power ($r\delta_{T0}$, p_{rest} = 0.007, p_{task} = 0.011), PRI (PRI_{T0} p_{rest} = 0.038, p_{task} = 0.039), and DAR (DAR_{T0}, p_{rest} = 0.036, p_{task} = 0.035) in both resting and task state data. These relationships are illustrated in Fig. 2. Importantly, the strength of relationship between many QEEG features and $\Delta FMA(0,2)$ vs $\Delta FMA(0,4)$ was very different and Dunn's z-test revealed that this difference was statistically significant for resting state PRI_{T0} (p = 0.019). Finally, both resting and task state EEG features demonstrated very similar correlations with functional improvements in the tDCS-BCI group.

In the BCI group, the pdBSI ($pdBSI_{T0}$, p = 0.024) and rBSI ($rBSI_{T0}$, p = 0.028) calculated from the resting state EEG were significantly correlated with the two weeks FMA gains. The same two features were also correlated with the four weeks motor gains ($pdBSI_{T0}$, p = 0.022; $rBSI_{T0}$, p = 0.024). On the other hand, in the task state features, only the significant correlation was only observed between the $\Delta FMA(0,4)$ and pdBSI ($pdBSI_{T0}$, p = 0.025). These significant relationships are illustrated in Fig. 2. Noticeably, no significant correlation was observed between intervention gains and any EEG power ratio features in the BCI group.

From Table II, it can be noted that the EEG features showing prognostic capabilities in tDCS-BCI and BCI groups are different. The outcomes of tDCS-BCI rehabilitation are strongly correlated with power ratio features whereas brain asymmetry features display strong relation with the clinical gains in the BCI rehabilitation. Statistical comparison confirmed these evident differences and it was observed that inter-intervention differences in the predictive capabilities of resting state PRI_{T0} (p = 0.014), $r\delta_{T0}$ (p = 0.016), $pdBSI_{T0}$ (p = 0.047), and $rBSI_{T0}$ (p = 0.006) features are statistically significant. This comparison supports the observation that resting state PRI_{T0}, $r\delta_{T0}$ are significantly better predictors of recovery following the tDCS-BCI intervention whereas resting state $pdBSI_{T0}$, $rBSI_{T0}$ have stronger relationship with the intervention gains following the BCI intervention. The differences in task state features did not reach statistical significance. Also, in both the groups, the difference in the prognostic capabilities of any

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TABLE II
CORRELATION ANALYSIS: PRE-INTERVENTION EEG FEATURES (EEG_{T0}) AND CLINICAL IMPROVEMENT (ΔFMA(0,2), ΔFMA(0,4))

EEG Features	tDCS-BCI				BCI			
	ΔFMA(0,2)		ΔFMA(0,4)		ΔFMA(0,2)		ΔFMA(0,4)	
	Rest	Task	Rest	Task	Rest	Task	Rest	Task
$r\delta_{T0}$	***-0.74**	-0.62	****-0.90**	****-0.84**	-0.22	0.12	-0.25	-0.08
$r\theta_{T0}$	-0.11	-0.32	0.49	0.29	-0.22	-0.49	-0.02	-0.25
$r\alpha_{T0}$	0.42	0.42	0.49	0.63	0.27	-0.05	0.37	0.20
$r\beta_{T0}$	0.42	0.49	0.06	0.13	0.68	0.42	0.46	0.10
PRI_{T0}	****-0.96**	****-0.86**	***-0.70**	***-0.70**	-0.59	-0.24	-0.47	-0.46
DAR_{T0}	-0.54	-0.43	***-0.70**	***-0.71**	-0.22	0.15	-0.41	-0.24
TBR_{T0}	-0.51	-0.55	0.02	0.03	-0.46	-0.46	-0.2	-0.20
TAR_{T0}	***-0.66**	-0.59	-0.39	-0.41	-0.44	-0.24	-0.36	-0.29
$TBAR_{T0}$	-0.58	-0.60	-0.10	-0.04	-0.51	-0.51	-0.25	-0.25
$pdBSI_{T0}$	-0.35	0.03	-0.20	0.03	***-0.80**	-0.56	***-0.81**	***-0.80**
$rBSI_{T0}$	0.07	0.24	0.30	0.49	***-0.76**	-0.39	***-0.80**	-0.64

