Quantitative Assessment of Deep Brain Stimulation on Tremor in Multiple Sclerosis Disease

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ABSTRACT

Background and Purpose: Multiple sclerosis (MS) is a chronic disease that gives rise to a number of unpleasant symptoms that can be difficult to manage by conventional means. There are some aspects of MS-related disability which can be improved by using Deep Brain Stimulation (DBS); particularly movement disorders, such as tremor. The research aim is to study the effect of DBS on MS tremor with a quantitative approach.
Methods: Raw tremor data was provided by the Surgical Center for Movement Disorders at the University of British Columbia, Canada. The hand tremor signal was collected on 8 MS subjects and 10 healthy individuals during finger-to-nose test (FNT) by using motion analysis system. Patients executed the FNT with DBS OFF and ON. Nonlinear and statistical features were extracted from tremor spectrum as tremor indexes. Tremor reduction by using DBS was determined by classifying mentioned features into three groups of healthy, DBS ON and DBS OFF.
Results: Several dominant peaks were observed in power spectrum of the recorded signals which indicate MS tremor consists of several tremor subtypes due to different sites of demyelinating lesions affecting cerebellum and its output pathways. Results of frequency analysis revealed tremor spectrum dominant frequency in healthy group was significantly greater than for the patients with DBS ON and OFF ($p<0.05$). Additionally, classification results demonstrated that tremor of 6 patients out of 8 decreased significantly when their DBS was ON.
Conclusion: Overall, in 75% of patients with MS who suffered from tremor, thalamic DBS significantly reduced their tremor. In addition, power spectrum dominant frequency has high potential for a quantitative and objective measure of MS tremor.

Keywords: Deep Brain Stimulation, MS tremor, classification, nonlinear analysis.

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INTRODUCTION

Multiple Sclerosis (MS) is a degenerative chronic disease of the central nervous system. Movement disorder is one of the complications of MS which may include different elements such as tremor, Proximal postural instability and dysmetria [1]. Tremor is of great importance in the above-mentioned elements because of its strong association with disability and resistance to symptomatic treatment [2]. MS tremor is defined as "*intermittent or continuous, involuntary movements of the upper extremity* *that appeared rhythmic and oscillatory to visual inspection*" [3]. It is not easy to estimate the prevalence and severity of tremor in MS patients due to relapsing and remitting patterns of the disease. Furthermore, it is hard to distinguish between tremor and other movement disorder elements, such as ataxia. Tremor can greatly decrease the quality of life by interfering with daily activities such as writing, washing, wearing, eating and etc. MS tremor is mostly postural or intention tremor [1,4] and affects one or both upper limbs. However, other parts of body such as lower limbs, head and trunk can be involved [4-6]. However, the pathophysiology of MS tremor has not been definitively described because of the heterogeneity in the number, site and size of lesions, experiments show that demyelinating lesions may be important in tremor development due to its effect on the cerebellum and its output pathways via the midbrain and thalamus [4,7]. Drugs such as botulinum toxin and Isoniazid are effective in MS tremor treatment and other drugs like Propranolol are prescribed even though there are inadequate evidences of their effectiveness. In general, beneficial effects of drugs in MS tremor treatment is low or short-lived because of progressive nature of this disease. Therefore, surgery techniques in the form of thalamotomy or DBS is used for treating MS tremor[1]. The principal benefit of DBS over stereotactic lesional surgery is its reversible treatment with lower chance of side effects[8]. Normally the success of DBS in tremor reduction is determined by physical examination[9]. With regard to inaccuracy of these approaches and susceptibility of the results to the examiner, researchers seek an approach for accurate measurement of tremor [10,11].

In this paper, hand movements of the subjects (including MS tremor and voluntary movement) during finger-to-nose test (FNT) are recorded noninvasively with camera. Furthermore, the effect of DBS on MS tremor is assessed quantitatively by choosing suitable frequency features and classifiers. To the best of our knowledge, such quantitative approach has not been applied to MS tremor signal yet.

MATERIALS AND METHODS

Raw tremor data was provided by the Surgical Center for Movement Disorders at the University of British Columbia, Canada. This study consisted of four men and four women with the average age of 47 years (range 32-67 years). The median duration of MS and tremor prior to surgery was 6.5 and 4 years, respectively. All the patients had secondary progressive MS and the ones that were under treatment because of tremor and responded well to medical treatment were excluded. Also Patients with disabling upper-limb tremor were selected and the ones with limb weakness or numbness were excluded. The patients went through unilateral ventral intermedius (VIM) DBS for MS related tremor. Ten healthy individuals were randomly selected from hospital staffs with the average age of 45 years and no record of neuromuscular disease in order to specify how much DBS can improve tremor pattern by comparing the tremor pattern of patients with DBS ON with that of healthy subjects. Participants were notified of the non-invasive experiment and signed an informed consent.

