A novel technique for assessment of neuromuscular coupling in pathological tremor

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Abstract

We describe a novel technique for identification of cortical centres that have electrical activity coupled to the activity of skeletal muscles in pathological tremor. This technique utilises concurrent recordings of high-density surface electromyograms (EMG) and electro-encephalograms (EEG). First, the discharge patterns of individual motor units are identified from surface EMG signals by previously introduced Convolution Kernel Compensation technique. Next, spike-triggered averaging is applied to the EEG signals, using the identified motor unit discharges as triggering spikes. As a result, the cortical activities coupled to the discharges of a selected skeletal muscle are identified. The extracted EEG averages are then inserted into Statistical Parametric Mapping (SPM) tool and used to identify the cortical sources contributing to the observed EEG averages. When tested on 5 Parkinsonian and 5 essential tremor patients, this methodology consistently identified two cortical centres, one in the contralateral sensorimotor cortex, and the other in the contralateral prefrontal/premotor cortex.

1 Introduction

The central origin of essential (ET) and Parkinsonian (PD) tremor is widely accepted [1],[2] and identification of the brain structures that participate in pathogenesis of tremor received considerable attention over the past decades. ET is believed to originate at the cerebello-thalamocortical pathways [1],[3] connecting cerebellum, thalamus, red nucleus, globus pallidus and primary sensorimotor cortex. In PD patients, the loss of dopaminergic nigrostriatal neurons is believed to cause abnormal oscillations in the pathways linking the cortex, basal ganglia and thalamus [1],[3].

The involvement of somatosensory cortex in tremor pathogenesis is supported by many studies addressing corticomuscular coupling in ET [4]-[7] and PD tremor [7]-[10]. Development of advanced neuroimaging techniques that localize coherent sources in the brain offered further insight into the participation of other brain structures in the generation of tremor. In this regard, "Dynamic imaging of coherent sources" (DICS) [11] and "Renormalized partial directed coherence" (RPDC) [12] proved to be a very powerful tools for investigation of the pathophysiology of PD [7]-[11], [12] and ET tremor [7],[13]. However, these techniques are computationally relatively complex, requiring around 100 s of artefact free electroencephalographic (EEG) recordings.

Practically all the studies of the corticomuscular coupling rely on rectified bipolar EMG recordings [4]-[7],[8]-[13] for the assessment of motor neuron pool behaviour. This is a problematic step as surface EMG amplitude is known to reflect various anatomical properties of the investigated muscles [14]. The latter significantly interfere with the neural commands (in this case the concurrent voluntary and tremorogenic drives to muscle) from the spinal and supraspinal circuits and thus hinder the accurate estimation of neuromuscular coupling.

Recently, Convolution Kernel Compensation (CKC) technique for identification of motor unit discharges from surface EMG recordings was introduced [15],[16]. This technique provides highly accurate characterization of the neural drive to muscles [14], requires only 10 s of recorded signals and is fully automatic. In this study, the results of this motor unit identification were used to derive a novel technique for assessment of EEG-EMG coupling, so called EEG averaging, phase-locked to identified motor unit discharges. The extracted EEG averages can then be used for identification of tremorogenic activity of the central brain structures in ET and PD patients.

2 Methods

2.1 Patients and recordings

The experiments were performed at Hospital 12 de Octubre, Madrid, Spain. 5 ET patients (2 females, 3 males; age, mean ± SD: 71 ± 7 years, range 61–79 years) and 5 PD patients (5 males; age, mean ± SD: 71 ± 7 years, range 61–77 years) with mild, moderate or severe tremor participated to the study. Three ET patients were taking anti-tremor drugs, which in all cases were withheld for at least 12 h before the recordings. Five PD patients were taking dopaminergic drugs and continued their medications during the recordings.

Hand movements were measured by two pairs of Inertial measuring units (Technaid S.L., Madrid, Spain) placed on the dorsum of the hand and the distal third of the forearm, by computing their difference. The raw IMU signals were sampled at 100 Hz by a 12-bit A/D converter, and low pass filtered (< 20 Hz).

