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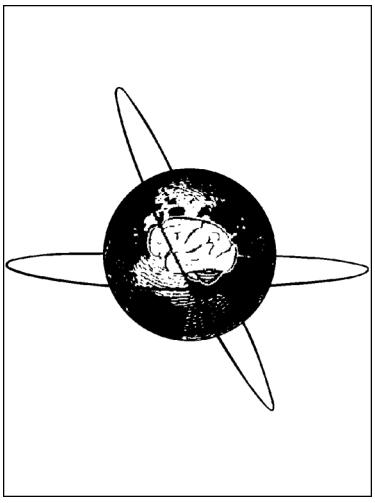

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Task-related brain activity in upper limb dystonia revealed by simultaneous fNIRS and EEG

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Keywords: Dystonia, fNIRS, EEG, task-related brain activity.

Abbreviations

EEG: electroencephalography

fNIRS: functional near-infrared spectroscopy

Oxy-Hb: oxyhemoglobin

Deoxy-Hb: deoxyhemoglobin

GLM: General Linear Model

ERS: event-related synchronization

ERD: event-related desynchronization

FIR: finite impulse response

SMCL: left sensorimotor cortex

SMCR: right sensorimotor cortex

SMA: Supplementary motor cortex

AR: Autoregressive

ROI: Region of interest

ANOVA: Analysis of variance

Highlights

- We used simultaneous EEG and fNIRS to examine task-specific changes during finger-tapping and handwriting tasks in dystonia.
- Patients with dystonia show altered connectivity between the supplementary motor area and left sensorimotor during writing.
- Differences in cortical blood flow and EEG spectral power between controls and patients with dystonia are task dependent.

Abstract

Objective

The aim of this study was to explore differences in brain activity and connectivity using simultaneous electroencephalography and near-infrared spectroscopy in patients with focal dystonia during handwriting and finger-tapping tasks.

Methods

Patients with idiopathic right upper limb focal dystonia and controls were assessed by simultaneous near-infrared spectroscopy and electroencephalography during the writing and finger-tapping tasks in terms of the mu-alpha, mu-beta, beta and low gamma power and effective connectivity, as well as relative changes in oxyhemoglobin (oxy-Hb) and deoxyhemoglobin using a channel-wise approach with a mixed-effect model.

Results

Patients exhibited higher oxy-Hb levels in the right and left motor cortex and supplementary motor area during writing, but lower oxy-Hb levels in the left sensorimotor and bilateral somatosensory area during finger-tapping compared to controls. During writing, patients showed increased low gamma power in the bilateral sensorimotor cortex and less mu-beta and beta attenuation compared to controls. Additionally, patients had reduced connectivity between the supplementary motor area and the left sensorimotor cortex during writing. No differences were observed in terms of effective connectivity in either task. Finally, patients failed to attenuate the mu-alpha, mu-beta, and beta rhythms during the finger-tapping task.

Conclusions

Cortical blood flow and EEG spectral power differ between controls and dystonia patients, depending on the task. Writing increased blood flow and altered connectivity in dystonia patients, and it also decreased slow-band attenuation. Finger-tapping decreased blood flow and slow-band attenuation.

Significance

Simultaneous fNIRS and EEG may show relevant information regarding brain dynamics in movement disorders patients in unconstrained environments.

1. Introduction

Dystonia is characterized by sustained, involuntary muscle contractions, leading to repetitive twisting movements and/or postural changes (Albanese et al., 2013). The underlying mechanisms of dystonia are not fully understood, and the development of effective treatments remains a challenge. Electroencephalography (EEG) and functional near-infrared

spectroscopy (fNIRS) are non-invasive neuroimaging techniques that have been used to study various neurological disorders.

EEG can potentially provide valuable information about the neural activity underlying dystonia. Previous EEG studies have reported changes in brain oscillations, including alterations in power and coherence in various frequency bands, in patients with dystonia compared to healthy controls. The beta rhythm has been extensively explored in dystonia. Abnormal patterns of event-related desynchronization and power are believed to be implicated in abnormal cortical function in patients (Baltazar et al., 2020; Herrojo Ruiz et al., 2009; Jin et al., 2011a; Kristeva et al., 2005; Toro et al., 2000). The mu rhythm is associated with sensorimotor processing and can be divided into mu-alpha and mu-beta frequencies. While mu-alpha rhythm originates from the postcentral cortex during somatosensory processing, mu-beta rhythm originates from the precentral cortex during motor execution (Hari, 2006; Ritter et al., 2009). The dynamics of both rhythms were not yet investigated in dystonia. The gamma rhythm is believed to reflect the activity of subcortical and basal ganglia structures (Headley and Weinberger, 2011; Litvak et al., 2012) which could be functionally impaired in dystonia (Miocinovic et al., 2018).

Previous studies suggest that both hemispheres may present abnormal functional activation even during unilateral motor tasks. Patients with dystonia showed less reduction of task-related beta spectral power in bilateral somatomotor cortex during writing (Kristeva et al., 2005; Thirugnanasambandam et al., 2020) as well as altered functional connectivity and interhemispheric coherence (Baltazar et al., 2020; Thirugnanasambandam et al., 2020). Other studies have also found less attenuation of beta power during self-paced finger movements in contralateral and midline channels (Toro et al., 2000) and altered connectivity in somatomotor channels in tasks that do not induce dystonic postures (Jin et al., 2011b, 2011a). Despite the fact many studies found functional alternations in brain connectivity in patients with upper limb dystonia during motor tasks (Butz et al., 2006; Jin et al., 2011b, 2011a; Thirugnanasambandam et al., 2020), only few investigated effective connectivity (Baltazar et al., 2020; Rothkirch et al., 2018), which provide information regarding directed interactions between brain regions (Friston, 1994) and may be used to access brain dynamics after intervention (Baxter et al., 2017; Qi et al., 2019). Knowing that both hemispheres may present functional differences in dystonia, it remains unclear whether interhemispheric connectivity plays a role in dystonia pathophysiology.

Although previous neuroimaging studies have attempted to uncover brain activation differences in patients with dystonia during motor tasks, the results have been inconsistent, with some studies showing increased activation and others decreased activation depending

on the task (Zoons et al., 2011). A combination of near-infrared spectroscopy (fNIRS) and electroencephalography (EEG) may offer a promising solution. fNIRS allows the measurement of functional brain activity through changes in hemodynamics and metabolism (Quaresima and Ferrari, 2019) while EEG provides a high temporal resolution of electrical activity resulting from postsynaptic potentials (Olejniczak, 2006).

The use of hybrid EEG/fNIRS in the investigation of dystonia has yet to be explored, but it could offer the potential to shed new light on the pathophysiology of dystonia by examining various motor tasks in unconstrained environments. Given the variance of dystonia literature involving neurovascular coupling and oscillatory brain activity, by using both techniques in the same set of individuals, we may elucidate whether EEG and fNIRS findings converge in tasks that may induce dystonic postures.

In this study, our aim was to compare the brain activation patterns of patients with focal dystonia and healthy controls during writing and finger-tapping using fNIRS and EEG simultaneously. We used a general linear model (GLM) to conduct channel-wise analyses in terms of relative changes in oxyhemoglobin (oxy-Hb) and deoxyhemoglobin (deoxy-Hb), in the case of fNIRS data, and the power of mu-alpha (7.5 -12 Hz), mu-beta (12 - 15Hz), beta (15 - 25Hz) and low gamma (25 - 50Hz) rhythms for EEG. Furthermore, we compared sensorimotor and supplementary motor area (SMA) as well as inter-hemispheric connectivity in regions of interest between patients and controls using generalized partial directed coherence (gPDC) on EEG data and autoregressive correlations on fNIRS data. We hypothesized that patients with focal dystonia would reveal changes in the pattern of activation of the sensorimotor cortex during motor activities. As dystonic postures involve the involuntary abnormal recruitment of muscle groups, we expected patients to have a non-specific activation of regions of the sensorimotor cortex during dystonia-inducing tasks. On EEG data, we expected to find less attenuation of band powers associated with motor activity and altered effective interhemispheric connectivity in dystonia patients compared to healthy controls.

2. Methods

2.1. Subjects

Participants were recruited by neurologists at participating movement disorders centers or from the community by advertisement. This study was approved by the Institutional Review Boards of all participating sites: Hospital Israelita Albert Einstein, Hospital do Servidor Público Estadual de São Paulo, and Department of Neurology and Neurosurgery of

Universidade Federal de São Paulo. All subjects provided informed written consent. The diagnosis of idiopathic focal dystonia was established according to current recommendations (Albanese et al., 2013), including a normal brain image exam before recruitment. Exclusion criteria were neurological diseases (except for the dystonia), history of neurosurgery, moderate to severe head or upper limb trauma, cancer, uncontrolled metabolic disorders, current use of neuroleptics, antidepressants, benzodiazepines, vasodilators/constrictors, and history of substance abuse. Patients under botulinum toxin treatment had to wait for at least three months after receiving the last injection to participate in the study.

