Motor Unit Properties and Underlying Determinants in Pathological Tremor

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Abstract: Pathological tremors are accepted to originate from the projection of supraspinal pathological oscillations to motor neurons that innervate the affected muscles. These oscillations interact with other neural mechanisms such as reflexes, and, together with the mechanical properties of the limb, determine the characteristics of the tremor. However, much is yet unknown about the exact mechanisms that mediate the different types of tremor, and how they interact. Given that the neural drive to muscle encodes information about all pathways that regulate movement, we are investigating the properties of motor unit activities in tremor patients and the factors that determine them as a means to further our understanding of the disorder. This paper presents a simulation study that supports our departure hypothesis (that tremor is a common cortical projection to the motor neuron pool), and first experimental evidences on a patient with essential tremor. The latter illustrate that the predictions derived from the model provide significant support for the analysis of real data, and demonstrate the potential of the analysis techniques here employed.

1 INTRODUCTION

The term pathological tremor encompasses a series of disorders that originate disabling involuntary oscillatory activity of a body part (Deuschl et al., 1998). Such oscillatory movement may be ultimately generated by different mechanisms, such as pathological oscillations at cortical and subcortical structures–the underlying cause in most types of tremor–, or a peripheral neuropathy–a rare type of tremor– (Deuschl et al., 2001). In addition, due to the intrinsic properties of the neuromuscular system, other factors such as the mechanical properties of the limb (muscles) and spinal and supraspinal afferent loops are also thought to participate in tremorogenesis (McAuley and Marsden, 2000).

A motor unit, understood as a motor neuron and all the fibers it innervates, is the smallest element that the nervous system can activate (Heckman and Enoka, 2004). The sum of the action potentials fired by all active spinal motor neurons, which is referred to as neural drive to muscle, encodes information about descending and afferent neural commands (Farina et al., 2010). Thus we believe that the elucidation of the properties of the neural drive to muscle in tremor patients may help to further what is known about the pathophysiology of these disorders.

Few studies to date have investigated the specific properties of motor unit spike trains in tremor patients. A characteristic consistently reported in those available was the presence of paired or tripled discharges, which occurred rhythmically with the tremor bursts (Das Gupta, 1963) (Dietz et al., 1974) (Elek et al., 1991) (Baker et al., 1992) (Christakos et al., 2009). Further, although many works have put forward that motor unit spike trains in tremor patients exhibit higher synchronization than in healthy subjects (Dietz et al., 1974) (McAuley and Marsden, 2000) (Christakos et al., 2009) (Elble and Deuschl, 2009), no study has specifically addressed this observation. Importantly, all of the previous works were constrained by the limited number of units concurrently identified, typically less than 5–6 per contraction (Stashuk et al., 2004), a drawback that arises

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from state of the art technologies for recording intramuscular electromyograms (EMG). To circumvent this limitation, in our study we employe a novel technique that decomposes the multichannel surface EMG into constituent motor unit spike trains. This technique, called Convolution Kernel Compensation (CKC) (Holobar and Zazula, 2007) (Holobar et al., 2009), has been largely employed to identify motor unit spike trains in healthy subjects (Holobar et al., 2010), and deals effectively with the specific firing properties observed in tremor patients (Holobar et al., 2012).

This work presents an overview of our current work on the investigation of tremor properties based on the analysis of motor unit spike trains. We hypothesize that, in tremor patients, the characteristics of motor unit firing patterns are determined by the presence of a strong synaptic input related to (i.e at the frequency of) the tremor, which is commonly projected from supraspinal centers to the entire motor neuron pool. Thus, here we review a study with a multiscale model of pathological tremor in which we tested this departure hypothesis (Gallego et al., 2011), and compare these results with data obtained from one patient with essential tremor (ET), the most common type of tremor, and that originates at the cerebellothalamocortical loops (Benito-León and Louis, 2006).

2 Methods

2.1 Computational Model

We employed a multiscale model of a pair of antagonist muscles to simulate tremor (Dideriksen et al., 2011). This model comprised a realistic representation of a motor neuron pool (Fuglevand et al., 1993), which served to continuously estimate motor unit firings during dynamic contractions. The net synaptic input to each motor neuron integrated a descending voluntary drive and a descending tremor component, both of which were commonly projected to the entire motor neuron pool, and afferent input from muscle spindles and Golgi tendon organs. EMG was simulated employing a model of multilayer cylindrical volume conductor that comprised anisotropic muscle tissue and isotropic bone (Farina and Merletti, 2004). Joint dynamics and afferent inputs were calculated with a model that accounted for the viscoelastic properties of muscles. The muscles simulated were the first dorsal interosseus (FDI) and its antagonist, the second palmar interosseus. Model parameters were set to those in in (Dideriksen et al., 2011). Simulations were performed at four different contraction levels (0, 5, 10 and 20 % of the maximum voluntary contraction [MVC]), and with three different imposed tremor frequencies (5, 8 and 11 Hz); see (Gallego et al., 2011) for details.