Surface EMG was recorded with four 13×5 electrode grids (1 missing electrode) with an interelectrode distance of 8 mm (LISiN–OT Bioelettronica, Torino, Italy). The grids were placed over the extensors/flexors of both wrists, centred laterally above the extensor digitorum communis/flexor carpi radialis, and longitudinally above the muscle belly. A wrist bracelet soaked in water served as common reference. The signal was amplified (EMGUSB, OT Bioelettronica, Torino, Italy), band-pass filtered (10–750 Hz), and sampled at 2048 Hz by a 12-bit A/D converter.

At the same time, EEG signals were recorded from 32 positions on the scalp, following the International 10-20 system (AFz, F3, F1, Fz, F2, F4, FC5, FC3, FC1, FCz, FC2, FC4, FC6, C5, C3, C1, Cz, C2, C4, C6, CP5, CP3, CP1, CPz, CP2, CP4, CP6, P3, P1, Pz, P2, and P4), with either passive Au or active Ag/AgCl electrodes depending on the session. The reference was set to the common potential of the two earlobes, and Az was used as ground. The signal was amplified (gUSBamp, g.Tec gmbh, Graz, Austria), band-pass (0.1–60 Hz) and notch (50 Hz) filtered, and sampled at 256 Hz by a 16 bit A/D converter.

Recordings were carried out while patients were seated in a comfortable armchair in a dimly illuminated room. Postural and rest tremor was elicited by asking the patients to perform the following 20 s long tasks:

- Arms outstretched (AO): the patient kept his/her arms outstretched, parallel to the ground, with the palms down and the fingers apart.
- Arms outstretched with weights (WE): the same as the AO task, but with one 1-kg weight fixed to the hands.
- Rest test (RE): the patient rested both arms on his/her lap, with the hands hanging freely.
- Arms supported + postural tremor elicited (PO): the same as RE task, but with wrists held extended against gravity.

The patients were instructed to stay relaxed and keep their gaze fixed on a wall about 2 m in front of them. Those with mild tremor severity were asked to mentally count backwards during the recordings to enhance their tremor.

The EEG and EMG recording systems were synchronized using a common clock signal. The data were stored and analysed offline using Matlab (The Mathworks Inc., Natick MA, USA).

2.2 Signal processing

The proposed technique for assessment of neuromuscular coupling builds on the results of motor unit identification from surface EMG signals (Figure 1). First, the surface EMG signals were decomposed by CKC technique into discharge patterns of individual motor units [16] and newly proposed Pulse-to-Noise (PNR) metric [17] was used to assess the accuracy in identification of each individual motor unit discharge pattern. In this study, only the motor units with highly accurately identified discharge patterns (PNR ≥ 30 dB, sensitivity in identification of motor unit discharges ≥ 90%) were used for further analysis, whereas all the remaining motor units were discarded. On average, 7.5 ± 3.5 motor units were kept per contraction. Next, the spike-triggered averaging of EEG was performed, using the identified discharge patterns of all reliably identified motor units as triggers. The length of averaging window was set to 4 s (± 2 seconds with respect to the individual motor unit discharge).

The extracted EEG averages were inserted into SPM tool [18] and used to calculate the cortical activity maps. For all the patients we used a standard template cortical mesh to describe scalp surface (2562 vertices), skull surface (2562 vertices), and cortex surface (8196 vertices). For head tissue (volumetric) model, a standard Boundary Element Method (BEM) model was used as supplied with SPM. For each patient, we manually verified registration between the recorded EEG electrode positions and the standard head models. Then, a forward model was calculated, followed by calculation of the inverse solution based on Greedy Search (GS) on Multiple Sparse Priors (MSP) with Restricted Maximum Likelihood (ReML) estimates. This has been shown to be superior to standard minimum norm or maximal smoothness solutions like LORETA [19]. Finally, the estimated source activity was interpolated across the template MRI image to produce the cortical activity maps.