correlation coefficients, * implies p < 0.05 and ** implies p <0.01

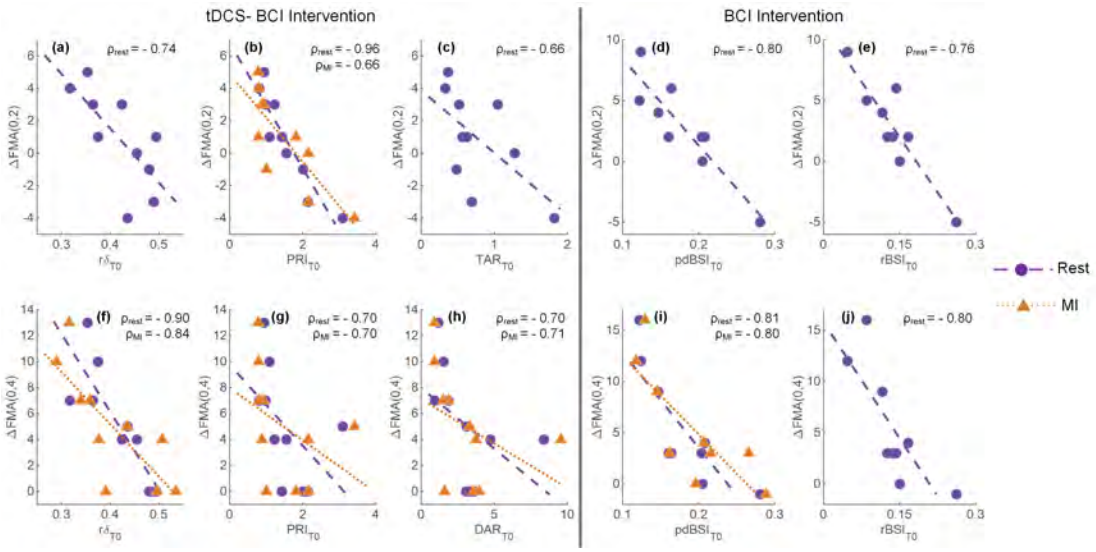

Fig. 2. Statistically significant relationships for the prediction of intervention gains. Significant correlation between pre-intervention EEG features and two-week FMA gains for the tDCS-BCI group are presented in panels (a)-(c), whereas panels (d)-(e) represent the same relationship for the BCI group. Similarly, significant association between four-week FMA gains and pre-intervention EEG features is displayed in panels (f)-(h) for the tDCS-BCI group and panels (i)-(j) for the BCI group.

QEEG features during rest and task state was not significant.

D. Monitoring

To assess the ability of EEG features in characterization of intervention-induced gains and for monitoring of recovery evolution, a three-fold analysis was performed. First, the association between pre-intervention motor status and pre-intervention EEG features was investigated. Next, the relationship between the intervention-induced changes in the EEG features and motor improvements was explored. Finally, the correlation between post-intervention EEG features and post-intervention motor status was studied. The entire analysis was performed on the FMA_{T0}, and FMA_{T2} features and the FMA_{T4} was not considered due to unavailability of week-4 EEG data.

1) Correlation between pre-intervention EEG features and pre-intervention FMA: Initially, a separate group analysis of the correlation between pre-intervention EEG features (EEG_{T0}) and FMA_{T0} was performed and it resulted in significant negative correlation of FMA_{T0} with rest and task state TBR (TBR_{T0}, p_{rest} = 0.033, p_{task} = 0.034) and significant positive correlation with task state relative beta power ($r\beta_{T0}$, p = 0.033), for the BCI group. In the tDCS-BCI group, only task state features, specifically, relative theta power ($r\theta_{T0}$, p = 0.040), TBR (TBR_{T0}, p = 0.042), and TBAR ($TBAR_{T0}$, p = 0.019) displayed significant correlations with the FMA_{T0}. The inter-intervention comparison of correlation coefficients was performed to investigate the possibility of inter-intervention difference in the monitory capabilities of any EEG_{T0} features. No such statistically significant differences in the correlation as well as in the values of EEG features were observed (all p>0.17) and hence, a combined group analysis (all subjects) was performed. This correlation analysis considering all the patients revealed significant relationship of FMA_{T0} with task

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TABLE III
CORRELATION BETWEEN PRE-INTERVENTION EEG FEATURES (EEG_{T0}) AND PRE-INTERVENTION FMA SCORES (FMA_{T0}).

