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Abnormal functional connectivity in focal hand dystonia: Mutual information analysis in EEG

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Abstract

The aim of the present study was to investigate functional connectivity (FC) in focal hand dystonia (FHD) patients to understand the pathophysiology underlying their abnormality in movement. We recorded EEG from 58 electrodes in 15 FHD patients and 15 healthy volunteers during rest and a simple finger-tapping task that did not induce any dystonic symptoms. We investigated the mutual information (MI), which provides a quantitative measure of linear and nonlinear coupling, in the alpha, beta and gamma bands. Mean MI of all 58 channels and mean of the channels of interest (COIs) representative of regional FC over sensorimotor areas (C3, CP3, C4, CP4, FCz and Cz) were evaluated. For both groups, we found enhanced MI during the task compared to the rest condition specifically in the beta and gamma bands for mean MI of all channels, and in all bands

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for mean MI of COIs. Comparing the FHD patients to the healthy volunteers, for both rest and task, there was reduced MI in the beta band for both mean MI of all channels and mean MI of COIs. Regarding the properties of the connectivity in the beta band, we found that the majority of the MI differences were from linear connectivity. The abnormal beta band FC in FHD patients suggests deficient brain connectivity.

Keywords

focal hand dystonia; mutual information; functional connectivity; sensorimotor integration

Dystonia is a severely debilitating movement disorder characterized by co-contraction of agonist and antagonist muscles, giving rise to abnormal postures and twisting repetitive movements.^{1,2} Focal dystonia is restricted to a single body part in various task-specific dystonias such as writer's cramp (WC) and musician's dystonia (MD). In terms of the pathophysiology of dystonia, evidence for abnormalities of cortical dysfunction include abnormal levels of activity in sensorimotor cortex, supplementary motor cortex (SMA) and premotor cortices during motor tasks and abnormal sensorimotor processing.³ Several neurophysiologic studies have demonstrated sensorimotor integration abnormalities in FHD using transcranial magnetic stimulation (TMS).^{4–6} PET activation and fMRI studies have demonstrated abnormal activity in premotor, SMA, and primary motor cortex during movement in patients with primary torsion dystonia or secondary dystonias.^{7–12} These findings suggest subtle alterations in brain structure and abnormalities in sensorimotor integration in the cortex.^{3,13} Using EEG, Toro et al.¹⁴ found less reduction in the beta spectral power compared to controls for the movement pre-execution state. Deficits in beta-range oscillatory activation over the contralateral sensorimotor area during cramp in patients with FHD have been reported as evidence for motor cortex malfunctioning.¹⁵

Regardless of which types of measurements were employed, the above-mentioned studies involved in dystonia mainly focused on changes in select cortical areas rather than FC between these areas. As a result, FC in FHD has not been well studied. FC, broadly defined as the statistical association or dependency between distant brain regions²⁸, is a well-known approach to investigate large-scale brain networks. It is worthwhile to understand FC because it could account for how the brain regions are connected each other. We aimed to investigate FC in FHD patients compared to healthy volunteers.

We hypothesize that there is an abnormal pattern of FC in FHD. Abnormal coupling at specific frequencies between sensorimotor regions may represent the physiologic substrate for abnormal sensorimotor integration in dystonia. To investigate this hypothesis, based on the fact that neural communication depends on transmitting information mediated by synchronization of neural oscillations,¹⁶ frequency band-specific FC was derived from EEG data in healthy volunteers and FHD patients during both rest and a simple finger-tapping task that did not induce dystonic symptoms. MI including linear and nonlinear connectivity was used as a measure of FC^{17–19}. In addition, we estimated the properties of connectivity to investigate the underlying dynamic system by employing proper surrogate tests.^{20,21}

Methods

Subjects

The study involved 15 patients with FHD affecting the right hand (mean age: 51.4 ; 11 males) and 15 healthy volunteers (mean age 45.93; 12 males). The data from healthy volunteers is also being used for a functional network study (not published yet), different from the current analysis. No difference in age was found ($t_{28}=1.302$, $p=0.204$, two-sample

t-test). All subjects were right-handed. Six patients were diagnosed with MD and the others with WC; we believe these entities to be two manifestations of the same disorder. For patients treated with botulinum toxin (BTX) injections, the last injections were always more than 3 months prior to testing. All participants were recruited from the NINDS database. The protocol was approved by the Institutional Review Board and all subjects gave written informed consent. Clinical details of FHD patients are described in Table 1.