All participants were right-handed as evaluated by the Edinburgh handedness inventory (Oldfield, 1971). All patients presented dystonic symptoms in their dominant (right) hand. From 30 patients and 31 controls evaluated in the finger-tapping and writing task acquisitions (total=244), data from 44 acquisitions were excluded after pre-processing due to incomplete or unacceptable data quality in either EEG or fNIRS (Figure 1). Patients and controls in which both EEG and fNIRS were validated for each task were selected. The criteria for data exclusion are described in the EEG and fNIRS Acquisition section. Twenty-one patients with upper limb dystonia (age = 43.81 ± 10.4 years; 16 females) and 24 age-matched healthy controls (age = 43.1 ± 12.5 years; 10 females) were analyzed. Twenty controls and 21 patients were analyzed in the finger-tapping task and 21 controls and 20 patients were analyzed for the writing task. Demographic characteristics of the participants, as well as which subjects were included in each task, are described in Supplementary Table S1.

2.2 Tasks

EEG and fNIRS were recorded during resting-state, finger-tapping and writing tasks. The paradigm used in this study is described elsewhere (Baltazar et al., 2020; Prôa et al., 2021). The following parameters were used: 1 min of resting-state to characterize the basal neuronal activity looking at a black cross on a white background; 2 min of writing task, that consisted of four epochs of alternating writing/resting blocks (30 s duration each); as we wanted to avoid sentences that could demand significant cognitive efforts, focusing on the neural correlates of the motor task, participants were required to write the sentence of the song “Happy Birthday to You” in Portuguese (*Parabéns para você*) due to its universal knowledge. The writing task was performed with the right hand only.

The finger-tapping task consisted of 12 blocks of 30 s interspersed by 30 s of rest. This task was randomly alternated between right, left and both hands (four blocks each). Subjects had to tap each finger against the thumb, from the index to the little finger, as fast and accurately as possible. They were videotaped during all tasks. For quantification of behavior performance of the writing task, the number of written letters was counted, and for the finger-tapping task, the number of correct taps was counted through recorded video. Between-

group statistical analysis was conducted using a one-tailed student t-test under the hypothesis that patients would write fewer letters and perform fewer finger taps.

2.3 EEG and fNIRS Acquisition

As shown in Figure 2, for the hybrid acquisition of EEG and fNIRS, 32 electrodes were placed on the scalp according to the international 10-20 system (Homan et al., 1987) and 16 fNIRS optodes were placed in the supplementary motor area and sensorimotor cortex with reference to the 10-5 system (Oostenveld and Praamstra, 2001). Electrodes and optodes were placed on the same cap, with compatible EEG and fNIRS holders. The EEG data were acquired using a 32-channel set, with active electrodes from ActiCap and a LiveAmp amplifier (Brain Products, Gilching DE). The electrodes' impedance was kept between 10 and 20 kΩ. The data was recorded with the Brain Vision Recorder (Brain Products, Gilching DE) at 250 Hz of sampling rate.

The fNIRS hemodynamic data were collected using an NIRSport system (NIRx Medical Technologies, LLC) with eight LED sources with two wavelengths (760 and 850nm) and eight photodiode detectors, with a sampling frequency of 7.8125 Hz. The spatial distribution of the optodes (source-detector) in the cap was chosen based on the recommended distance of approximately 30mm (Yücel et al., 2021). The anatomical landmarks for fNIRS optodes are shown in Supplementary Table S2.

2.4 fNIRS processing

Before processing data, channels that displayed gain settings higher than 3% and coefficients of variation higher than 7.5% were verified. Those channels were considered bad channels and participants that had more than five bad channels were excluded from the analysis. The optical signals from each channel were then converted into concentration changes of oxy-Hb and deoxy-Hb using the modified Beer-Lambert equation (Delpy and Cope, 1997). The differential path length factor (DPF) was calculated based on the age of each subject (Scholkmann and Wolf, 2013).

A GLM was applied to the fNIRS time series with conditions of interest, which modeled the 30 s duration of each experimental condition (writing and finger tapping). These regressors were constructed using a canonical hemodynamic response function. An autoregressive filtering was performed based on iteratively reweighted least squares (AR-IRLS) to eliminate

the serial correlations in the model residue (Barker et al., 2013). In addition, age and sex information were used as regressors in the model to correct demographic bias. Groups were compared using a two-tailed t-test for independent samples. The significance value was corrected by the false positive rate ($q < 0.05$) using the method of Benjamini and Hochberg (Benjamini and Hochberg, 1995).

2.5 EEG processing

EEG data were pre-processed using Brain Vision Analyzer 2.1 software (Brain Products, Gilching DE). Data were filtered with a bandpass filter (0.5 - 50 Hz) and a notch filter at 60 Hz. Muscle and eye artifacts were removed using independent component analysis (ICA) and a semi-automatic correction feature. Channels were referenced with their average value. Participants who had motor artifacts throughout the task, problems in stimuli markers, or incomplete data were excluded.

Changes in the frequency bands during the task blocks in the mu-alpha (7.5 -12 Hz), mu-beta (12 - 15 Hz), beta (15 - 25 Hz) and low gamma (25 - 50 Hz) bands were analyzed using the continuous wavelet transform to extract the power distribution in the time-frequency domain (Daubechies, 1990), implemented using the AnalyzIR (Santosa et al., 2018) brain toolbox in the Matlab® 2020a program. After computing variations in the time-frequency domain of each band of interest, we selected channels from the sensorimotor cortex, supplementary motor area and temporal cortex (Fc5, Fc6, Cz, C3, C4, T7, T8, Cp1, Cp2, Cp5 and Cp6) and downsampled them to conduct a pre-whitening using the autoregressive filtering (AR-IRLS) (Barker et al., 2013). In this process, a GLM was used to average the powers of the activity blocks comparing to the baseline, using a finite impulse response (FIR) function. Finally, we performed the channel-to-channel analysis of group contrast and respective band power using the mixed-effect model (Santosa et al., 2018).

2.6 Effective connectivity analysis

For EEG connectivity analysis the same pre-processing was conducted, except for the ICA filter, as it could eliminate other signal properties and influence the analysis (Pester and Ligges, 2018). Using eight channels from the sensorimotor cortex (FC5, CP5, FC6, CP6, C3, C4, Fz, Cz) we detrended the time series and calculated model order using *Akaike's Information Criteria* (Akaike, 1974). The gPDC calculation was conducted using the toolbox AsympPDCPackage associated with the textbook from Sameshima and Baccala (2014). The gPDC area under the curve for each pair of channels was calculated for each band. We used a non-parametric Mann-Whitney U corrected for multiple comparisons to test differences

between groups among the 55 possible combinations. Finally, we calculated the bidirectional information flow among regions of interest, including channels of the left sensorimotor cortex (SMCL): C3, Fc5, Cp5; right sensorimotor cortex (SMCR): C4, Fc6, Cp6; and suppletory motor area (SMA): Cz and Fz. For region of interest connectivity analysis, we tested data distribution using Shapiro wilk test. In the cases where variables had a normal distribution, we used an independent sample t-test, and in case it did not, we used the Mann-Whitney U test. All comparisons were corrected using Benjamini and Hochberg correction.

2.7 fNIRS connectivity

For the fNIRS task-based connectivity analysis, we targeted the same regions of interest as employed in the EEG effective connectivity analysis.

Following the estimation of oxy-hemoglobin (oxy-hb) and deoxy-hemoglobin (deoxy-hb) levels, a region of interest (ROI) was created by averaging the time series from specific channels within the SMCL (ch6, ch7, ch9, ch16, ch17, ch18), SMCR (ch13, ch14, ch15, ch21, ch22, ch23) and SMA (ch3, ch5, ch8, ch10.)

To quantify connectivity, a whitened auto-regressive correlation (AR-correlation) was employed, utilizing robust regression techniques (Santosa et al., 2018, 2017). The maximum model order was set to four times the sampling rate (7.1 Hz) to capture relevant temporal dynamics. Significant correlations were detected using a mixed-effects model, which accounted for group and task effects to obtain the Fisher Z-transform of R correlation coefficients. Between-group comparisons involving control and dystonia patients were conducted within each task, employing a corrected p-value threshold of 0.05 to determine statistical significance.