In order to stabilize the conditions of the patients after surgery, the hand tremor data were recorded six month after implantation of DBS. The samples were provided by research team of mechanic group of university of British Colombia [9]. Tremor signals were recorded by utilizing a motion analysis system (Optotrak) with active markers. The markers themselves are infrared-emitting (active markers) and individually identifiable. The system consists of a three camera as position sensor placed in a distance of one meter of each other. Output of the system is 3D coordinates of each marker which changes with time and is called marker trajectory. The infrared marker was placed on index fingertip of each participant. Two other infrared markers were, respectively, placed along the Anterior/posterior (AP) direction on a table at the distance of 10 cm and of 50 cm of the subject. Each subject was seated on a chair such that his/her sternum is at the same level as the table, and was asked to touch the near and far markers with his/her index finger in a back-and-forth manner. This motion is similar to one of the maneuvers the neurologists use to investigate the hand tremor of patients (Finger-to-Nose test). This experiment was repeated three times for healthy group and six times for patients, three times with DBS ON and three times with DBS OFF. Matlab as well as SPSS software were used for processing and statistical analysis of data. In order to investigate the effect of stimulation on tremor, it is required to recognize the tremor from voluntary movement, and then find appropriate indexes of tremor and finally evaluate the effect of stimulation on tremor by classifying the indexes. Therefore at first, signal power spectrum was derived. Power spectrum determines power distribution of a signal in frequency domain. Then nonlinear (entropy), linear (dominant frequency and its amplitude) and statistical features (mean, variance, median) were extracted from the signals and then were applied as the inputs to the classifier. K Nearest Neighbor (KNN) Classifier is utilized to discriminate stated features into three groups of healthy, patient with DBS ON and Patient with DBS OFF. Considering the data were normally distributed, variables were described by mean values and analyzed by means of parametric statistical methods. In particular, comparisons among groups of subjects (healthy controls and MS subjects with DBS ON and OFF) were performed using the student's t-test. The level of significance was set at ($p<0.05$).

RESULTS

Several dominant peaks with different frequency ranges were observed in the power spectrum of the MS tremor signal. Results revealed that the dominant frequency of signal was more capable of quantizing MS tremor in comparison with other features. The mean dominant frequency values in superior/inferior direction were respectively 3.9, 1.6 and 1.7 Hz for healthy, DBS ON and DBS OFF groups. According to the results of student's t-test, the mean dominant frequency value in healthy group was significantly greater than that of both patients with DBS ON ($p=0.001$) and OFF ($p=0.0001$). In addition, dominant frequency values for patients with DBS ON and OFF were slightly different ($p= -0.184$).

Investigation of above mentioned three directional spatial data in FNT experiment revealed that anterior/superior direction data was common among all subjects. Removing common information is required for better discrimination of these three groups. Furthermore, by using feature selection method, features such as variance, threshold entropy, mean and dominant frequency were recognized as effective and appropriate features with classifier structure for quantitative investigation of MS tremor. Mentioned indexes were applied to discriminate healthy, DBS ON and OFF groups from each other. Based on the classification results, by making DBS ON the hand tremor of 6 patients out of 8 were suppressed significantly but in other 2 patients the hand tremor did not reduce much. It seems that younger patients who had shorter disease duration as well as no superimposed ataxia, weakness or sensory loss in tremulous limb might experience better results.

DISCUSSION

In this research, signal power spectrum was used because of the periodic nature of the tremor. Since MS tremor consists of different tremor subtypes (Postural, action and intention tremors) [1,5], several dominant peaks were observed in its power spectrum which were complicated MS tremor while only one dominant peak was reported in other pathologic tremor spectrums (Essential and Parkinson tremors) [12]. In order to remove voluntary movement from MS tremor, anterior/superior(AP) direction data of FNT test was omitted since voluntary movement was supposed to be done mainly in AP direction and was included most of the common data between the healthy and patient groups. With AP direction omission, classifying signals into three groups of healthy, DBS ON and DBS OFF was seemed more probable.

In this study, the target for DBS was VIM nucleus which showed efficacious result in suppression of MS tremor. This obtained quantitative result based on MS tremor reduction with VIM stimulation is in agreement with other studies showing effectiveness of this nucleus on MS tremor reduction with DBS [1,6,7,13,14]. Although some studies have been reported other target nuclei such as Ventral Oralis anterior (VOA), Ventral Oralis Posterior (VOP), Zona Incerta (ZI) and Basal Ganglia Outflow nucleus for MS tremor treatment with DBS [1,7,14]. However, further work is necessary to determine whether nucleus can have more benefit for MS tremor reduction with using DBS.

CONCLUSION

The results obtained from the classifier showed significant tremor reduction for %75 of patients with DBS ON. It is noted that the usage of stimulation was ineffective in suppressing tremor in %25 of patients. However, reduced tremor does not always implement improved quality of life; postoperatively, the patients in our test were improved in particular activities, such as feeding themselves. Patients should be carefully notified preoperatively about the limited expectations of the surgery (tremor reduction only), and the specific capabilities that may be enhanced by tremor reduction. It is observed that younger patients with no prior problem in tremulous limb might experience better results. Therefore, restricting entry criteria to include only this subgroup would improve the surgical results.

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