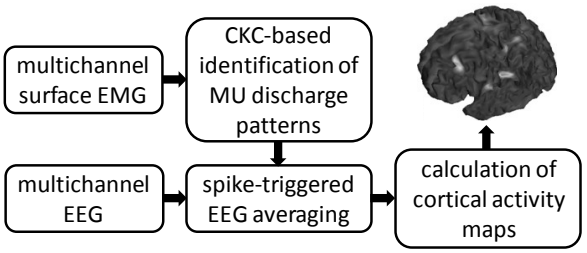

Figure 1: Schema of newly proposed technique for assessment of neuromuscular coupling; MU – motor unit

3 Results

Representative results of the proposed EEG averaging in one PD patient are exemplified in Figure 2. In agreement with the studies in the literature [8], [10], [17], clear tremorogenic oscillations were identified in the contralateral sensorimotor cortex (electrode location C2 in this case). Tremorogenic oscillations were much less pronounced in other cortical regions, though some tremorogenic activity was detected in contralateral F region. Similar results were observed in other PD patients and also in ET patients.

The SPM tool [19] was used to project the identified tremorogenic components back to the generic cortex model. For each separate task and each investigated muscle, these projections were averaged over all the PD patients and all the ET patients, respectively, identifying the consistently active cortical sources. The resulting averages of cortical activities are exemplified in Figures 3 and 4.

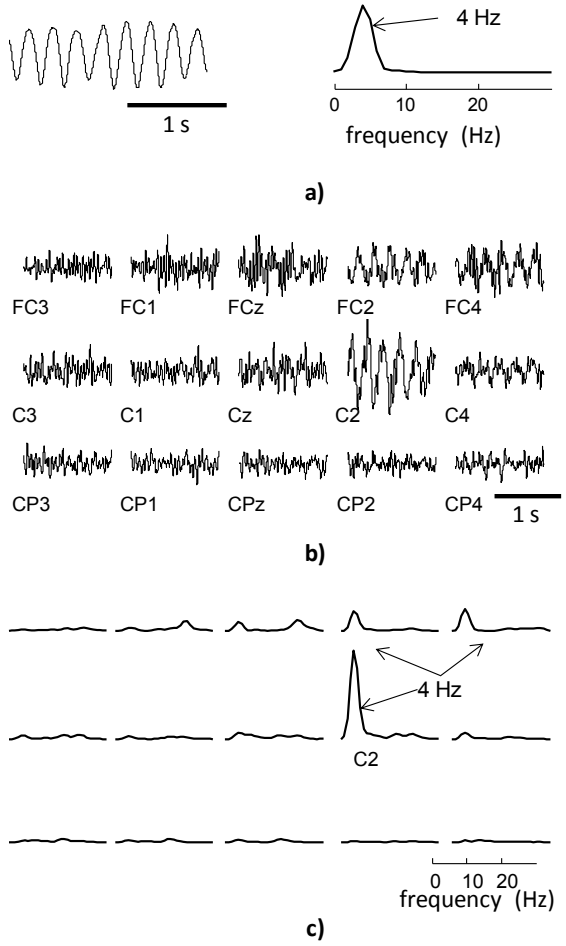

Figure 2: EEG averages, phase-locked to the motor unit discharges of the left extensor during the rest (RE) task in PD01 patient. The panel a) depicts the mechanical oscillations of the left wrist, panel b) illustrates EEG averages in time domain, whereas their Fourier transforms are presented in panel c).

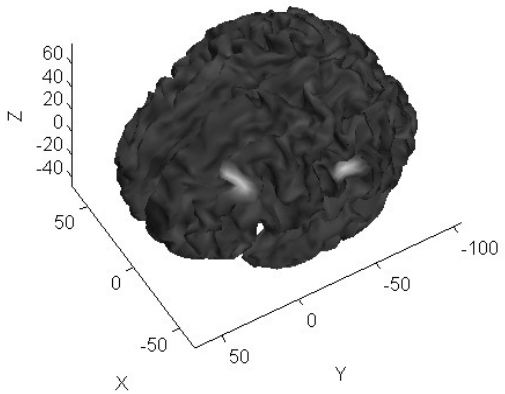

Figure 3: Cortical activity (bright areas) as reconstructed by SPM tool from EEG averages, phase-locked to the motor unit discharges in right flexor during the rest (RE) task. Results are averaged over 5 PD patients.

