Editorial

Nonlinear irregularities in Parkinson's disease tremor and essential tremor

Pathological tremor represents one of the most severe but common examples of movement impairment debilitating patients' ability to perform daily activities. Tremulous movements are involuntary, rhythmic, and oscillatory movements of body parts that can differ in clinical features as well as etiologies (Bhatia et al., 2018). Among the most common phenotypes are Parkinson's disease (PT) and essential tremor (ET). A major challenge consists of the characterization of specific features of tremulous movements to uncover differences and commonalities, and enrich our understanding of the underlying pathophysiological mechanisms to improve existing diagnostic tools and therapeutic options.

The application of neurophysiology and kinematic analyses has revealed several distinct characteristics differing between these two tremor variants (Hossen et al., 2010; Muthuraman et al., 2012; Brittain et al., 2015; Morrison et al., 2017). Although different types of tremor may occur in PT, the most prevalent form is a resting tremor of the relaxed hand, lower limb, jaw, tongue, or foot, referring to a 4-6 Hz oscillating movement that usually vanishes during movement initiation but may re-emerge after commencing a static posture (Bhatia et al., 2018). In ET, however, tremor usually emerges during a movement or by holding a static position and is characterized by a broader frequency range between 3–11 Hz (Raethjen et al., 2013).

Although there is an overlap in the tremor frequencies of PT and ET, distinct power peaks are usually present at integer harmonics of the main frequency in PT (Muthuraman et al., 2011). Advanced neurophysiologic techniques combining EEG- and EMG-recordings demonstrate the engagement of different brain networks in relation to either the peak frequency or the double peak frequency in PT. Increases in harmonic power may therefore represent meaningful oscillatory activities, possibly caused by an additional tremor generator, rather than pure harmonic frequencies related to the waveform characteristics (Muthuraman et al., 2012; Muthuraman et al., 2018). The significance of harmonic frequencies is reflected in promising classification success by solely calculating the average harmonic power as well as applying a soft-decision wavelet technique (Hossen et al., 2010; Muthuraman et al., 2011; Hossen et al., 2020).

Focusing on the dynamics of tremor evolution, Brittain et al. (2015) and di Biase et al. (2017) studied the variation of the instantaneous tremor frequency in PT and ET over time. By analyzing cycle-to-cycle frequency fluctuations, both studies demonstrated that PT is characterized by an increased frequency tolerance representing a broader range of stable frequencies. In contrast, small deviations from a very narrow frequency range are followed by frequency alterations in the subsequent cycles in ET. The resulting tremor stability index, which is smaller in PT, is another promising marker to distinguish between PT and ET, and thus demonstrates the benefit of investigating dynamic parameters in addition to time invariant measures (di Biase et al., 2017).

Another approach to studying signals that are generated by biological systems borrows tools from nonlinear dynamical systems theory (Richman and Moorman, 2000). Underlying is the assumption that complex systems like a living person are governed by the coordination of their elements (e.g. the brain, brain regions, muscles, limbs, etc.) by nonlinear, stochastic, and complex interactions that occur over multiple temporal and spatial scales. In this regard, measures of complexity and irregularity like sample entropy and approximate entropy have been applied to tremor analysis in writing and drawing movements (López-de-Ipiña et al., 2016) and accelerometer data to distinguish PT from ET or healthy controls (Morrison et al., 2013; Morrison et al., 2017).

In the current issue of *Clinical Neurophysiology*, Su et al. (2021) follow a dynamical systems approach to investigate the nonlinear characteristics of tremor in PT and ET with the help of multiscale entropy (MSE). MSE is an extension of sample entropy, which examines time series data for its regularity. Importantly, by dividing the original time series into coarse grained time series, MSE considers long-range interactions particularly over multiple time scales, a crucial feature in complex systems. Entropy increases with the amount of irregularity and is maximal for completely random systems. Aging as well as disease appear to degrade complexity, reflecting a diminished capacity to adapt to environmental perturbations (Costa et al., 2002). On the other hand, enhanced complexity is present in patients that exhibit an increased amount of movement instabilities that may result from reduced sensorimotor integration (Coates et al., 2020). Healthy systems should therefore exhibit an optimal amount of complexity to guarantee stable functionality.

Following this approach, Su et al. (2021) demonstrate for the first time that the tremor of Parkinson's disease patients is characterized by an increased amount of irregularities over multiple time scales in comparison to ET. Furthermore, MSE is associated with the duration and severity of the movement disorders and distinguishes patients between the two groups. These results blend in well with the previous findings of Brittain et al. (2015) and di Biase et al. (2017) that suggest that ET might be generated by a central oscillator, whereas multiple uncoupled oscillators in PT may render responsible for an increased frequency tolerance. It is easily conceivable that the presence of multiple oscillators may cause the tremor to be less regular and reduce the amount of long-range interactions.

To uncover alterations of MSE in comparison to physiologic tremor as a reference of healthy systems, future studies should include control subjects. While Morrison et al. (2017) demonstrated that PT and ET are less complex than physiologic tremor on a single time scale these findings remain to be confirmed for multiple time scales. Nonetheless, the current findings demonstrate that the analysis of tremulous motions over multiple temporal scales using nonlinear parameters provides unique insights into the complex characteristics of ET and PT. Another important future step is now to investigate the neurophysiologic mechanisms underlying differences in tremor complexity. Furthermore, the classification results have to be validated in other cohorts and especially in patients with less distinguishable early symptoms, where the clinical diagnosis is particularly challenging (Rizzo et al., 2016).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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