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MACHINE LEARNING-BASED IDENTIFICATION OF TES-TREATMENT NEUROCORRELATES

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ABSTRACT: This study presents a Machine Learning-based identification of electroencephalographic (EEG) features related to transcranical Electrical Stimulation (tES) in Multiple Sclerosis (MS) patients. The contribution is a first step toward an automated system capable of adjusting electrical stimulation according to the EEG feedback (EEG-based adaptive tES). Five MS patients underwent both tES or sham treatments and a Theory of Mind (ToM) training, and the EEG signal before and after treatments was acquired both in Eyes-Open (EO) and in Eyes-Closed (EC) condition. tES was administered by fixed cathode electrodes on the right deltoid muscle. Power differences between post and pre tES treatment in six bands of interest were explored. Support Vector Machine classifier achieved 92.5 % and 100.0 % accuracy in classifying a subject treated with tES, by exploiting power differences within high beta in T3 and gamma in T3 and P3 in EO condition and power differences within gamma in T3, Pz, Cz in EC condition, respectively. In particular, absolute power in gamma band was reduced after the treatment. The result is clinically significant due to the tendency of MS patients to have high values in this band, caused by the compensation determined by the neurons as a result of the demyelination process.

INTRODUCTION

Multiple Sclerosis (MS) is a neurological disease with recurrent episodes of focal disorders influenced by the location and extent of demyelinating lesions within the Central Nervous System (CNS) [1]. MS can cause deficits of Theory of Mind (ToM), namely the capacity to infer mental states causing action and to reason on the contents of one's own and others' minds [2, 3]. However, how ToM subcomponents (cognitive and affective) are affected in MS it's not yet well understood. Typically, MS symptoms are pharmacologically treated. Currently, multidisciplinary approaches based on symptom type are emerging, including disease-modifying therapies, lifestyle modifications, psychological support, and rehabilitation interventions. [4–6].

In recent years, also transcranial Electrical Stimulation (tES) has been considered among the treatments used to relieve MS symptoms.

tES consists in the administration of small currents applied to the scalp [7]. The applied current can induce acute or long-lasting effects depending on the signal specifications [8]. Three tES modalities, distinguished by current administration methods, are commonly used : low-intensity Direct Current (tDCS), Alternating Current (tACS) and Random Noise Current (tRNS) [9, 10].

tDCS is the most widely used technique for the treatment of various medical conditions [7]. tDCS microscopically produces a series of effects including resting threshold modification, changes in synaptic processes, enhancement of synaptic plasticity and effects on glial cells [11–14]. tDCS treatment effects on MS-related impairments have rarely been addressed, despite stimulating neuronal activity is an important promoter of the remyelination process [15]. Some studies suggest positive effects, including attention enhancement, executive function and motor improvement, as well as reduction of associated symptoms [16, 17][18].

tDCS technique has been demonstrated to be effective but without following precise guidelines on stimulation parameters and brain areas to be stimulated. In most cases, the effectiveness of the treatment is assessed only by the improvement of pathology symptoms [19].

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Studies on healthy patients demonstrated the EEG-based effects of tDCS treatment by describing changes in the five frequency bands: delta ([0.5-4] Hz), theta ([4-8] Hz), alpha ([8-12] Hz), beta ([12-30] Hz) and gamma ([30-45] Hz). According to Boonstra et al. [20], stimulation causes an increase in power especially below 5 Hz (delta band). Theta band is also involved in this study and the literature observes a specific increase in spectral power during tDCS stimulation specifically in the cingulate cortex and the dorsolateral prefrontal cortex (DLPFC) [21, 22]. Some results showed significantly changes in the alpha band power after anodal tDCS over the left DLPFC [23, 24], while Mangia et Al.[21] reported variations in the beta band during and after stimulation. Song et al. [25] observed an increase in beta frequency power after tDCS treatment, resulting in a change in the state of efficient cognitive functioning of the brain. Also an increase in gamma power associated with the engagement of proactive control in DLPFC was demonstrated [26].
Changes in EEG frequency bands indicating neuron deterioration are also connected with Multiple Sclerosis. MS patients have shown abnormally low Posterior Dominant Rythm (PDR), a reliable predictor of baseline neural activity, with a significantly lower mean value [27]. Literature demonstrates a significant increase in power in the delta band in the fronto-temporo-central regions and significant increase in delta and theta waves has been observed in MS patients with a high load of subcortical lesions [28, 29]. Increased amplitude in gamma band was also observed in Relapsing-Remitting Multiple Sclerosis (RRMS) patients. Moreover, decreased alpha frequency during rest indicates pathological desynchronization of widespread neural networks regulating cortical arousal fluctuation and tonic attention [29]. Although the use of EEG signal has been widely used for the treatment and diagnosis of Multiple Sclerosis, there are few studies using tES treatments referring to changes in EEG features to improve health condition of MS patients [30, 31]. This study aims to identify EEG features on tES-treated MS patients and the analysis of start and finish EEG condition correlated with clinical condition changes in ToM framework.