EEG Features	tDCS-BCI		BCI		All	
	Rest	Task	Rest	Task	Rest	Task
$r\delta_{T0}$	-0.16	-0.10	0.13	-0.02	0.07	-0.13
$r\theta_{T0}$	-0.59	***-0.68**	-0.68	-0.57	****-0.61**	***-0.59**
$r\alpha_{T0}$	0.24	0.03	-0.25	-0.18	-0.02	0.01
$r\beta_{T0}$	0.22	0.60	0.55	***0.77**	0.34	****0.64**
PRI_{T0}	-0.21	-0.15	-0.40	-0.55	-0.18	-0.36
DAR_{T0}	-0.04	-0.03	0.12	0.05	0.06	-0.12
TBR_{T0}	-0.27	***-0.68**	***-0.75**	***-0.75**	***-0.48**	****-0.70**
TAR_{T0}	-0.39	-0.39	-0.50	-0.53	-0.33	-0.38
$TBAR_{T0}$	-0.56	***-0.78**	-0.60	-0.60	***-0.50**	****-0.64**
$pdBSI_{T0}$	-0.20	0.39	-0.45	-0.33	-0.38	-0.04
$rBSI_{T0}$	-0.50	-0.19	-0.33	-0.20	***-0.46**	-0.18

correlation coefficients, * implies p < 0.05 and ** implies p <0.01

and rest state relative theta power ($r\theta_{T0}$, p_{rest} = 0.008, p_{task} = 0.012), TBR (TBR_{T0}, p_{rest} = 0.043, p_{task} = 0.003), TBAR ($TBAR_{T0}$, p_{rest} = 0.033, p_{task} = 0.006), rest state rBSI ($rBSI_{T0}$, p = 0.046), and task state relative beta power ($r\beta_{T0}$, p = 0.007). The complete list of correlation coefficient values is presented in Table III.

2) Post-intervention change in the EEG features and their correlation with the functional improvement: The statistical analysis of pre and post-intervention EEG feature values revealed that there was a significant intervention-induced change in the relative theta band power (p=0.039) in the BCI group during rest state. Also, although not significant, BCI group displayed a marginal change in resting state TAR (p = 0.054) and TBAR (p = 0.074). No significant intervention-induced change was observed in task state EEG features in the BCI group. In the tDCS-BCI group, resting state pdBSI (p=0.019) and task state rBSI (p = 0.037) changed significantly during the intervention. Although the EEG features displaying significant changes in the tDCS and BCI group were mutually exclusive, no statistically significant between-intervention difference in change of EEG features was observed.

Following the identification of the EEG variables that changed significantly, we investigated if this change correlated with clinical improvements. The correlation analysis between ΔEEG and $\Delta FMA(0,2)$ revealed that there was a significant negative correlation between $\Delta FMA(0,2)$ and resting state $\Delta r\theta$ (p = 0.032), ΔTAR (p = 0.048), and $\Delta TBAR$ (p = 0.049) in the BCI group. Coherent with the resting state features, the task state $\Delta r\theta$ (p = 0.086), and $\Delta TBAR$ (p = 0.102) also demonstrated relationship with $\Delta FMA(0,2)$ in the BCI group but only correlation with ΔTAR (p = 0.038) was statistically significant. Despite the significant change, resting state $\Delta pdBSI$ and task state $\Delta rBSI$ did not show any significant correlation with $\Delta FMA(0,2)$ in the tDCS-BCI group. Moreover, right-tailed Fisher z-test revealed that the correlation between $\Delta FMA(0,2)$ and resting state $\Delta r\theta$, ΔTAR, and $\Delta TBAR$ was marginally stronger in the BCI group than the tDCS-BCI group (p = 0.064, 0.076, 0.079). In the analysis of task state features, this trend was only observed for $\Delta r\theta$ (p = 0.076). Table.IV (A) reports the correlation between all the ΔEEG features and $\Delta FMA(0,2)$. Also, the significant correlations are presented in figure 3.