2.8 Region of interest analysis

For both fNIRS and EEG, we conducted a ROI analysis regarding brain activation in both finger-tapping and writing tasks. The channels for EEG ROI approach encompassed the same channels as described above for connectivity analysis. For fNIRS, we extracted the GLM ß-coefficients regarding the averaged channels of the oxy and deoxy time series. For EEG, ROI spectral power was calculated by averaging channel power estimates.

To investigate the effect of affected vs non-affected hand movement, we conducted a repeated measures ANOVA test for the finger-tapping task. We used group (dystonia and

controls) as the between-subject factor, and hand (right-hand and left-hand tapping) and brain region (SMCL, SMCR and SMA) as repeated factors. We conducted the described ANOVA tests for all analyzed contrasts (oxy-hb, deoxy-hb, mu-alpha, mu-beta, beta and gamma power estimates).

2.9 fNIRS and EEG correlation

We extracted the GLM ß-coefficients from both oxy-hb and beta power to perform fNIRS and EEG correlation. Using a ROI approach, the mean fNIRS and EEG coefficients among SMA, SMCR and SMCL were calculated. The channels for EEG ROI approach encompassed the same channels as described above. We tested whether the ROI beta values between fNIRS (oxy-hb) and EEG (beta power [15 - 25 Hz]) had a significant correlation for dystonia patients and controls using Pearson correlation.

3. Results

The dynamics of brain activation and connectivity in patients with dystonia were investigated using simultaneous EEG and fNIRS data. Patients with upper limb dystonia and healthy volunteers were assigned finger-tapping and writing tasks. From the fNIRS and EEG data, we performed a channel-wise analysis using a General Linear Model to infer alterations in levels of oxy-Hb, deoxy-Hb and power of the mu-alpha (7.5 -12 Hz), mu-beta (12 - 15 Hz), beta (15 - 25 Hz) and low gamma (25 - 50 Hz) bands. Also, we investigated differences in directed inter-hemispheric connectivity from the EEG data. During the writing task, 19 of 20 patients presented dystonic posture characterized either by sustained extension or flexion of the wrist and a tight grip of the pen. During the finger-tapping task, six participants exhibited dystonic posture.

Between-group evaluation of motor tasks showed that patients wrote fewer letters relative to controls ($t(39) = 3.45$, $p = 0.00038$, one-tailed). On average, patients wrote 156.35 (SD=66.68) words during the task, and controls wrote 227.33 (SD=61.71) words, the magnitude of the difference was high (Cohen's D =1.10).

For the finger-tapping task with the right hand, on average, patients tapped 55.0 (SD=24.30) times and controls tapped 71.85 (SD=27.99) times. Patients performed fewer taps than controls ($t(39) = 2.01$, $p = 0.012$, one-tailed) and the effect size was moderate (Cohen's D = 0.64).

For the finger tapping with the left hand, on average, patients tapped fingers 56.9 (SD=21.56) and controls 72.85 (SD=33.95) times. Patients showed fewer taps than controls (t (39)=1.75, p=0.021, one-tailed) and the effect side was moderate (Cohen's D = 0.56).

For both-hands tapping, on average, patients performed 53.9 (SD=21.45) taps and controls 70.0 (SD=28.07) taps. Patients showed fewer taps than controls (t (39)=2.01, p=0.012, one-tailed) and the effect side was also moderate (Cohen's D = 0.64).

3.1 Task-based brain activation

3.1.2 Writing

During the writing task, in fNIRS analysis, controls showed positive variations in oxy-Hb levels from baseline in channels of the left sensorimotor cortex, contralateral to the hand used, while patients showed bilateral activation of the sensorimotor cortex ($q<0.05$). There was no significant difference from the baseline in deoxy-Hb contrasts. Compared to controls, patients showed an increase in oxy-Hb levels in channels over the left somatomotor cortex, supplementary motor area and right sensorimotor cortex. Activation maps and channel statistics regarding oxy and deoxy-Hb changes during the writing task and group comparison are shown in Supplementary Material S3, S4 and S5.

In terms of EEG activation, patients and controls showed attenuation in the mu-beta and beta bands, as shown in Table 1. Topographic maps and channel statistics can be seen in Supplementary Material S6 and S7. Patients showed decreased attenuation of the mu-beta band in Cp1 relative to controls and increased low gamma power in Cp5, Cz and Cp2.

Overlapping maps regarding fNIRS and EEG results for group comparison of the writing task are shown in Figure 3.

3.1.3 Finger tapping

During the finger-tapping task, in fNIRS analyses, patients and controls had increased oxy-Hb levels and decreased deoxy-Hb levels in the bilateral sensorimotor cortex compared to baseline. The fNIRS topographic statistical maps for the right hand, left hand, and both hands finger tapping task are available as Supplementary Material (S8, S9, S10, S11, S12, S13). The comparison between groups for the finger-tapping task showed, throughout conditions,

decreased levels of oxy-Hb in bilateral primary sensory cortex and left motor cortex in the dystonia group relative to controls. In addition to the primary sensory cortex and left motor cortex, we found that patients had lower oxy-Hb levels in the frontal cortex for right-hand tapping. We also detected decreased levels of oxy-Hb in both motor cortices for the both-hands tapping.

For EEG activation, we observed attenuation of spectral power in all four rhythms analyzed (mu-alpha, mu-beta, beta, and low gamma) relative to the baseline in the bilateral sensorimotor channels in both patients and controls. Overall, patients showed decreased attenuation in the spectral power of the rhythms analyzed in sensorimotor channels relative to controls. Channels with significant power attenuation relative to the baseline and group comparison for each condition are shown in Table 2, with additional information regarding channel statistics in Supplementary Material (S14, S15, S16).

In Figure 4, we show the overlapping maps of oxy-hb and beta power for the finger-tapping task regarding patients and controls.

To investigate the effect of affected vs non-affected hand in dystonia patients, we conducted a repeated measures ANOVA, comparing dystonia vs. controls for right vs. left-hand tapping in each brain region (SMCL, SMCR and SMA). No interaction of brain region * hand * group was significant for oxy-hb, deoxy-hb, mu-alpha, mu-beta, beta and gamma power. Both oxy and deoxy-hb had a significant brain region * hand interaction ($F=17.11$, $p< 0.001$; $F=1.71$, $p<0.001$). Mu-alpha and mu-beta power showed significant effects of the tapped hand ($F=9.15$, $p= 0.004$; $F=7.61$, $p=0.009$) and of the brain region ($F=5.47$, $p=0.006$; $F=6.61$, $p=0.002$) alone, but no significant interaction between brain region and tapped hand ($p=0.711$, $p=0.178$). Finally, beta and gamma bands showed significant interaction effects between brain region and group ($F=3.31$, $p=0.042$; $F=4.86$; $p=0.01$). *Post hoc* tests show that for group and brain region interaction, controls had significant differences between SMCL and SMA gamma power in the finger tapping task ($t=3.42$, $p=0.0015$). Controls showed higher power in SMCR than in SMA (mean difference=0.240, SE=0.070), but no difference was observed in patients. For the beta band, the interaction between group and brain region did not survive multiple comparisons correction in the *post hoc* analysis. Box plots regarding brain activation parameters of right- and left-hand finger-tapping task, repeated measures ANOVA results and *post hoc* tests can be seen as Supplementary Material S17 and S18.

3.2 Task-based connectivity

For EEG data, bidirectional connectivity analysis via Directed Partial Coherence was conducted among the channels of interest in the sensorimotor cortex during the writing task. The mean order of the model obtained by the Akaike criterion was 13.99 (SD = ± 0.79) for controls and 14.11 (SD = ± 0.90) for patients. There was no significant difference in the order of the model between groups (p = 0.619). For the finger-tapping task, the model obtained by the Akaike criterion was 14.12 (SD = ± 0.88) for controls and 14.61 (SD = ± 2.27) for patients, there was no significant difference between groups (p = 0.331).

The averages of the gPDCs between each block were computed for the patient and control groups and the area relative to the interaction of each channel pair (56 variables) was calculated for each frequency range for the rhythms of interest (mu-alpha, mu-beta, beta, low gamma). Mann-Whitney U tests showed no statistical difference in channel-to-channel connectivity between patients and controls neither for writing nor the finger-tapping task. Figure 5 shows bidirectional connectivity among SMCR, SMCL and SMA in beta rhythm for writing, right and left finger tapping. No group difference was detected for mu-alpha, mu-beta, beta and gamma rhythm when correcting for multiple comparisons. To visualize effective connectivity in the other analyzed rhythms in writing and right-hand tapping, check Supplementary Material S19 and S20.