2.2 Patient and Protocol

We present data for one female ET patient (79 years old) with bilateral postural and kinetic tremor of moderate severity, recruited at Hospital Universitario "12 de Octubre," Madrid, Spain. The patient, who was on medication (propanolol, 120 mg/day) during the recordings, did not exhibit head or trunk tremor. The Ethical Committee at the hospital approved the experimental protocol, and the patient signed a written informed consent to participate.

The recordings were carried out while the patient was sitting on an armchair in a dimly illuminated room. Tremor was triggered by asking the patient to outstretch both hands, with the palms down and the fingers slightly outspread, while the forearm was fully supported. Data were recorded for 4 min.

Hand tremor at the most affected side (right) was recorded with a multichannel EMG electrode grid (13 x 5 electrodes, 8 mm inter-electrode distance, LISiN–OT Bioelettronica, Torino, Italy) placed over the extensor digitorum communis; a moistened bracelet attached to the wrist served as common reference. Concurrently, we recorded electroencephalographic activity (EEG) from 32 positions at the somatosensory-cortex (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 according to the 10-20 system) with passive Au electrodes; the common potential of the two earlobes was used as reference, and Az as ground. EMG signals were amplified (EMGUSB, OT Bioelettronica, Torino, Italy), band-pass filtered (10–750 Hz), and sampled at 2,048 Hz by a 12-bit A/D converter; EEG signals were 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.

2.3 Data Processing and Analysis

The analysis focused on two aspects. First we assessed, with the model, how the tremor drive commonly projected from supraspinal centers to the entire motor neuron pool would be transmitted to the output of such motor neuron population. We expected that linear sampling would arise after the spike trains of a few motor neurons were considered together, as observed for the voluntary drive in healthy subjects (Ne-

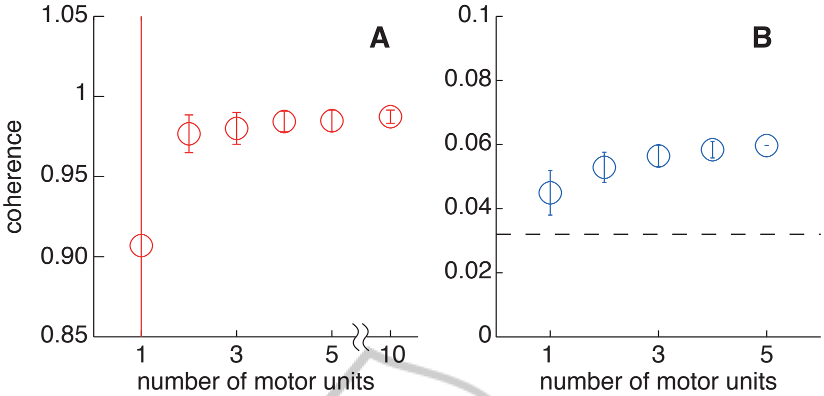

Figure 1: Coherence between the supraspinal tremor oscillations and the CSTs, as function of the number of motor units considered in the CST. Data in (A) corresponds to the model, in (B) to the patient. The plot represents the mean ± SD for all possible combinations (in the case of the model considering 1 out of 10 motor units recruited). In (B) the dashed line represents the significance threshold ($P < 0.05$); in the case of (A) it is now visible (it was 0.145 for $P < 0.05$).

gro and Farina, 2011). Then, we investigated whether the patient data replicated the behavior expected from the model. In a second phase, we compared qualitatively the simulated and observed (in the patient) properties of motor unit spike trains, in terms of firing statistics and synchronization between the activities of different motor units.