TABLE IV
CORRELATION BETWEEN CLINICAL IMPROVEMENT ($\Delta FMA(0,2)$) AND INTERVENTION INDUCED CHANGE IN THE EEG FEATURES (ΔEEG)

EEG Features	tDCS		BCI	
	Rest	Task	Rest	Task
$\Delta r\delta$	0.01	0.09	-0.02	0.15
$\Delta r\theta$	-0.16	0.09	***-0.76**	-0.61
$\Delta r\alpha$	0.24	0.37	0.37	0.46
$\Delta r\beta$	-0.64	-0.54	0.12	0.19
ΔPRI	0.12	0.10	0.08	-0.17
ΔDAR	0.13	0.10	0.05	0.14
ΔTBR	0.05	0.19	-0.59	-0.54
ΔTAR	-0.07	-0.31	***-0.70**	***-0.73**
$\Delta TBAR$	-0.06	-0.10	***-0.70**	-0.58
$\Delta pdBSI$	0.27	0.25	-0.63	-0.66
$\Delta rBSI$	-0.34	0.02	-0.54	-0.56

correlation coefficients, * implies p < 0.05 and ** implies p <0.01

TABLE V
CORRELATION BETWEEN POST-INTERVENTION FMA SCORE (FMA_{T2}) AND POST-INTERVENTION EEG FEATURES (EEG_{T2}).

EEG Features	tDCS		BCI	
	Rest	Task	Rest	Task
$r\delta_{T2}$	-0.22	-0.38	-0.25	-0.37
$r\theta_{T2}$	-0.26	-0.33	-0.61	-0.64
$r\alpha_{T2}$	0.31	0.43	0.21	0.23
$r\beta_{T2}$	0.04	0.43	***0.82**	****0.94**
PRI_{T2}	-0.44	***-0.67**	-0.55	-0.44
DAR_{T2}	-0.16	-0.35	-0.25	-0.16
TBR_{T2}	0.07	-0.41	***-0.76**	***-0.83**
TAR_{T2}	-0.52	-0.65	***-0.71**	***-0.71**
$TBAR_{T2}$	-0.39	-0.53	-0.66	***-0.69**
$pdBSI_{T2}$	-0.05	0.09	-0.51	-0.55
$rBSI_{T2}$	-0.27	-0.01	-0.59	-0.54

correlation coefficients, * implies p < 0.05 and ** implies p <0.01

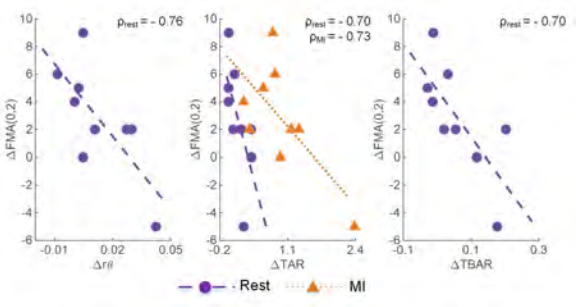

Fig. 3. Statistically significant relationships for monitoring the evolution of intervention gains. All the panels represent the significant association observed between two-week intervention gains and intervention-induced changes in the EEG features in BCI group. No significant relationships where observed in the tDCS-BCI group.

3) Correlation between post-intervention EEG features and post-intervention FMA: The analysis of relation between post-intervention clinical score (FMA_{T2}) and post-intervention EEG features (EEG_{T2}) revealed that, in the BCI group, FMA_{T2} has statistically significant negative correlation with

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both task and resting state TBR_{T2} (p_{rest} = 0.030, p_{task} = 0.018), and TAR_{T2} (p_{rest} = 0.041, p_{task} = 0.046) and a marginal negative trend with $r\theta_{T2}$ (p_{rest} = 0.078, p_{task} = 0.072), and $TBAR_{T2}$ (p_{rest} = 0.061, p_{task} = 0.048). Also, a strong positive correlation was observed between $r\beta_{T2}$ and FMA_{T2} (p_{rest} = 0.020, p_{task} = 0.008) in the BCI group. In tDCS-BCI group only task state PRI_{T2} was significantly correlated with EEG_{T2} (p = 0.038). Complete correlation results are presented in Table.V.