For fNIRS data, AR-correlations were employed among ROI to evaluate brain connectivity in dystonia patients and controls during motor tasks. For the writing task, a significant difference was detected in the deoxy-Hb connectivity. Patients showed decreased correlation coefficients between SMA and SMCL during the writing task, as shown in Figure 6. No group difference was detected in ROI connectivity in terms of oxy-Hb and deoxy-Hb for the finger-tapping task. Correlation matrices for the right, left and both-hands finger tapping are shown as Supplementary Material S21.

3.3 fNIRS and EEG correlation

We investigated the correlation between oxy-Hb and beta power in SMCL, SMCR and SMA during both motor tasks. No significant results were found in fNIRS and EEG correlations, neither in patients nor controls. The scatter plots, correlation coefficients, and p-values for each motor task and hemisphere are available as Supplementary Material (S22 and S23).

4. Discussion

The present study aimed to evaluate brain activity and connectivity in patients with upper limb dystonia using EEG and fNIRS. We applied two motor tasks with varying complexities in ecologically relevant contexts: the writing task, which induces dystonic postures in most patients with upper limb dystonia, and the finger-tapping task which, due to its high reproducibility, allows comparisons with other findings in the dystonia literature.

Dystonia is a highly complex disease. To better understand its underlying mechanisms, using tools that can measure neural activity in a naturalistic setting is crucial. This allows for the investigation of deficient motor programs in dystonia patients. According to the current theories of dystonia pathophysiology, the disorder is linked to impairments in sensorimotor integration. This is supported by evidence of alterations in sensory processing (Avanzino et al., 2015; Quartarone et al., 2008; Wu et al., 2010) and motor planning (Delnooz et al., 2012), failures in the mechanisms of inhibition in different regions of the nervous system (Gallea et al., 2018; Hanajima et al., 2008; Mink, 2003), and maladaptive plasticity derived from failures in the mechanisms that regulate synaptic modulation (Gilbertson et al., 2019; Opavsky et al., 2006).

4.1 Spectral power differences during writing in dystonia patients

To evaluate brain activity during writing, a recent study by Thirugnanasambandam et al., (2020), which measured the spectral power alpha and beta rhythms, showed that patients with dystonia failed to attenuate the beta rhythm not only in the cortex contralateral to movement (C3 and P3) but also in the ipsilateral hemisphere (C4), addressing the relevance of abnormal activity in the non-symptomatic hemisphere. Our findings show that both patients and controls had power attenuation relative to the baseline in mu-alpha, mu-beta and beta during writing. Patients had decreased attenuation in the contralateral sensorimotor cortex (Cp1) in mu-beta rhythm and in the right temporal cortex (T8) in beta rhythm, relative to controls. Moreover, controls showed a significant increase in low gamma power in the contralateral somatomotor channel (C3) and attenuation in the midline channel (Cz), whereas patients showed no difference.

Interestingly, patients showed increased low gamma power in bilateral and midline channels (Cp5, Cz and Cp2) during writing. Previous studies using subdural electroencephalography (ECoG) suggest that the low gamma rhythm is associated with event-related synchronization (ERS) in the contralateral cortex during motor response, whereas alpha and beta rhythms are related to event-related desynchronization (ERD) in bilateral sensorimotor cortex (Crone et al., 1998a, 1998b). In motor tasks, gamma activity is also related to the initiation of voluntary movements, peaking at the beginning of a motor sequence, and going silent as the

movement goes on. It has a role in movement force, directionality and is apparently independent from sensory feedback (Ulloa, 2022).

Our results suggest that dystonia patients may show both failures in ERD in mu-beta and beta rhythm and increased ERS in low gamma rhythm. The former result is in line with previous studies that found less reduction of beta rhythm during handwriting (Kristeva et al., 2005; Thirugnanasambandam et al., 2020). Although the gamma rhythm has not been largely studied in dystonia, the ERS increase in gamma rhythm observed in our sample may indicate an excessive activity originating from the thalamo-cortical pathway that can be triggered by voluntary movements in focal dystonia (Miocinovic et al., 2018).

4.2 Differences in oxy-Hb levels during writing in dystonia patients

The fNIRS results show increased levels of oxy-Hb in the contralateral motor cortex for controls and a more spread and intense activation for patients, including ipsilateral and bilateral somatosensory cortex during the writing task. We hypothesized that, as patients recruit antagonist muscles, a non-specific brain activation pattern would be obtained. These results are well in line with our previous study (Prôa et al., 2021), which used part of our dataset and evaluated the brain activity of dystonia patients with fNIRS during writing. They used region of interest analysis and detected increased oxy-Hb levels in the right motor cortex of dystonia patients. We do not know, however, whether non-specific brain activation is due to a compensatory process and, therefore, secondary to other dysfunctional brain regions, including subcortical areas, or whether cortical hyperexcitability causes dystonia.

*4.3 Finger-tapping task functional differences in dystonia patient*s

In the finger-tapping task, both groups showed suppression of mu-beta, beta and low gamma bands (EEG) in the somatomotor and sensorimotor cortices and increased levels of oxy-Hb (fNIRS) relative to baseline. Patients with dystonia had fewer finger taps than controls in all experimental conditions, even though in most cases patients did not show dystonic posture during the task. Previous studies suggest that, in healthy individuals, it is expected to find an attenuation of the mu-beta and beta rhythms in the hemisphere contralateral to the movement (Chatrian et al., 1959; Cochin et al., 1999). Our findings point to bilateral attenuation in both patients and controls. However, patients showed less attenuation of beta rhythm in the hemisphere contralateral to the movement, and patients showed less attenuation in both hemispheres at mu-alpha and mu-beta rhythms. The failure of the beta-rhythm attenuation contralateral to the movement is in line with the findings of Toro et al.

(2000), who reported loss of event-related desynchronization during the index finger movement in patients with focal dystonia. Although both mu-beta and beta rhythms are mostly associated with event-related desynchronization in the contralateral hemisphere, studies have shown some topographical independence of these frequency ranges (McFarland et al., 2000). Thus, even in the absence of dystonic posture, failures in specific frequency-band attenuation can play an important role in dystonia pathophysiology. Our repeated measures ANOVA using ROI show that, for the finger tapping task, controls had reduced gamma-band power of SMA relative to the left sensorimotor cortex, but patients did not. Although the interaction among brain region, tapped hand and group was not significant in this analysis, the invariance of SMA and SMCL gamma power in the patient group may indicate failure of SMA attenuation during voluntary hand movements, in addition to differences in hemisphere the sensorimotor cortex observed in mu-alpha and mu-beta rhythms in channel-wise analysis.

During the finger-tapping task, fNIRS findings showed decreased oxy-Hb levels mainly in primary sensory, motor and premotor cortex channels in patients compared to controls in all conditions. These findings are in line with other neuroimaging studies of brain hemodynamic techniques (de Faria et al., 2020; Wu et al., 2010), which investigated brain dynamics during tasks that do not cause dystonic symptoms, showing hypoactivation in somatosensory, motor, and supplementary motor areas. Interestingly, we found lower levels of oxy-Hb during the execution of the task with the non-symptomatic hand in patients with dystonia. This result contributes to the hypothesis of sensory processing failure in the pathophysiology of dystonia regardless of motor symptoms (Avanzino et al., 2015; Fiorio et al., 2003; Tinazzi et al., 2009). It is also suggested that the lower cortical activation during motor tasks may indicate the long-term consequences of dystonia or inherent impairments of the motor network (Popa et al., 2012).

The reduced brain activation and fewer taps among dystonia patients in the finger-tapping task raise intriguing questions about their potential relationship. While connected, the association is intricate due to dystonia's complex pathophysiology. One explanation is that altered brain activation influences motor control, suggesting a potential cause-and-effect relationship resulting in fewer taps. Another possibility is that dystonia's sensory-motor interactions directly contribute to the reduced taps. Dystonia involves complex interactions between sensory and motor systems, and it's plausible that the reduced number of taps could be a direct result of the sensory processing abnormalities inherent to the condition. Impaired sensory feedback, altered proprioception and abnormal processing of afferent signals could collectively contribute to the observed motor deficits (Avanzino et al., 2015; Bara-Jimenez et al., 2000). Both scenarios emphasize the multifaceted impact of dystonia on motor function.

It is relevant to emphasize, however, that unlike other studies (Jin et al., 2011b, 2011a), we did not find differences in functional connectivity during the finger-tapping task in either fNIRS or EEG. Variations in data acquisition, preprocessing techniques and analysis

methodologies can all contribute to disparate results. Further investigations could delve into these nuances to provide a comprehensive understanding of dystonia's impact on functional connectivity during motor tasks.