EEG recording and pre-processing

EEGs were recorded from 58 surface electrodes mounted on a cap (Electro-Cap International, Inc., Eaton, OH, USA) using the international 10–20 system referenced to the right earlobe electrode (A2). The left earlobe electrode (A1) was recorded as a separate channel; we converted the EEGs into the digitally linked earlobe reference before further analysis to reliably estimate the scalp EEG potential.^{22,23} Bipolar recordings of the vertical and horizontal electro-oculogram and surface electromyogram from the extensor digitorum communis, flexor digitorum sublimis, and first dorsal interossei muscles were simultaneously recorded. Signals from all channels were amplified (Neuroscan Inc., El Paso, TX, USA), filtered (DC–100 Hz), and digitized with sampling frequency 1 kHz.

Resting state EEGs were recorded for 5 minutes with eyes open. For the simple sequential finger-tapping task, subjects were asked to press the button of a commercial keypad (Neuroscan Inc., El Paso, TX, USA) with their right hand paced by a metronome beat at 2 Hz for 5 minutes. The sequence performed was 2-3-4-5 with each digit corresponding to index, middle, ring and little finger, respectively. After recording, we extracted 120 trials of the 4-item sequence equivalent to a total of 480 key presses to assess behavioral performance. The exact sequence of key presses was considered as the accuracy. Subjects were instructed to keep their eyes open and to fixate on a target 3 m away during the entire recording to avoid extraneous movements or eye blinks and to remove any visual feedback during their performance. None of the patients became symptomatic or experienced any discomfort during the task.

Linear trend and eye movement-related artifacts were removed.²⁴ Finally, 5 artifact-free epochs (each epoch 10 sec) in each subject were obtained to calculate wavelet coefficients and evaluate MI values between wavelet coefficients for each pair of electrodes. EEG was down-sampled to 500 Hz before applying Morlet wavelet transformation. The pre-processing steps were performed with the same MATLAB (MathWorks, Natick, MA) scripts as used in Bai et al.²⁵

Mutual information estimation

Wavelet coefficients of the alpha (7.97~13.10 Hz), beta (15.05~31.25 Hz), and gamma (31.25~45.14 Hz) frequency bands were obtained from Morlet wavelet transformation. MI values of wavelet coefficients were estimated between electrodes. MI can be computed as follows using probability density function (PDF):

$$MI = MI_{XY} = MI_{YX} = MI(X(t), Y(t)) = - \sum_n p(X(t), Y(t)) \log \frac{p(X(t), Y(t))}{p(X(t))p(Y(t))}$$

Where, $p(X(t))$ and $p(Y(t))$ are PDFs of two time series $X(t)$ and $Y(t)$ ($t=1, \dots, T$) at T discrete points, respectively, and $p(X(t), Y(t))$ is the joint PDF between $X(t)$ and $Y(t)$. The detailed derivation of the equation is presented by Cover and Thomas.²⁶ In this study, 32 bins were adopted for 4,096 samples. We took logarithm with base 2, so the maximum MI in

our study is 5 bits. We added a corrective term to compensate the effect of finite data and quantization on the PDF.²⁷

After estimating wavelet coefficients, we calculated MI values between wavelet coefficients for each pair of electrodes. For network visualization, Pajek software (<http://vlado.fmf.uni-lj.si/pub/networks/pajek/>) was used.

Properties of connectivity

MI includes linear and nonlinear components which can be separated by employing uni- and bi-variate surrogate tests. If MI of the original data passes only the uni-variate surrogate test, it has a purely linear connectivity between them. If it passes both the uni- and bi-variate surrogate tests, then this connectivity includes a nonlinear dependence.²¹ When there is mixed connectivity, to separate the linear and nonlinear contributions to MI, the average MI of all 19 bivariate surrogate data corresponding to the linear contribution of MI was subtracted from the MI of the original data.²⁰ The result would be the nonlinear contribution of MI. A detailed explanation was presented in previous studies.^{20,21}

Statistical analysis

A two-sample *t*-test was performed to detect statistical differences in the error rate as a behavioral performance between groups.

For each frequency bands, MI values were averaged across either all 58 channels or the selective channels over the sensorimotor areas, thus yielding one average MI per condition per subject, respectively. Two measurements, one for each condition, within a subject are treated as correlated through data analysis. As for the regional FC over sensorimotor areas, electrodes at SM1 of the left and right hemispheres (left, C3, CP3; right, C4, CP4) and the mesial frontocentral cortex including SMA (FCz, Cz) were included as COIs.

Statistics were performed using multivariate analysis of variance (MANOVA) models to examine the difference between healthy volunteers and FHD patients, and the difference between rest and task conditions simultaneously. The covariance structure was assumed to be compound and symmetric. Analyses were implemented in SPSS (version 18) with a significance level of 0.05. All data are given as mean±standard deviation (SD).