IV. Discussion

Previous studies have demonstrated the utility of QEEG features for post-stroke clinical prognosis and monitoring in acute/sub-acute stages [65]. This study demonstrated that QEEG features are informative in the chronic stage as well, pointing their potential use as rehabilitation biomarkers. In the BCI group, significant intervention-induced changes in resting state relative theta power, and marginally significant change in TAR, and TBAR were observed and these changes were negatively correlated with clinical gains. The task state features also resulted in similar negative correlations. These negative correlations signify that improvement in motor functions is associated with the reduction in power of low-frequency oscillations, which is in accordance with the previous literature [27], [65]. All these features have major involvement of theta band power and in acute stroke; theta band has been associated with the ischemic penumbra, a region with intact but deactivated neurons[45]. Moreover, pre and post- intervention FMA scores displayed positive correlation with the task state beta power in the BCI group and it indicates that presence of higher power in high frequency oscillations is associative of better motor status which is also reported in the stroke literature [27]. Hence, motor recovery in the BCI group can be inferred to be facilitated by training-induced reactivation of dysfunctional neuronal population. This inference is also supported by a recent report of CBF analysis performed on a subset cohort [24]. The restoration of CBF by perfusion of ischemic penumbra is associated with the reactivation of neuronal tissues, and a widespread change in CBF and its positive correlation with FMA change has been reported for the subset group, representing coherent conclusions from both EEG and CBF analysis [24]. Very different from the BCI group, significant changes in the resting and task state inter-hemispheric brain asymmetry were characteristic of tDCS-BCI intervention. This indicates that tDCS indeed resulted in modification of hemispheric activations. Although, the observations are in accordance with the significant change in inter-hemispheric CBF asymmetry observed in the tDCS-BCI group alone[24], the changes were not correlated with the observed motor gains. Therefore, it is difficult to establish any direct relationship between brain asymmetry and functional motor gains, and more investigation is necessary to understand the exact mechanism of recovery following tDCS-BCI intervention.

Notably, both the tDCS-BCI and BCI groups resulted in similar clinical gains and despite the absence of any inter-group differences in pre-treatment conditions and BCI training parameters, the QEEG features which changed significantly during these interventions were mutually exclusive. This indicates that similar clinical recovery may be achieved by different interventions through distinct mechanisms of neuronal repair. This justifies the rationale behind intervention-specific monitory biomarkers and their presence was validated in this study. Also, in the BCI group, the pre and post-intervention TBR showed significant correlation with the pre and post-intervention motor status, respectively. The post-intervention correlation was found to be specific to the BCI group, which indicates that TBR changed only following the BCI intervention and the final value of TBR was related to the final motor status. Biomarkers of this type can be used to assess patients' progress on a neurological scale when they are undergoing an intervention and can aid in recommending the appropriateness of an intervention.

The unique mechanisms of recovery facilitated by rehabilitative intervention also suggest the presence of a distinct set of intervention-specific prognostic biomarkers. In this study, for the tDCS-BCI group, a strong negative correlation of pre-intervention relative delta power, and PRI with two-week motor gains was observed, which implies that the presence of large value of slow oscillations is representative of poor expected recovery. Furthermore, the prediction of four-week gains in tDCS-BCI group also resulted in similar observations with relative delta power, DAR and PRI displaying significant negative correlations. These observations are consistent with the previous literature, where a high value of relative delta power, DAR and PRI has been associated with the poor prognosis in acute/sub-acute stages [44], [45], [47], [50], [66] and less intervention-induced motor recovery in the chronic stage [27]. Since the presence of large delta oscillations has been associated with severe ischemia and hypo-perfused neuronal population in the acute stage [38], [40], [43], it can be inferred that observed correlations may dictate the direct relationship between the extent of affected neuronal population and expected motor recovery. Distinct from the tDCS-BCI group, the prognostic information in the BCI group was entirely quantified using brain asymmetry features. A significant negative correlation was observed between two, four weeks clinical gains and pre-intervention pdBSI, rBSI; indicating that symmetrical pre-intervention brain activation favours motor recovery. This observation has been reported in the sub-acute state [47], [66], and this study confirmed the same relationship in the chronic stage as well. Importantly, a mutual exclusiveness in the significant prognostic features between two interventions was observed and the difference in the strength of prognostic correlation was statistically significant for resting state PRI, relative delta power, pdBSI, and rBSI. These observations depict the existence of intervention-specific prognostic biomarkers which distinctly predict the clinical gains from a given intervention. These intervention-specific biomarkers quantify the expected interaction between the intervention and the patient thereby uniquely predicting the rehabilitation gains following the given intervention. Following this approach, the clinical gains from all available interventions can be predicted and clinicians may then recommend the intervention with the highest predicted gains to the patient, thereby achieving maxi-