4.4 Brain connectivity abnormality in dystonia

The results of our study reveal an alteration in brain connectivity that holds implications for our understanding of dystonia. We observed a reduction in connectivity between the left sensorimotor area and the supplementary motor area (SMA) in terms of deoxygenated hemoglobin in patients with dystonia.

The SMA is a crucial hub within the motor network, responsible for orchestrating complex motor planning, execution and inhibition processes. The lower correlation between the SMA and the left sensorimotor cortex observed in patients with dystonia may reflect disruptions in the intricate interplay between these regions, leading to motor control deficits and the generation of abnormal motor patterns. This result resonates with prior research that has documented abnormalities in sensorimotor integration and motor planning among dystonia patients (Blood et al., 2004; Dresel et al., 2014; Neychev et al., 2011).

Nonetheless, it is essential to underscore that despite the observed differences in deoxygenated hemoglobin between SMCL and SMA, our investigation did not yield significant differences in inter-hemispheric EEG effective connectivity between these areas. The lack of evidence to support our initial hypothesis perhaps points to the resilience of specific facets of neural network among dystonia patients, despite alterations in hemodynamic responses.

While the finger-tapping task involves a simpler and paced movement of sequential flexion and extension of the fingers, the writing task is more complex, involving dynamic and complex movements of the fingers and wrist that vary in speed and amplitude. Bilateral activation of the motor cortex during high-precision tasks has been described in healthy subjects (Barany et al., 2020; Wischnewski et al., 2016). In our protocol, the writing task, even though more complex than finger-tapping, was not highly demanding in terms of precision, so we hypothesize that the ipsilateral cortical activation in dystonia patients could be due to either failure of interhemispheric inhibition mechanisms or alterations involving supplementary motor area connectivity, possibly as part of an endophenotype. Our initial hypothesis of inter-hemispheric alterations in patients with dystonia could not be confirmed by our findings.

4.5 fNIRS and EEG correlation

We aimed to investigate the relationship between neurovascular coupling and oscillatory brain activity during unilateral motor tasks in patients with dystonia and healthy controls. Previous research using fNIRS and EEG has revealed negative correlations between neurovascular coupling and alpha and beta rhythms in the contralateral sensorimotor cortex during finger tapping movements (Lachert et al., 2017) and the sensorimotor cortex during fMRI-EEG studies (Ritter et al., 2009).

Correlations between sensorimotor and supplementary motor channels of oxy-hb and beta power were not statistically significant. The lack of correlation could be attributed to the specific placement of regions of interest (ROIs) chosen for analysis in each modality. Another possibility is that, due to the sample size, regression lines based on individual's beta power and oxy-hb estimates are limited to draw significant associations between fNIRS and EEG data. Using contrast parameters from oxy-Hb and beta power of shorter segments may be a strategy for data augmentation in future studies to disentangle neurovascular coupling and oscillatory electrical activity in dystonia patients.

4.6 Limitations

The limitations of this study need to be acknowledged. Our decision to only use data from participants who had both EEG and fNIRS data may have reduced the sample size and impacted some of the findings of our exploratory and correlation analyses. However, our goal was to examine cortical activation in patients with dystonia using both neuroimaging methods, so using the same dataset was necessary to account for inter-individual differences. The physiological mechanisms behind the topographic statistical maps of fNIRS and EEG are different, making it challenging to directly correlate the data. The electrical signals from the brain must pass through the skull and meninges to be picked up by electrodes, making it hard to pinpoint the exact sources of the signal, a phenomenon known as volume conduction (Holsheimer and Feenstra, 1977). Meanwhile, fNIRS measures hemodynamic responses, which are slower, taking 5 to 9 seconds after the motor stimulus (Obrig et al., 1996), and reflect an indirect metric of cortical blood flow. Although there are studies that have used a combination of EEG and fNIRS to improve brain-machine interfaces (Fazli et al., 2012; Khan et al., 2014; Koo et al., 2015), the relationship between hemodynamic states and electrical potentials remains to be explored. Additionally, using block activities in the experimental paradigm may not be ideal for ERP analysis, which would benefit from a larger number of repetitions. To obtain meaningful information using simultaneous EEG and fNIRS, we had to make a trade-off between skull coverage and an experimental paradigm to optimize spatial and temporal resolution.

5. Conclusion

We confirmed an alteration in the pattern of cortical activation and brain connectivity during motor tasks in dystonia patients. We have demonstrated that functional alterations in patients with dystonia are task dependent. The connectivity between the supplementary motor area and the left sensorimotor cortex is altered in dystonia during writing, but we did not observe that during finger tapping. Although patients with dystonia performed worse in both motor tasks, the blood flow measurements differed for each task. Patients had increased brain activation while performing complex muscle contractions during the writing task, but during the finger-tapping task had decreased brain activation. For both tasks, patients showed lower spectral power attenuation in EEG. For fNIRS, we suggest that the type of muscle contraction and task complexity play a fundamental role in the specific direction of functional changes. The use of fNIRS holds a relevant potential to identify differences in brain activity and connectivity in dystonia-inducing tasks.

Declaration of competing interest

None of the authors have potential conflicts of interest to be disclosed.

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References

Akaike H. A new look at the statistical model identification. IEEE Trans Automat Contr 1974;19:716–23.

Albanese A, Bhatia K, Bressman SB, DeLong MR, Fahn S, Fung VSC, et al. Phenomenology and classification of dystonia: a consensus update. Mov Disord 2013;28:863–73.

Avanzino L, Tinazzi M, Ionta S, Fiorio M. Sensory-motor integration in focal dystonia. Neuropsychologia 2015;79:288–300. https://doi.org/https://doi.org/10.1016/j.neuropsychologia.2015.07.008.

Baltazar CA, Machado BS, de Faria DD, Paulo AJM, Silva SMCA, Ferraz HB, et al. Brain connectivity in patients with dystonia during motor tasks. J Neural Eng 2020;17:56039. https://doi.org/10.1088/1741-2552/abbbd6.

Bara-Jimenez W, Shelton P, Sanger TD, Hallett M. Sensory discrimination capabilities in patients with focal hand dystonia. Ann Neurol 2000;47:377–80.

Barany DA, Revill KP, Caliban A, Vernon I, Shukla A, Sathian K, et al. Primary motor cortical activity during unimanual movements with increasing demand on precision. J Neurophysiol 2020;124:728–39.

Barker JW, Aarabi A, Huppert TJ. Autoregressive model based algorithm for correcting motion and serially correlated errors in fNIRS. Biomed Opt Express 2013;4:1366–79. https://doi.org/10.1364/BOE.4.001366.

Baxter BS, Edelman BJ, Sohrabpour A, He B. Anodal transcranial direct current stimulation increases bilateral directed brain connectivity during motor-imagery based brain-computer interface control. Front Neurosci 2017;11:691.

Beck S, Shamim EA, Pirio Richardson S, Schubert M, Hallett M. Inter-hemispheric inhibition is impaired in mirror dystonia. Eur J Neurosci 2009;29:1634–40.

Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc Series B Stat Methodol 1995;57:289–300.

Blood AJ, Flaherty AW, Choi J, Hochberg FH, Greve DN, Bonmassar G, et al. Basal ganglia activity remains elevated after movement in focal hand dystonia. Ann Neurol 2004;55:744–8.

Butz M, Timmermann L, Gross J, Pollok B, Dirks M, Hefter H, et al. Oscillatory coupling in writing and writer's cramp. J Physiol Paris 2006;99:14–20.

Chatrian GE, Petersen MC, Lazarte JA. The blocking of the rolandic wicket rhythm and some central changes related to movement. Electroencephalogr Clin Neurophysiol 1959;11:497–510.

Cochin S, Barthelemy C, Roux S, Martineau J. Observation and execution of movement: similarities demonstrated by quantified electroencephalography. Eur J Neurosci 1999;11:1839–42.

Crone NE, Miglioretti DL, Gordon B, Lesser RP. Functional mapping of human sensorimotor cortex with electrocorticographic spectral analysis. II. Event-related synchronization in the gamma band. Brain 1998a;121:2301–15. https://doi.org/10.1093/brain/121.12.2301.

Crone NE, Miglioretti DL, Gordon B, Sieracki JM, Wilson MT, Uematsu S, et al. Functional mapping of human sensorimotor cortex with electrocorticographic spectral analysis. I. Alpha and beta event-related desynchronization. Brain 1998b;121 (Pt 1:2271–99. https://doi.org/10.1093/brain/121.12.2271.