Linear sampling of the (supraspinal) tremor input by the motor neuron pool was investigated by calculating the coherence between groups of motor unit spike trains (referred to as composite spike trains [CST]) and the tremor drive. We also assessed how coherence varied as more motor units were included in the CST in order to verify the hypothesis that, in patients, the tremor is a common cortical input to the motor neuron pool; if the projection were common, the coherence at the tremor frequency should increase until reaching a plateau (saturation) for a few motor units (Negro and Farina, 2011), meaning that the motor neuron pool had linearized the transmission of the tremor drive. In the case of the model, the tremor drive was directly available for the computations, while for the patient it was assessed from the raw EEG. In both cases, coherence was estimated in 1-s disjoint Hann windows (Halliday et al., 1995); in the case of the patient, windows contaminated with artefacts were carefully removed. Significance was estimated following (Rosenberg et al., 1989).

Motor unit behavior was assessed by computing histograms of their inter-spike intervals (ISI), in order to have a global representation of their statistical properties. Special attention was paid to the presence of paired or tripled discharges (Das Gupta, 1963) (Dietz et al., 1974) (Elek et al., 1991) (Baker et al., 1992) (Christakos et al., 2009). Further, we assessed the synchronization between pairs of motor units to investigate whether synchronization is greater in tremor patients than in healthy counterparts. In the model, we expected that abnormally large synchronization would arise due to the presence of a common synaptic input related to tremor. In the case of patients, it would be suggestive of the presence of a strong common input (Kirkwood and Sears, 1978). A standard metric based on the computation of cross-correlograms between pairs of motor unit spike trains, the Common Input Strength index (CIS) (Nordstrom et al., 1992) was employed. Significant synchronization was inferred from the cumulative sum of the cross-correlogram (Ellaway, 1978). For the calculation, we followed the methodology in (Dideriksen et al., 2011) (Gallego et al., 2011).

For the patient, we identified motor unit spike trains from the decomposition of the multichannel EMG using the CKC technique (Holobar et al., 2012), as mentioned above. Motor unit spike trains were verified by an experienced operator, and motor neurons that were not active for a significant proportion of the trial (<65 %) or identified with great accuracy (height of spike trains compared to baseline jitter ≥26 dB) were discarded for the analysis. In the case of the model, motor unit spike trains were directly available.

Results are reported as mean ± SD.

3 RESULTS

For the patient, the total number of identified motor units that satisfied the criteria presented above were 5. The number of high quality 1-s EEG windows was 93. These data were employed for the subsequent experimental analyses, except where mentioned otherwise.

3.1 Common Supraspinal Input

For all simulated conditions (amount of voluntary contraction and imposed tremor frequency), the coherence at the tremor frequency was largely significant even when 1 single motor unit was considered (grand mean for all conditions 0.953 ± 0.027; the confidence limit was 0.145 for $P < 0.05$), as expected from the implementation of the model (Dideriksen et al., 2011) (Gallego et al., 2011). Even for a such a large coherence with CSTs comprising 1 motor unit, when assessing the relationship between coherence and number of motor units in the CST (see Fig. 1A), we observed that there was an exponential trend that reached a plateau when $\sim$4 motor neurons were considered (visual inspection). This suggests that the existence of a common synaptic input related to tremor could be inferred, even in the concurrent presence of a voluntary drive, by observing the trend of the coherence peak at the tremor frequency as function of the number of motor units sampled, as previously observed for healthy subjects (Negro and Farina, 2011).

As to the patient, we obtained significant coherence at the tremor frequency (5.750 Hz) between the contralateral cortical activity (largest at CP3) even when 1 motor unit was sampled (coherence 0.045; the confidence limit was 0.032 for $P < 0.05$). As expected, the coherence was considerably smaller than for the model given the presence of interneurons in the descending pathways, which distorted the transmission process due to their nonlinear transfer function (Gerstner and Kistler, 2002). Interestingly, the analysis of corticospinal coherence as function of the number of motor units also indicated that there was an exponential trend (see Fig 1B), and thus suggested that the descending tremor drive was a common input at the tremor frequency.

3.2 Motor Unit Firing Properties and Synchronization

In the model, the analysis of motor unit behavior yielded that motor unit firing characteristics were largely influenced by motor neuron size (which determines its recruitment threshold (Fuglevand et al., 1993)) and by the strength of the voluntary drive and the frequency of the tremor. As motor neuron size increased, at low contraction levels, motor neurons exhibited less likelihood to fire paired and tripled discharges. On the contrary, at strong voluntary contractions small motor units exhibited a firing pattern that resembled that observed during voluntary contractions in the absence of tremor, and larger motor neurons fired paired and tripled discharges depending on several factors (such as the strength of the voluntary drive, tremor frequency, and motor neuron size). Higher tremor frequencies appeared to facilitate the transition from rhythmic motor unit firing (entrained with the tremor) to a tonic firing pattern. Accordingly, the ISI histograms of the simulated motor unit spike trains followed both unimodal and bimodal (with one peak reflecting the paired and tripled discharges) distributions. Interestingly, motor unit synchronization as estimated with the CIS was remarkably larger (grand mean for all conditions 6.745 ± 1.870 pps) than when simulating voluntary contractions in the absence of tremor (mean CIS for the 4 contraction levels 0.203 ± 0.159 pps). Fig. 2 illustrates the influence of strength of voluntary contraction and tremor frequency on motor unit synchronization as estimated with the CIS.