mum clinical recovery, better patient stratification and optimal allocation of resources. Although a vast number of studies have been conducted to investigate prognostic biomarkers of intervention-induced post-stroke motor recovery [3], [8], [16], [22], the lack of studies exploring same neurological features as a predictor for different interventions and common practice of reporting only positive results has made the task of identifying intervention-specific biomarkers difficult. Hence, more investigation in this direction is necessary, and a systematic review of prognostic biomarkers with a stratification based on rehabilitative interventions may shed some light on this topic.

Next, for both the interventions, we observed a very similar relationship of clinical features with both task and rest state QEEG features. There was no statistically significant difference in the strength of prognostic and monitory correlations between task and rest state data, which indicates that both types of features provide coherent results. However, only pdBSI and rBSI displayed considerable difference in the relationship of clinical features with task vs. rest state features. This difference can be mainly attributed to contralateral activation patterns associated the hand MI during the task state [67]. In our investigation, only resting state EEG features qualified as intervention-specific prognostic biomarkers on the statistical grounds. Yet, taking into account the absence of significant differences between task vs. rest state relationships, both task and rest features should be considered equally informative and further studies with higher sample size may provide some conclusive remarks.

Finally, there are few limitations to this study. The main limitation is the small sample size from the statistical viewpoint which was restricted by the complexity and length of the rehabilitation protocol but it is at par with the other studies in this field [10]. Despite this, remarkably coherent results from both task and resting state data are observed, and these results are consistent with the neuroimaging findings reported on the subset cohort [24], indicating the soundness of the results. Still, a confirmatory study with higher sample size will be useful for verification of results of this study. Also, the primary motivation of this study was to demonstrate the possibility of intervention-specific prognostic and monitory biomarkers, and QEEG features were selected for this purpose because of their simplicity in calculations and interpretations. As the selected QEEG features lacked spatial resolution, further complementary EEG features, such as those derived from the signal and source space connectivity analysis may provide more comprehensive insights into the brain dynamics during motor recovery. Moreover, correlation analysis when accompanied with causal inferencing may provide more robust neurological interpretations of the observed results. Nonetheless, alone the capabilities of QEEG features to uniquely predict and monitor the intervention induced recovery as reported in this paper, are highly relevant in clinical decision making.

V. Conclusions

In this study, it was found that the QEEG features can act as prognostic and monitory biomarkers in the chronic state post-stroke motor recovery following tDCS-BCI and BCI rehabilitation. Despite similar clinical recovery, the mechanism of neuronal recovery facilitated by these interventions were very different. The relative theta power was observed to be the signature monitory biomarker for BCI intervention whereas the tDCS group was characterized by a change in brain symmetry index. Also, pre-intervention relative delta power and power ratio index were the best predictors of clinical gains following tDCS-BCI intervention, whereas, the clinical gains following BCI intervention were best predicted using brain symmetry index. Consequently, prognostic and monitory biomarkers of motor recovery were observed to be significantly different between the two groups suggesting the possibility of intervention-specific biomarkers. This approach can be pursued to uniquely predict the expected response of a patient to an intervention and the intervention with the highest predicted gains may then be recommended to the patient, thereby enabling a highly personalised motor rehabilitation.

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