Daubechies I. The wavelet transform, time-frequency localization and signal analysis. IEEE Trans Inf Theory 1990;36:961–1005.

Delnooz CCS, Helmich RC, Toni I, van de Warrenburg BPC. Reduced parietal connectivity with a premotor writing area in writer's cramp. Mov Disor 2012;27:1425–31.

Delpy DT, Cope M. Quantification in tissue near–infrared spectroscopy. Philos Trans R Soc Lond B Biol Sci 1997;352:649–59.

Dresel C, Li Y, Wilzeck V, Castrop F, Zimmer C, Haslinger B. Multiple changes of functional connectivity between sensorimotor areas in focal hand dystonia. J Neurol Neurosurg Psychiatry 2014;85:1245–52.

de Faria DD, Paulo AJM, Balardin J, Sato JR, Junior EA, Baltazar CA, et al. Task-related brain activity and functional connectivity in upper limb dystonia: a functional magnetic resonance imaging (fMRI) and functional near-infrared spectroscopy (fNIRS) study. Neurophotonics 2020;7:45004.

Fazli S, Mehnert J, Steinbrink J, Curio G, Villringer A, Müller K-R, et al. Enhanced performance by a hybrid NIRS–EEG brain computer interface. Neuroimage 2012;59:519–29.

Fiorio M, Tinazzi M, Bertolasi L, Aglioti SM. Temporal processing of visuotactile and tactile stimuli in writer's cramp. Ann Neurol 2003;53:630–5.

Friston KJ. Functional and effective connectivity in neuroimaging: a synthesis. Hum Brain Mapp 1994;2:56–78.

Gallea C, Herath P, Voon V, Lerner A, Ostuni J, Saad Z, et al. Loss of inhibition in sensorimotor networks in focal hand dystonia. Neuroimage Clin 2018;17:90–7.

Gilbertson T, Humphries M, Steele JD. Maladaptive striatal plasticity and abnormal reward-learning in cervical dystonia. Eur J Neurosci 2019;50:3191–204. https://doi.org/10.1111/ejn.14414.

Hanajima R, Okabe S, Terao Y, Furubayashi T, Arai N, Inomata-Terada S, et al. Difference in intracortical inhibition of the motor cortex between cortical myoclonus and focal hand dystonia. Clin Neurophysiol 2008;119:1400–7. https://doi.org/10.1016/j.clinph.2008.02.009.

Hari R. Action–perception connection and the cortical mu rhythm. Prog Brain Res 2006;159:253–60.

Headley DB, Weinberger NM. Gamma-band activation predicts both associative memory and cortical plasticity. J Neurosci 2011;31:12748–58. https://doi.org/10.1523/JNEUROSCI.2528-11.2011.

Herrojo Ruiz M, Senghaas P, Grossbach M, Jabusch H, Bangert M, Hummel F, et al. Defective inhibition and inter-regional phase synchronization in pianists with musician's dystonia: an EEG study. Hum Brain Mapp 2009;30:2689–700.

Holsheimer J, Feenstra BWA. Volume conduction and EEG measurements within the brain: A quantitative approach to the influence of electrical spread on the linear relationship of activity measured at different locations. Electroencephalogr Clin Neurophysiol 1977;43:52–8. https://doi.org/https://doi.org/10.1016/0013-4694(77)90194-8.

Homan RW, Herman J, Purdy P. Cerebral location of international 10–20 system electrode placement. Electroencephalogr Clin Neurophysiol 1987;66:376–82.

Jin S-H, Lin P, Auh S, Hallett M. Abnormal functional connectivity in focal hand dystonia: mutual information analysis in EEG. Mov Disord 2011a;26:1274–81. https://doi.org/10.1002/mds.23675.

Jin S-H, Lin P, Hallett M. Abnormal reorganization of functional cortical small-world networks in focal hand dystonia. PLoS One 2011b;6:e28682.

Khan MJ, Hong MJ, Hong K-S. Decoding of four movement directions using hybrid NIRS-EEG brain-computer interface. Front Hum Neurosci 2014;8:244.

Koo B, Lee H-G, Nam Y, Kang H, Koh CS, Shin H-C, et al. A hybrid NIRS-EEG system for self-paced brain computer interface with online motor imagery. J Neurosci Methods 2015;244:26–32.

Kristeva R, Chakarov V, Losch F, Hummel S, Popa T, Schulte-Mönting J. Electroencephalographic spectral power in writer's cramp patients: Evidence for motor cortex malfunctioning during the cramp. Neuroimage 2005;27:706–14. https://doi.org/https://doi.org/10.1016/j.neuroimage.2005.05.004.

Lachert P, Janusek D, Pulawski P, Liebert A, Milej D, Blinowska KJ. Coupling of Oxy- and Deoxyhemoglobin concentrations with EEG rhythms during motor task. Sci Rep 2017;7:15414. https://doi.org/10.1038/s41598-017-15770-2.

Litvak V, Eusebio A, Jha A, Oostenveld R, Barnes G, Foltynie T, et al. Movement-related changes in local and long-range synchronization in Parkinson's disease revealed by

simultaneous magnetoencephalography and intracranial recordings. J Neurosci 2012;32:10541–53.

Mink JW. The Basal Ganglia and involuntary movements: impaired inhibition of competing motor patterns. Arch Neurol 2003;60:1365–8. https://doi.org/10.1001/archneur.60.10.1365.

Miocinovic S, Swann NC, de Hemptinne C, Miller A, Ostrem JL, Starr PA. Cortical gamma oscillations in isolated dystonia. Parkinsonism Relat Disord 2018;49:104–5. https://doi.org/10.1016/j.parkreldis.2018.01.017.

Neychev VK, Gross RE, Lehéricy S, Hess EJ, Jinnah HA. The functional neuroanatomy of dystonia. Neurobiol Dis 2011;42:185–201.

Obrig H, Hirth C, Junge-Hulsing JG, Doge C, Wolf T, Dirnagl U, et al. Cerebral oxygenation changes in response to motor stimulation. J Appl Physiol 1996;81:1174–83.

Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 1971;9:97–113.

Olejniczak P. Neurophysiologic basis of EEG. J Clin Neurophysiol 2006;23:186–9.

Oostenveld R, Praamstra P. The five percent electrode system for high-resolution EEG and ERP measurements. Clin Neurophysiol 2001;112:713–9.

Opavsky R, Hlustik P, Kanovsky P. Cortical plasticity and its implications for focal hand dystonia. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2006;150:223–6. https://doi.org/10.5507/bp.2006.031.

Pester B, Ligges C. Does independent component analysis influence EEG connectivity analyses? Annu Int Conf IEEE Eng Med Biol Soc 2018;2018:1007–10. https://doi.org/10.1109/EMBC.2018.8512425.

Popa T, Velayudhan B, Hubsch C, Pradeep S, Roze E, Vidailhet M, et al. Cerebellar processing of sensory inputs primes motor cortex plasticity. Cerebral Cortex 2012;23:305–14.

Prôa R, Balardin J, de Faria DD, Paulo AM, Sato JR, Baltazar CA, et al. Motor Cortex Activation During Writing in Focal Upper-Limb Dystonia: An fNIRS Study. Neurorehabil Neural Repair 2021:15459683211019340.

Qi F, Hong X, Lu Z, Teh I, Teo W, Ang K, et al. How transcranial direct current stimulation facilitates post-stroke rehabilitation. ArXiv Preprint ArXiv:190205702 2019.

Quaresima V, Ferrari M. Functional near-infrared spectroscopy (fNIRS) for assessing cerebral cortex function during human behavior in natural/social situations: a concise review. Organ Res Methods 2019;22:46–68.

Quartarone A, Morgante F, Sant'Angelo A, Rizzo V, Bagnato S, Terranova C, et al.

Abnormal plasticity of sensorimotor circuits extends beyond the affected body part in focal dystonia. J Neurol Neurosurg Psychiatry 2008;79:985–90.

Ritter P, Moosmann M, Villringer A. Rolandic alpha and beta EEG rhythms' strengths are inversely related to fMRI-BOLD signal in primary somatosensory and motor cortex. Hum Brain Mapp 2009;30:1168–87.

Rothkirch I, Granert O, Knutzen A, Wolff S, Gövert F, Pedersen A, et al. Dynamic causal modeling revealed dysfunctional effective connectivity in both, the cortico-basal-ganglia and the cerebello-cortical motor network in writers' cramp. Neuroimage Clin 2018;18:149–59.