Results

Behavioral results

No difference was detected in behavioral results between groups ($F_{1, 28} = 0.01, p = 0.925$), indicating that FHD patients' task performance accuracy (0.9567 ± 0.0280) was similar to that of the healthy volunteers (0.9576 ± 0.0284).

Functional connectivity

First, MANOVA, with group and condition as main effects, was performed on mean MI from all channels for each band separately. In the alpha band, no significant group and condition effects were found. In the gamma band, an average mean MI of rest condition was significantly different from that in task condition that indicates enhanced MI during the task, while no significant difference was found between groups. For the beta band, the mean MI was significantly enhanced during the task compared to rest condition, and a group main effect was revealed demonstrating smaller mean MI values of all channels in FHD patients. No significant interaction between group and condition was found in any band.

Second, MANOVA was performed for mean MI of COIs to explore a regional FC over sensorimotor areas. Condition main effect was found in the alpha, beta, and gamma bands, which shows enhanced mean MI values of COIs during the task. However, in terms of group effect, the average of mean MI values of COIs over sensorimotor area in FHD patients was significantly smaller compared to healthy volunteers only in the beta band. No significant interaction between group and condition was found in any band.

In Table 2, mean and SD values are reported for each group and condition per band with final MANOVA analyses. Figure 1 displays box-plots for mean MI of all channels and COIs in each band, group, and condition.

In addition, no significant differences were found in a *post hoc* analysis between WC and MD groups, and between the BTX treated and untreated groups.

Properties of the beta band functional connectivity

Since there was a significant group difference in the beta band FC with the previous analysis, we assessed the characteristics of FC in the beta band network.

First, a MANOVA was performed on mean MI from all channels in the beta band FC with the values of the purely linear and the mixed connectivity. In the purely linear connectivity, a significant difference between rest and task conditions was found indicating increased connectivity in the task. In the linear contribution of MI in a mixed connectivity, a group main effect was shown indicating smaller mean MI values of all channels in FHD patients than those in healthy volunteers, which is the only result showing a group main effect. No significant interaction between group and condition was found.

Second, a MANOVA was performed on mean MI from COIs in the beta band FC with the values of each type of connectivity. In the purely linear connectivity, there was a significant difference between rest and task conditions indicating increased connectivity with the task. Significant difference between conditions was also found in the nonlinear contribution of MI in the mixed connectivity. However, a group main effect appeared only in the linear contribution of MI in a mixed connectivity, similar to the result of mean MI of all channels. No significant interaction between group and condition was found in any type of connectivity. In Table 3, mean and SD values are reported for each group and condition per the type of connectivity with final MANOVA analyses. [Table 3]

Network visualizations

To visualize functional network in the beta band connectivity which shows a group main effect, grand averaged MI matrices at each group and condition were thresholded by a mean MI value of all channels of healthy volunteers (i.e., 0.476 in Table 2). Figure 2 demonstrates functional networks in healthy volunteers and FHD patients in both conditions. FHD patients demonstrate less dense functional networks in both rest (c) and task (d) conditions than healthy volunteers (a, b), indicating a lower level of FC in FHD patients than in healthy volunteers. To visualize group-related changes, the networks at rest were subtracted from the networks during the task. Task-related changes are shown in (e) and (f), which emphasize the fact that FHD patients have less dense functional networks compared to healthy volunteers.

Discussion

The present study explored the FC assessed by MI measures in patients with FHD. We found that FHD patients have small mean MI values of all channels or COIs over sensorimotor areas in the beta band FC when compared with healthy volunteers, while there

are no group differences in the alpha and the gamma bands. To our knowledge, this is the first study to demonstrate abnormal FC of brain networks in FHD patients using EEG.

MI provides a quantitative measure of the linear and nonlinear components of coupling between two time series.²⁰ MI based methods have been used in many other studies, such as during anesthesia,¹⁷ stimulus processing,²⁹ cognitive performance,^{30–32} motor tasks,^{21,33} and drug effect assessment.²⁰ It should be noted that MI is not expected to directly estimate anatomical axonal connections. MI should be understood in a statistical sense to identify how much information could be obtained about the time series at one site from the time series at another site. However, MI changes can be explained by impaired or improved long/short cortico-cortical communications²⁰ or the dissociation or synchronization between cortical structures³⁴ as a measure of FC.