MATERIALS AND METHODS

Clinical protocol: Five MS patients (4 women, 1 man) ranging from 18 to 75 years with the Expanded Disability Status scale (EDSS) score between 1 to 7 were enrolled in this study [32]. The exclusion criteria were the following:

- History of psychiatric illness, head injury or other neuro-degenerative diseases (dementia or global cognitive impairment);
- Surgery;
- Intracranial metal implantation and pacemaker;
- Severe disability (score $>$ 7 on the EDSS scale);
- Pregnancy or lactation;
- Illiteracy.

The experimental protocol involved the following phases:

- Collection of demographic and clinical history data, a neuropsychological assessment and self-administration of questionnaires;
- 3 minutes EEG recording before treatment sessions in Eyes-Open (EO) condition;
- 3 minutes EEG recording before treatment sessions in Eyes-Closed (EC) condition;
- Non-pharmacological treatment conducted twice a week for 16 weeks, for a total of 32 sessions.
- 3 minutes EEG recording at the end of all treatment sessions in EO condition;
- 3 minutes EEG recording at the end of all treatment sessions in EC condition;
- Monitoring of the neuropsychological profile by administering the same battery of tests used during the first phase.

The order of EO and EC acquisitions was randomized both pre and post tES treatment. The non-pharmacological treatment was characterized by:

- Structured training on Theory of Mind conducted by a psychologist [33]. It consists of the viewing of short videos selected from films, or specially made, portraying various human social interactions requiring the recognition of emotions (happiness, sadness, anger, surprise, fear, and disgust) and ToM skills (decoding beliefs, irony, misunderstandings, and intentions) to be understood correctly. The training was conducted twice a week for 30 minutes, simultaneously with the tDCS intervention. In total, 64 short videos were prepared, of which 32 focus on the recognition of basic emotions (happiness, sadness, anger, surprise, fear, and disgust), and 32 represent social situations that require cognitive ToM skills to be understood (such as understanding irony and gaffes, attributing beliefs and intentions). In each session, two or three videos were presented which can be viewed several times, according to the patients' requests. Patients be asked to become 'social investigators', making interpretations on the emotions, mental states, and intentions of the protagonists of the social scenes presented.
- An electrical brain stimulation intervention using tDCS. During the active stimulation sessions, a 2.5x2.5 cm anode was applied on the left DLPFC area, while the cathode was placed on the right deltoid muscle. The tDCS was applied for 20 minutes at an intensity of 2 mA. The same procedure was used for the sham condition, but in this case, the electric current was applied only in the first 20 seconds of tDCS. The sham treatment, as well as the

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active ones, was applied twice a week for 16 weeks for a total of 32 sessions.

A flow chart of the experimental protocol is showed in Fig. 1

Figure 1: Experimental protocol flow chart.

Instrumentation: EEG data were acquired by Mitsar EEG 201 system. It is a QEEG 21 channel device arranged according to the international 10/20 positioning system. The sampling rate is 2000 Sa/s. For tDCS treatment, 1x1 tDCS mini-CT (Soterix Medical, New York, USA) was used. It is a low intensity transcranical stimulator with current intensity ranging between 0.1 and 5 mA, and current duration beetween 5 and 40 minutes.

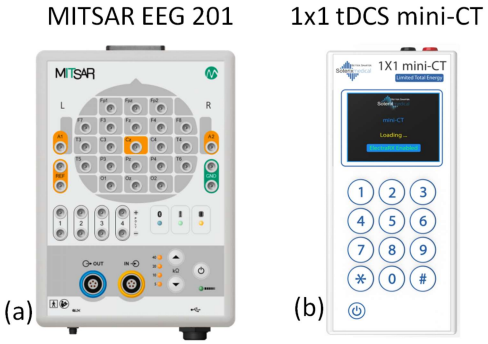

Figure 2: EEG acquisition (a) and tES (b) systems.