Sameshima K, Baccala LA. Methods in brain connectivity inference through multivariate time series analysis. CRC press; 2014.

Santosa H, Aarabi A, Perlman SB, Huppert T. Characterization and correction of the false-discovery rates in resting state connectivity using functional near-infrared spectroscopy. J Biomed Opt 2017;22:55002.

Santosa H, Zhai X, Fishburn F, Huppert T. The NIRS brain AnalyzIR toolbox. Algorithms 2018;11:73.

Sattler V, Dickler M, Michaud M, Meunier S, Simonetta-Moreau M. Does abnormal interhemispheric inhibition play a role in mirror dystonia? Mov Disord 2014;29:787–96.

Scholkmann F, Wolf M. General equation for the differential pathlength factor of the frontal human head depending on wavelength and age. J Biomed Opt 2013;18:105004.

Thirugnanasambandam N, Zimmerman T, Pillai AS, Shields J, Horovitz SG, Hallett M. Task-specific interhemispheric hypoconnectivity in writer's cramp - An EEG study. Clin Neurophysiol 2020;131:985–93. https://doi.org/10.1016/j.clinph.2020.01.011.

Tinazzi M, Fiorio M, Fiaschi A, Rothwell JC, Bhatia KP. Sensory functions in dystonia: insights from behavioral studies. Mov Disord 2009;24:1427–36.

Toro C, Deuschl G, Hallett M. Movement-related electroencephalographic desynchronization in patients with hand cramps: evidence for motor cortical involvement in focal dystonia. Ann Neurol 2000;47:456–61.

Ulloa JL. The control of movements via motor gamma oscillations. Front Hum Neurosci 2022;15:787157.

Wischnewski M, Kowalski GM, Rink F, Belagaje SR, Haut MW, Hobbs G, et al. Demand on skillfulness modulates interhemispheric inhibition of motor cortices. J Neurophysiol 2016;115:2803–13. https://doi.org/10.1152/jn.01076.2015.

Wu CC, Fairhall SL, McNair NA, Hamm JP, Kirk IJ, Cunnington R, et al. Impaired sensorimotor integration in focal hand dystonia patients in the absence of symptoms. J

Neurol Neurosurg Psychiatry 2010;81:659–65.

Yücel MA, Lühmann A v, Scholkmann F, Gervain J, Dan I, Ayaz H, et al. Best practices for fNIRS publications. Neurophotonics 2021;8:12101.

Zoons E, Booij J, Nederveen AJ, Dijk JM, Tijssen MAJ. Structural, functional and molecular imaging of the brain in primary focal dystonia—a review. Neuroimage 2011;56:1011–20.

Figure 1 Participants included in the analysis after pre-processing and validation. Raw data is shown in yellow, excluded data is shown in red and validated data is shown in green.

Figure 2 Hybrid EEG/fNIRS set up. fNIRS sources are shown in red and detectors are displayed in green (10-5 system), composing 23 channels in supplementary motor area and sensorimotor cortex, shown in purple lines with their respective number. The 32 Electrodes in 10-20 system are shown in gray. Reference and Ground electrodes are shown in blue and black, respectively.

Figure 3 Overlapping maps of low gamma-rhythm (25 – 50Hz) and oxy-Hb relative to contrast Patient > Control during writing. Channels that showed increased oxy-Hb levels for patients compared to controls are shown by red lines, electrodes that showed significant increase in power (C3 and Cp2) in patients compared to controls are circled in black. Maps corrected for false positive rate ($q<0.05$). Images shown in neurological view. oxy-hb: oxygenated hemoglobin.

Figure 4. Overlapping maps of the contrasts relative to the finger-tapping task with right, left and both hands, showing oxy-hb changes and beta (15 – 25Hz) power. The first two columns show changes from baseline and the third column shows the Patient > Control contrast. Channels that showed an increase or decrease in oxy-Hb are shown by red and blue lines, respectively. Electrodes that showed lower attenuation of beta power compared to the controls are shown in red. Maps corrected for false positive rate ($q<0.05$). oxy-hb: oxygenated hemoglobin.

Figure 5 Bidirectional connectivity among left sensorimotor cortex (SMCL), right sensorimotor cortex (SMCR) and supplementary motor area (SMA) comparing dystonia patients and controls during writing task, right-hand tapping, and left-hand tapping. Generalized partial directed coherence(gPDC) distribution computed in the beta (15 – 25Hz). Controls are shown in white and patients in grey. Arrows represent targeted connectivity between regions of interest.

Figure 6 fNIRS connectivity among left sensorimotor cortex (SMCL), right sensorimotor cortex (SMCR) and supplementary motor area (SMA) comparing dystonia patients and controls during the writing task. Dystonia patients showed decreased SMA-SMCL correlation in terms of deoxy-hb during writing. Numbers represent Fisher Z-transformed R correlations coefficients. oxy-hb: oxygenated hemoglobin, deoxy-hb: deoxygenated hemoglobin.

Table 1: Attenuation of spectral power in sensorimotor channels of controls and patients during the writing task

Band	Group	Writing		
		Attenuation of EEG power relative to the baseline	**Increased EEG power relative to the baseline**	**Group comparison ****
mu-alpha (7.5 – 12 Hz)	Controls	ns	ns	ns
	Patients	Cz, Cp2,		
mu-beta (12 – 15Hz)	Controls	T7, Fc5, Cp5, Cp1, Cz, Cp2, C4, Cp6, Fc6	ns	Cp1
	Patients	T7, Fc5, C3, Cz, Cp6, Fc6		

beta (15 – 25Hz)	Controls	C3, Cp5, Cz, T8, Fc6	ns	T8
	Patients	C3, Cp1, C4, Cp6,		
low gamma (25 – 50Hz)	Controls	Cz	C3	Cz, Cp5, Cp2
	Patients	ns		

Channels that showed significant spectral power attenuation (q<0.05) relative to the baseline, ** channels that show significant less spectral power reduction (q <0.05) in patients relative to controls, n.s. not statistically significant.

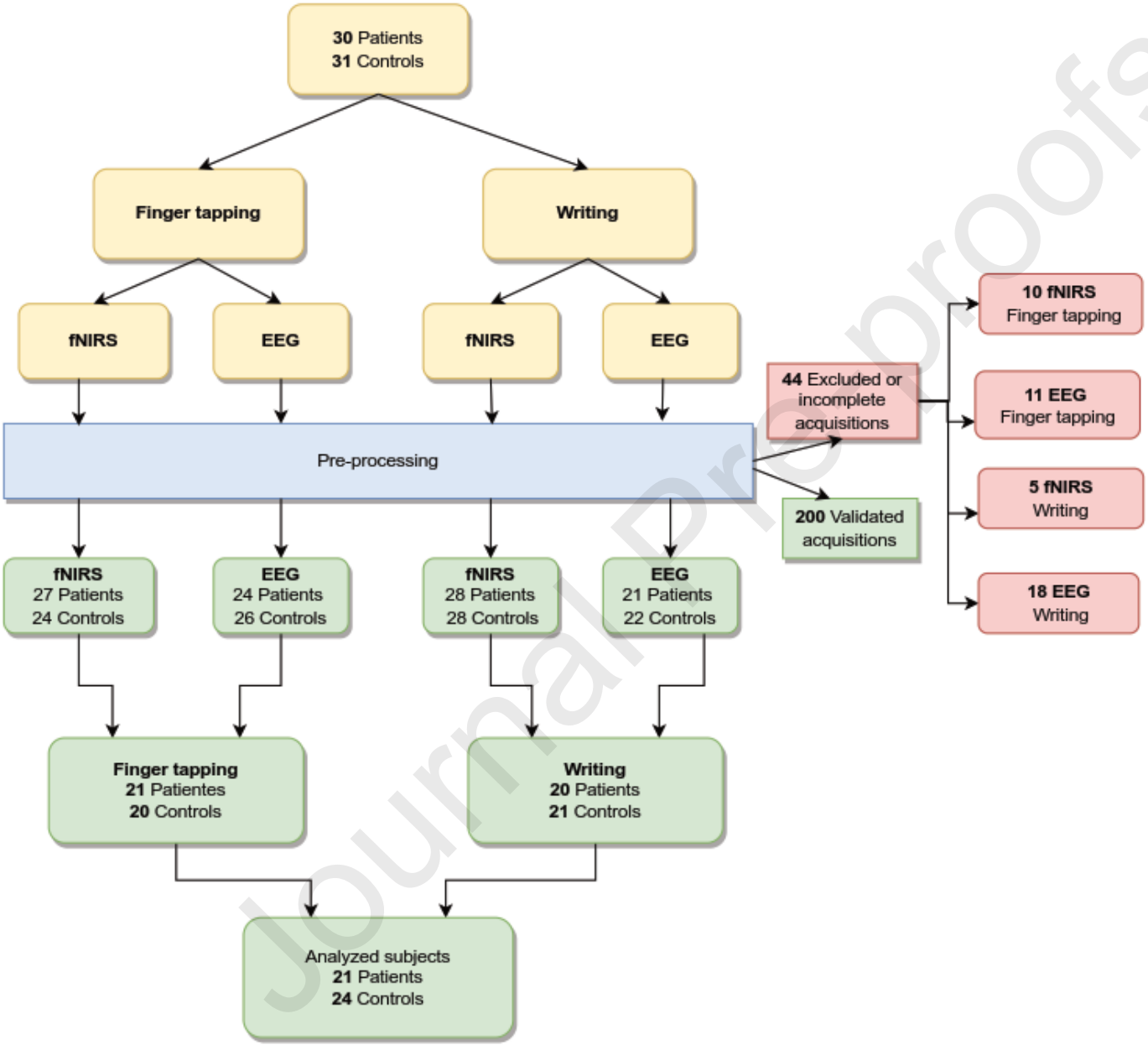
Table 2: Attenuation of spectral power in sensorimotor channels of controls and patients during the finger-tapping task