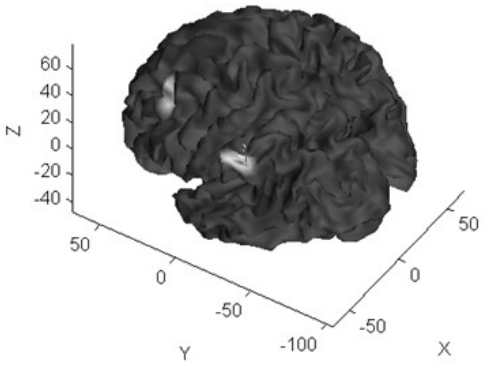

Figure 4: Cortical activity (bright areas) as reconstructed by SPM tool from EEG averages, phase-locked to the right flexor spike trains during the arms outreached with weights (WE) task. Results are averaged over 5 ET patients.

In both ET and PD patients, two different cortical sources were consistently identified, one in the contralateral sensorimotor cortex, and the other in the contralateral prefrontal/premotor cortex. The locations of both centres were highly consistent in both patient groups and practically in all the tremor triggering tasks studied. Weaker activity was also detected in the premotor cortex and also in the posterior-parietal cortex, but the activities of these centres were not consistent over different patients or different tasks.

4 Discussion

Although applied to relatively short (duration of ~20 s) and raw EEG signals (without any artefact rejection), the newly introduced methodology demonstrated considerable consistency in identification of tremorogenic EEG components. Furthermore, this method is fully automatic, supporting the batch processing of acquired EMG and EEG signals. It is also computationally efficient, requiring only few minutes of processing time on a standard personal computer. All these properties represent important steps forward with respect to the state-of-the-art EEG analysis of pathological tremor, where manual inspection of at least 100 s long EEG signals is usually required.

The identified centres of cortical activity are in agreement with the results of previous studies. For example, in PD patients, Timmermann et al. [9] utilized the DICS technique to identify the consistent cerebro-muscular coupling in contralateral primary motor (M1) area. Further cerebro-cerebral coherence, computed with the reference region in M1 revealed the involvement of cingulate/supplementary motor area, lateral premotor cortex, diencephalon, secondary somatosensory cortex, posterior parietal cortex and the contralateral cerebellum. Schnitzler et al. [20] extended this methodology to eight ET patients and identified the cerebro-muscular coupling in contralateral primary motor cortex and cerebro-cerebral coupling among the contralateral primary motor cortex, premotor cortex, thalamus, brainstem, and ipsilateral cerebellum. The muscular coupling with premotor cortex was identified in two out of eight ET patients, only. Muthuraman et al. [7] identified the systematic differences between the

basic tremor and first tremor harmonic cortical networks. The network for the basic tremor frequency consisted of the primary sensorymotor cortex, prefrontal/premotor cortex and thalamus. The network for the double tremor frequency was bound to cortical areas in the region of the primary sensory-motor cortex (next to the centres active at the basic tremor frequency), premotor cortex and posterior parietal cortex, similar to the results presented herein.

In conclusion, we utilized a highly accurate assessment of neural codes sent to skeletal muscles and introduced a novel technique for assessment of neuromuscular coupling in pathological tremor. This technique is fully automatic, needs no EEG artefact rejection and works with relatively short signals. In both PD and ET patients examined in this study, two cortical centres have been identified, one in the contralateral sensorimotor cortex, and the second in the contralateral prefrontal/premotor cortex.

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References

[1] R. J. Elble, "Origins of tremor.," Lancet, vol. 355, no. 9210, pp. 1113–4, 2000.

[2] J. Benito-León and E. D. Louis, "Essential tremor: emerging views of a common disorder.," Nature clinical practice. Neurology, vol. 2, no. 12, pp. 666–78; 2006.

[3] R. J. Elble, "Tremor: clinical features, pathophysiology, and treatment.," Neurologic clinics, vol. 27, no. 3, pp. 679–95, 2009.

[4] B. Hellwig, S. Häußler, B. Schelter, M. Lauk, B. Guschlbauer, J. Timmer, and C. H. Lücking, "Tremor-correlated cortical activity in essential tremor," The Lancet, vol. 357, pp. 519–523, 2001.