EEG data processing: EEG data were filtered by a fourth-order bandpass Butterworth filter ([0.5 - 45] Hz), then the *Artifact Subspace Reconstruction* (ASR) [34] procedure was used. ASR splits the EEG signal into components and once a threshold based on the signal variance distribution is identified, rejects noisy components above the threshold, reconstructing the signal by considering the remaining components. ASR was used with a cutoff equal to 15 to remove artifacts. Then EEG tracks were divided into 1–s epochs, organized in the form of [Epochs x Channels x Features].
In the features extraction phase, PDR amplitude and frequency and absolute and relative powers for all channels in delta, theta, alpha, low beta, high beta and gamma bands were computed in EC and EO conditions. Later, differences between pre and post both tES and sham treatment were calculated. The *Sequential Feature Selection* (SFS) [35] was applied in the feature selection phase. SFS is used to identify the most significant features to discriminate among different conditions. In this phase, the Support Vector Machine was the classifier embedded within the SFS. After creating the label vector with the 0 and 1 values associated with tES and sham treatments respectively, the training phase was carried out. Four patients were employed for training the classifiers: two from the stimulation group and two from the sham group. Subsequently, the epochs of a fifth patient were allocated for the test set. The training set comprised 480 epochs, while the test set 120 epochs. The most informative features were selected during the training phase. The number of the features selected by the SFS algorithm was defined as the minimum number maximizing the classification accuracy. Only the features selected during the training phase were considered for the test phase on the epochs from the fifth patient.

Results: Three EEG features maximizing the discriminability between treated and no-treated patients both in EO and in EC conditions were selected by the SFS algorithm (Figs 3, 4). SFS algorithm on the train subjects reported a mean accuracy of 88.75% with a standard deviation of 8.45% in EC condition and a mean accuracy of 88.75% with a standard deviation of 2.22% in EO condition. Subsequently, one-shot test on the fifth subject was applied. In the EO condition, the test accuracy was of 92.5 %. The considered features were i) Difference of absolute powers in high beta band in T3 channel, ii) Difference of absolute powers in gamma band in T3 channel, and iii) Difference of relative powers in gamma band in T5 channel. In the EC condition, the test accuracy was of 100.0 %. The considered features were i) Difference of absolute powers in gamma band in T3 channel, ii) Difference of absolute powers in gamma band in Cz channel, and iii) Difference of absolute powers in gamma band in Pz channel.

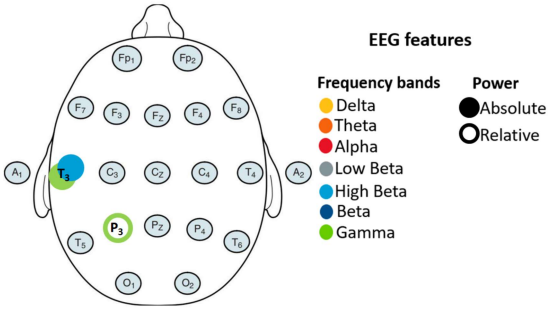

Figure 3: Most informative EEG features in Eye-Open condition for discriminating tDCS- and sham-treated patients.

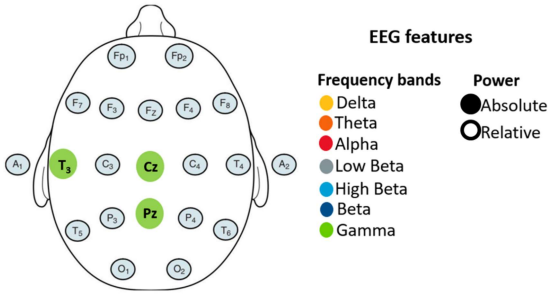

Figure 4: Most informative EEG features in Eye-Closed condition for discriminating tDCS- and sham-treated patients.

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DISCUSSION

Only two studies on EEG-based assessment of tDCS treatment effectiveness in MS patients are reported in literature, namely *Gholami et al.* [31] and *Ayache et al.* [30]. In particular, in *Gholami et al.* study, EEG acquisition with eyes closed in resting state was considered. An increase of Power Spectral Density (PSD) in alpha band and a decrease of PSD in beta and high beta bands over F3, C3, and P3 resulted between pre- and post-tDCS treatment. However, statistical tests did not confirm the significance of the results. The authors hhypothesize that the impact of tDCS causes a power shift from beta to alpha frequencies, associated with the improvement in cognitive function, attention, and information processing speed. A limitation arises from exclusively EEG measuring with eyes closed. Indeed, EEG measurements under eyes-open conditions can reveal alterations in the highly myelinated visual structures otherwise not visible in MS patients [36].