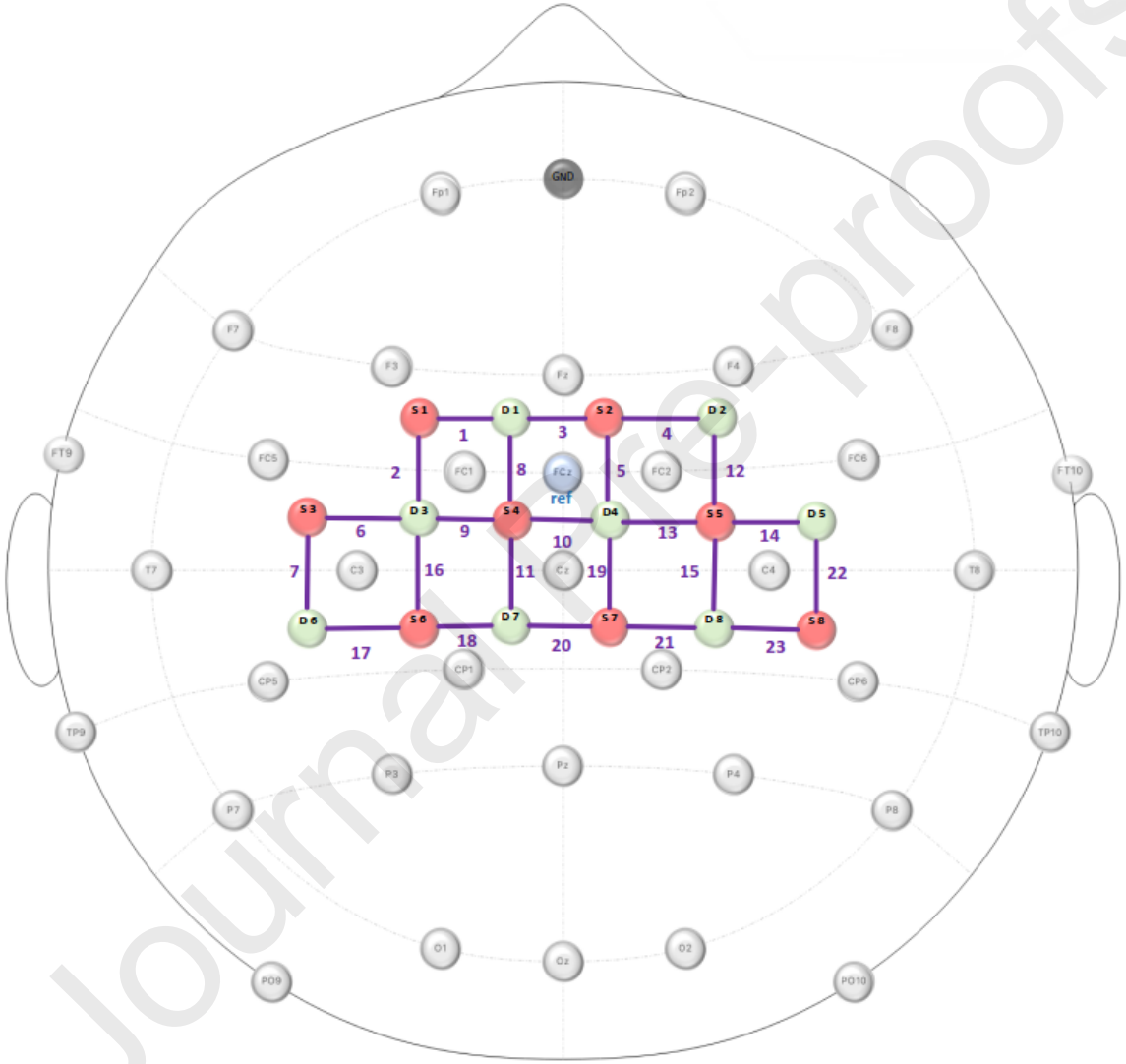
Band	Group	Attenuation of EEG power relative to the baseline					
		Right hand		Left hand		Both hands	
		Channels*	Group comparison **	Channels *	Group comparison **	Channel *	Group comparison **
mu-alpha (7.5 – 12 Hz)	Controls	T7, Fc5, C3, Cp5, Cp1, Cz, Cp2, C4, T8, Cp6, Fc6	Fc5, C3, C4	T7, Fc5, C3, Cp5, Cp1, Cz, Cp2, C4, T8, Cp6, Fc6	T7	T7, Fc5, C3, Cp5, Cp1, Cz, Cp2, C4, T8, Cp6, Fc6	Cz, Cp2, Fc6
	Patients	T7, Fc5, C3, Cp5, Cp1, Cz, Cp2, C4, T8, Cp6, Fc6		T7, Fc5, C3, Cp5, Cp1, Cz, Cp2, C4, T8, Cp6, Fc6		T7, Fc5, C3, Cp5, Cp1, Cz, Cp2, C4, T8, Cp6, Fc6	
mu-beta (12 – 15Hz)	Controls	T7, C3, Cp5, Cp1, Cz, Cp2, C4, T8, Cp6, Fc6		T7, Fc5, C3, Cp5, Cp1, Cz, Cp2, C4, T8, Cp6, Fc6	C3, Cp1	T7, Fc5, C3, Cp5, Cp1, Cz, Cp2, C4, T8, Cp6, Fc6	T7, Fc5

			ns					
	Patients	T7, Fc5, C3, Cp5, Cp1, Cz, Cp2, C4, T8, Fc6, Cp6		T7, Fc5, C3, Cp5, Cp1, Cz, Cp2, C4, T8, Cp6, Fc6		T7, Fc5, C3, Cp5, Cp1, Cz, Cp2, C4, T8, Cp6, Fc6		
beta (15 – 25Hz)	Controls	T7, Fc5, C3, Cp5, Cz, Cp2, C4, T8, Cp6, Fc6	Cp5	T7, Fc5, C3, Cp5, Cp1, Cz, Cp2, C4, T8, Fc6 e Cp6	Cp6	T7, Fc5, C3, Cp5, Cp1, Cz, Cp2, C4, T8, Fc6 e Cp6		C3
	Patients	T7, Fc5, C3, Cp5, Cp1, Cz, Cp2, C4, T8, Cp6, Fc6		T7, Fc5, C3, Cp5, Cp1, Cz, Cp2, C4, T8, Fc6 e Cp6		T7, Fc5, C3, Cp5, Cp1, Cz, Cp2, C4, T8, Fc6 e Cp6		
low gamma (25 – 50Hz)	Controls	T7, Fc5,C3, Cp1, Cz, Cp1, Cp2	ns	Fc5, Cp5, Cp2, C4, Fc6,	n.s	Cp1, Cz, Cp2, C4, Fc6, T8, Cp6,		n.s

Patients	Fc5, C3, Cp5, Cz, Cp2, C4, T8, Fc6	T7, Fc5,Cp5, C3, Cp1, C4, Cp6	T7, Fc5, C3, Cp5, Cp1, Cz, Cp2, Fc5, Cp6

*Channels that showed significant spectral power attenuation (q<0.05) relative to the baseline, ** channels that shows significant less spectral power reduction (q <0.05) in patients relative to controls,.n.s not statistically significant





Writing: Dystonia > Controls (oxy-hb and low-gamma power)