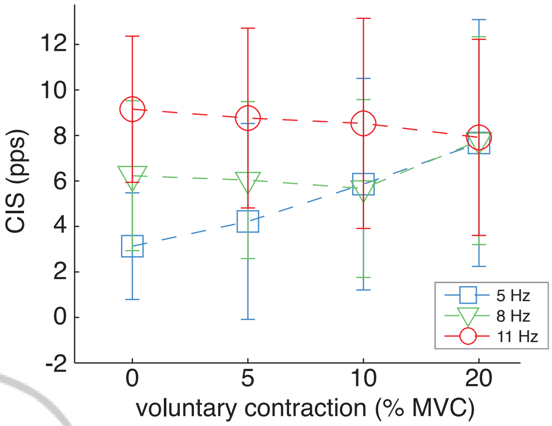

Figure 2: Motor unit synchronization as computed with the CIS. The plot illustrates the mean ± SD synchronization for all possible pairs of motor neurons (considering 1 out of each 10 simulated) for 4 contraction levels and 3 different tremor frequencies (see the legend).

The patient data followed an unimodal, slightly skewed distribution with a peak at $\sim$50 ms (joint data for the 5 identified motor units, i.e. cumulative ISI histogram). Unexpectedly, this value was not related to tremor frequency. However, the motor units often fired paired and tripled discharges (ISI 20–80 ms), as previously reported in a study on ET patients (Elek et al., 1991). Nine out of 10 pairs of motor unit spike trains exhibited significant correlation, and the mean CIS for the last 2 min of the trial was 1.61 ± 1.48 pps. This value was remarkably larger than previously reported for healthy subjects performing voluntary contractions ($\leq$0.7 pps (Keen and Fuglevand, 2004)), which indicates that the motor neuron pool receives a strong common synaptic input.

4 DISCUSSION

This paper showed, based on a multiscale simulation model and data on one representative tremor patient, that the supraspinal oscillations that mediate tremor are a common cortical projection to the motor neuron pool, as indirectly suggested in previous works computing EEG-EMG coherence. Furthermore it puts forward, based on physiologically plausible simulations, that the presence of a common tremor drive to the motor neuron pool may cause abnormally large motor unit synchronization, as largely hypothesized for tremor. Experimental results in one representative ET patient suggest that this abnormally large synchronization may be systematically found in patients, which would indirectly prove the existence of a strong common synaptic input related to tremor.

It must be noticed that the coherence values found in the model were notably larger than those observed in the patient. We believe that the reason for this is (at least) twofold. First, in the model the tremor was a narrowband colored noise that was directly projected to all motor neurons in the pool, which implies that it neglects the spectral distortion that interneurons introduce in the transmission of supraspinal oscillations, given their nonlinear response (Gerstner and Kistler, 2002) (Negro and Farina, 2011). Second, in the model the central (supraspinal) tremor was directly available, while for the case of the patient we had to assess its contribution from the EEG. Indeed, the amplitude spectrum of the EEG recorded in this patient did not shown a peak at the tremor frequency, opposite to the clear contribution observed in the case of the model. Remarkably, low coherence values are reported in other works studying EEG-EMG coherence in tremor patients (Raethjen et al., 2007) (Volkmann et al., 1996) (Timmermann et al., 2003).

As to motor neuron synchronization, for the model we showed that if a strong common tremor input was projected to the entire motor neuron population, the motor unit spike trains exhibited abnormally synchronization. Interestingly, synchronization was remarkably large for all tremor frequencies and levels of concurrent voluntary contraction. In the case of the patient, we observed that motor unit synchronization as computed with the CIS was more than two times larger than previously reported for healthy counterparts. Thus, given the well-established causal relationship between synchronization and common synaptic inputs (Kirkwood and Sears, 1978) we consider this as a further proof of the existence of a common cortical input to the motor neuron pool related to tremor.

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