For *Ayache et al.*, only the activity of theta band over Fz and Fpz channels during a cognitive task was focused. A statistically significant increase after tDCS with respect to sham treatment was highlighted.

The increased theta activity was associated with analgesic effects on MS symptoms. However, the study focuses only on the theta band within the region of stimulation. Other bands and other regions of the scalp are not explored.

Both studies have restricted EEG assessment to a limited number of frequency bands, thereby omitting evaluations of high-frequency activity such as the gamma band. This omission poses a limitation, considering that demyelination effects induced by MS are particularly evident at high-frequency [37]. In the present study, all EEG frequency bands are explored, revealing the impacts of tDCS treatment on both high beta and gamma bands. Furthermore, for three MS patients undergoing tDCS treatment, a reduction in the mean absolute power difference between pre- and post-treatment is observed in gamma and high beta bands. This result can be linked to the effectiveness of transcranical stimulation in restoring altered EEG features. In fact, alterations in the brain's functional connectivity network due to structural brain damage in MS patients are characterized by increased mean gamma power [29, 38]. This phenomenon is also correlated with partial disconnection of white matter pathways and significant cortical atrophy [39, 40].

The comparison between the presented study and the two aforementioned ones also encompasses the different electrode configuration employed for transcranial stimulation. In all studies, the anode is positioned over the DLPFC area but the cathode positioning is different. In particular, in the *Gholami et al.* and *Ayache et al.* studies, the cathode is positioned over the supraorbital region and on the Fp2 channel, respectively. Conversely, in the presented study it is situated on the right deltoid muscle (Fig 5). By employing this extracephalic reference, undesired cephalic hyperpolarization effects from brain areas beneath the reference electrode are mitigated [41, 42]. According to literature, the extracephalic positioning of the cathode in a tDCS treatment contributes to the decrease of absolute power in the high-frequency bands.[43]. However, this electrodes configuration has not been previously studied in the framework of EEG-based assessment of tDCS effectiveness in MS patients.

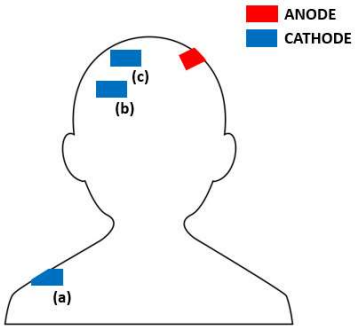

Figure 5: Comparison in tDCS cathode positioning among the different studies. For all the studies, the anode is collocated on the DLPFC area. The cathode is placed on the right deltoid muscle (a) in the present study, on the right supraorbital area (b) in *Ayache et al.* study [30], and on Fp2 channel (c) in *Gholami et al.* study [31].

Results show significant effects of tDCS treatment in brain areas having also a crucial role in ToM framework. Temporo-Parietal Junction (TPJ) is the most involved area in reasoning about the contents of another person's mind [44]. The resulting reduction in gamma-band power on TPJ can be related to a restoration of ToM processes [45, 46]. Analyses on clinical outcomes are ongoing, and early results are very encouraging. Patients treated with tES exhibit improvements in ToM consistent with the electroencephalographic changes noted following combined ToM and tES treatment. Therefore, the identified EEG features can be used to real-time assess the treatment effectiveness and manage adaptation.

Notably, it is not possible to consider the effects of tES treatment and ToM training separately. Consequently, the reported results should be considered only when tES is applied with ToM training, concurrently.

Finally, tDCS treatment has not yet been standardized and variations in anode and cathode placement across studies are frequent. Consequently, comparing results becomes challenging.

CONCLUSION

Neurocorrelates of transcranical Electrical Stimulation in Multiple Sclerosis patients were investigated. Power differences within high beta in T3 and gamma in T3 and P3 in EO condition and power differences within gamma in T3, Pz, Cz in EC condition were the most discriminative features. The selected EEG features allowed the test patient to be correctly classified as treated with 100.0 % accuracy in EC condition. This study poses the ba-

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sis for adaptive tES protocols and stimulation settings according to EEG measurements. In the future, the number of enrolled subjects and the analysed pathologies will be widened to improve the statistical significance of the results. Moreover, a single integrated system allowing both EEG measurement and tES therapy will be developed to improve i) home therapy and ii) the contribution of customized medicine.

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