Regarding the condition main effect in mean MI of all channels, FC was increased during the motor task in both the beta and gamma bands. Emergence of long-range connectivity in beta and gamma bands during a simple motor task was previously reported in a MEG study, which may facilitate sensorimotor binding³⁵ in accordance with other studies suggesting that correlated oscillations at higher frequencies in the gamma band are important as a physiological substrate for long-range sensorimotor binding.^{36–38} Thus, the enhanced FC in the gamma band seems consistent with a role for sensorimotor binding during a task. As for the alpha band, we found increased functional connectivity of mean MI of COIs during the task, which may imply a role of alpha oscillations over sensorimotor areas during a motor task.

Group difference was revealed in the beta band in both mean MI of all channels and COIs, indicating a lower level of FC in FHD patients than in healthy volunteers. Since the motor task conducted in the present study did not induce dystonic symptoms in patients and no difference was detected in behavioral results between groups, abnormalities would be intrinsic, which suggests the existence of inherent differences in functional dynamics.

In further analysis regarding the characteristics of the beta band FC, the important finding is that the properties of connectivity make the condition and group main effects differ from each other. A condition main effect mainly comes from a purely linear connectivity, whereas a group main effect comes from the linear contribution in a mixed connectivity. A possible explanation about the significant role of linear connectivity shown here would be due to our data analysis in which we are evaluating MI without time delay between two channels, and in this situation dominance of linear properties is expected. As seen for example in Alonso et al. (2010), the linear property of MI was dominant at no time delay, but rapidly decays as time delay increased. The purely linear analysis and the linear contribution of the mixed analysis can differ because the underlying mathematical models are different. The physiological correlates of the different models are not known and require further study.

The relevance of the abnormal beta oscillatory activation to FHD patients has been previously reported.^{14,15} These studies support the concept of impaired sensorimotor integration in FHD patients, which may be seen as beta band dynamic impairment as an electrophysiological correlate. In accordance with previous studies, we found a group difference only in the beta band FC. Since FC was assessed with signals obtained from the whole brain, our results provide strong evidence for the abnormal beta band FC in FHD patients.

Beta band oscillations are important in long-range synchronization.^{39–42} A large amount of evidence supporting the relevance of long-range synchronization between neural assemblies to movement execution has been accumulating.¹⁶ The functional impairment associated with various neurological disorders could be theoretically related to the abnormal integration of

spatially distributed brain regions that would normally constitute a large-scale network subserving function from the functional network point of view.⁴³ Therefore, the abnormal beta band FC seems to represent the disruption of long-range communication between parts of the brain in FHD patients and subsequent abnormal integration of brain function. Since FHD patients showed higher corticomuscular coherence during isometric contraction than controls⁵⁴ and we found an abnormal beta band FC, there might be a functional link between these two findings. Linking them would require future investigations, but we think this is unlikely since the topography of cortico-muscular coherence typically just reveals the motor cortex area.

In many studies, abnormalities in the sensorimotor system in dystonia have been reported³ using TMS,^{4–6} PET, and fMRI.^{7–12} Bilateral abnormality of the sensory and motor systems, despite unilateral symptoms, has been demonstrated in EEG/MEG,^{44,45} PET,⁴⁶ MRI⁴⁷ and TMS^{48,49} studies. In accordance with previous studies, our result indicating a weak regional FC over sensorimotor areas of FHD patients compared to healthy volunteers may support the concept of impaired sensorimotor integration in FHD patients.

A methodological limitation of the present study is that the FC studied is limited to the cortical level since we used EEG. To investigate subcortical or subcortical-cortical FC, neuroimaging techniques such as MEG⁵⁰, fMRI or invasive recordings of local field potentials⁵¹ would be required. Although Rosenkranz et al.⁵² reported different sensorimotor physiology between WC and MD, no significant differences were found between two groups. There is the possibility that a change in intrafusal feedback in dystonia⁵³ could explain impairment in beta band synchronization. However, in the present study, a *post hoc* analysis showed no significant difference between the BTX treated and untreated group. Future studies might examine FC patterns with various tasks such as writing, the correlation between deficient beta band FC and the severity of dystonia, and difference between the symptomatic and asymptomatic limb.

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Figure 1. Box-plots showing median, interquartile, and range for mean MI of all channels (left panel) and COIs (right panel) in the alpha, beta, and gamma bands in FHD patients and healthy volunteers (HV) in both conditions.

Figure 2.

Graphical representations of the network in the beta band FC in healthy volunteers in rest (a) and task (b), and in FHD patients in rest (c) and task (d) conditions. Second row indicates task-related changes in healthy volunteers (e) and FHD patients (f). Line and dotted line mean the increased or decreased connectivity during a task. Six bold nodes with labels are COIs.