[5] B. Hellwig, B. Schelter, B. Guschlbauer, J. Timmer, and C. . Lücking, "Dynamic synchronisation of central oscillators in essential tremor," Clinical Neurophysiology, vol. 114, no. 8, pp. 1462–1467, 2003.

[6] J. Raethjen, R. B. Govindan, F. Kopper, M. Muthuraman, and G. Deuschl, "Cortical involvement in the generation of essential tremor," Journal of neurophysiology, vol. 97, no. 5, pp. 3219–28, 2007.

[7] M. Muthuraman, U. Heute, K. Arning, a R. Anwar, R. Elble, G. Deuschl, and J. Raethjen, "Oscillating central motor networks in pathological tremors and voluntary movements. What makes the difference?," NeuroImage, vol. 60, no. 2, pp. 1331–1339, 2012.

[8] J. Volkmann, M. Joliot, a Mogilner, a a Ioannides, F. Lado, E. Fazzini, U. Ribary, and R. Llinás, "Central motor loop oscillations in parkinsonian resting tremor revealed by magnetoencephalography.," Neurology, vol. 46, no. 5, pp. 1359–70, 1996.

[9] L. Timmermann, "The cerebral oscillatory network of parkinsonian resting tremor," Brain, vol. 126, no. 1, pp. 199–212, 2002.

[10] J. Raethjen, R. B. Govindan, M. Muthuraman, F. Kopper, J. Volkmann, and G. Deuschl, "Cortical correlates of the basic and first harmonic frequency of Parkinsonian tremor.," Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology, vol. 120, no. 10, pp. 1866–72, 2009.

[11] J. Gross, J. Kujala, M. Hamalainen, L. Timmermann, a Schnitzler, and R. Salmelin, "Dynamic imaging of coherent sources: Studying neural interactions in the human brain.," Proceedings of the National Academy of Sciences of the United States of America, vol. 98, no. 2, pp. 694–9, 2001.

[12] B. Schelter, J. Timmer, and M. Eichler, "Assessing the strength of directed influences among neural signals using renormalized partial directed coherence.," Journal of neuroscience methods, vol. 179, no. 1, pp. 121–30, 2009.

[13] A. Schnitzler, C. Münks, M. Butz, L. Timmermann, and J. Gross, "Synchronized brain network associated with essential tremor as revealed by magnetoencephalography.," Movement disorders : official journal of the Movement Disorder Society, vol. 24, no. 11, pp. 1629–35, 2009.

[14] D. Farina, A. Holobar, R. Merletti, and R. M. Enoka, "Decoding the neural drive to muscles from the surface electromyogram.," Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology, vol. 121, no. 10, pp. 1616–23, 2010.

[15] A. Holobar and D. Zazula, "Multichannel Blind Source Separation Using Convolution Kernel Compensation," IEEE Transactions on Signal Processing, vol. 55, no. 9, pp. 4487–4496, 2007.

[16] A. Holobar, V. Glaser, J. A. Gallego, J. L. Dideriksen, and D. Farina, "Non-invasive characterization of motor unit behaviour in pathological tremor.," Journal of neural engineering, vol. 9, no. 5, p. 056011, 2012.

[17] A. Holobar, M. A. Minetto, D. Farina: Accurate identification of motor unit discharge patterns from high-density surface EMG and validation with a novel signal-based performance metric," J. Neural Eng., vol. 11, no. 1, p. 016008, 2014.

[18] Wellcome Trust Centre for Neuroimaging: Statistical Parametric Mapping, http://www.fil.ion.ucl.ac.uk/spm/.

[19] R. D. Pascual-Marqui: Standardized low resolution brain electromagnetic tomography, Methods Find. Exp. Clin. Pharmacol., 24D:5-12, 2002.

[20] A. Schnitzler, C. Munks, M. Butz, L. Timmermann, J. Gross: Synchronized Brain Network Associated with Essential Tremor as Revealed by Magneto-encephalography, Movement Disorders, Vol. 24, No. 11, pp. 1629–1635, 2009.