Table 1

Demographic and clinical details of FHD patients

no.	Gender	Age	Type of FHD	Duration (years)	Treatment
1	Male	29	M	2	None
2	Male	54	M	11	BTX
3	Male	45	M	12	BTX
4	Male	55	M	3	None
5	Male	56	M	5	BTX
6	Male	48	M	6	BTX
7	Female	56	W	18	BTX
8	Female	50	W	10	BTX
9	Male	40	W	19	BTX
10	Female	64	W	19	BTX
11	Male	57	W	17	None
12	Male	57	W	4	None
13	Male	59	W	24	BTX
14	Male	44	W	25	None
15	Female	57	W	3	None

For patients treated with injections of botulinum toxin (BTX), the last injections were more than 3 months prior to testing in all cases

Types of FHD: M; musician's cramp, W; writer's cramp

Table 2
MANOVA analyses with summary statistics of mean MI of all channels and COIs.

<i>Summary statistics of mean MI of all channels</i>						
Band	Group main effect		Condition main effect			
	HV	FHD patients	F statistic (p-value)	Rest	Task	F statistic (p-value)
Alpha	0.649 ± 0.083	0.606 ± 0.080	F _{1,28} = 2.760 (0.1078)	0.619 ± 0.090	0.636 ± 0.077	F _{1,29} = 1.173 (0.2878)
Beta	0.476 ± 0.083	0.410 ± 0.053	F _{1,28} = 8.173 (0.0080)	0.424 ± 0.065	0.462 ± 0.084	F _{1,29} = 17.742 (0.0002)
Gamma	0.463 ± 0.101	0.432 ± 0.075	F _{1,28} = 1.279 (0.2676)	0.422 ± 0.070	0.473 ± 0.099	F _{1,29} = 10.926 (0.0025)
<i>Summary statistics of mean MI of COIs</i>						
Band	Group main effect		Condition main effect			
	HV	FHD patients	F statistic (p-value)	Rest	Task	F statistic (p-value)
Alpha	0.850 ± 0.209	0.805 ± 0.185	F _{1,28} = 0.665 (0.4217)	0.741 ± 0.203	0.914 ± 0.149	F _{1,29} = 21.992 (< 0.0001)
Beta	0.647 ± 0.167	0.544 ± 0.156	F _{1,28} = 4.529 (0.0423)	0.515 ± 0.145	0.676 ± 0.153	F _{1,29} = 83.542 (< 0.0001)
Gamma	0.679 ± 0.204	0.611 ± 0.158	F _{1,28} = 1.235 (0.2759)	0.594 ± 0.172	0.697 ± 0.184	F _{1,29} = 21.662 (< 0.0001)

HV: Healthy Volunteers

Table 3

MANOVA analyses with summary statistics of mean MI of in the beta band functional network.

<i>Summary statistics of mean MI of all channels</i>						
Characteristics of connectivity		Group main effect			Condition main effect	
	HV	FHD patients	F statistic (p-value)	Rest	Task	F statistic (p-value)
Purely linear	0.398±0.078	0.355±0.064	$F_{1,28} = 4.008$ (0.0551)	0.349±0.058	0.404±0.079	$F_{1,29} = 21.071$ (< 0.0001)
Linear	0.064±0.041	0.039±0.018	$F_{1,28} = 7.754$ (0.0095)	0.056±0.039	0.046±0.026	$F_{1,29} = 1.991$ (0.1689)
Mixed						
Nonlinear	0.002±0.004	0.001±0.001	$F_{1,28} = 2.676$ (0.1142)	0.002±0.004	0.001±0.001	$F_{1,29} = 1.968$ (0.1761)
<i>Summary statistics of mean MI of COIs</i>						
Characteristics of connectivity		Group main effect			Condition main effect	
	HV	FHD patients	F statistic (p-value)	Rest	Task	F statistic (p-value)
Purely linear	0.548±0.187	0.501±0.167	$F_{1,28} = 0.965$ (0.3343)	0.440±0.149	0.609±0.165	$F_{1,29} = 29.739$ (< 0.0001)
Linear	0.098±0.088	0.043±0.049	$F_{1,28} = 10.687$ (0.0029)	0.072±0.086	0.069±0.066	$F_{1,29} = 0.022$ (0.8843)
Mixed						
Nonlinear	0.002±0.004	0.001±0.001	$F_{1,28} = 4.148$ (0.0513)	0.002±0.004	0.001±0.001	$F_{1,29} = 4.342$ (0.0459)
HV: Healthy Volunteers						