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Mechanisms and Emerging Therapies in Tremor Disorders

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Preface

Who could claim they've never experienced trembling at least some point in their lifetime? Indeed, everybody has perceived some tremor some time in life. For instance, the postural tremor observed when using the pointer during one's first lecture… In fact, a slight, rapid, and postural physiological tremor is permanently present, as shown when placing a piece of paper on the hand when the upper limb is extended. Tremor is thus a very common phenomenon when one looks around carefully.

Medical doctors are aware that the observation of an unexpected tremor in a given subject can result either from diseases of non-neurological origin (hyperthyroidism, drug treatments, etc.) or from an affliction of the nervous system. The most known of the latter are Parkinson's disease (PD), although the classical rest tremor is not always present, and Essential Tremor (ET), characterized by a postural/kinetic tremor and whose prevalence is six times higher than the prevalence of PD. By contrast with what is usually believed, the diagnosis of tremor is far from being easy. When its intensity is minimal, it is often difficult to distinguish ET from physiological tremor (for instance in subjects pertaining to ET families). When tremor is severe, its large amplitude may wrongly orient towards other disorders such as repetitive movements observed in PD treated by levodopa. Even more difficult, a tremor can mimic rhythmic myoclonus as seen in dystonic patients or depressed patients overtreated with various medications (lithium, etc.). In all these difficult cases, a polygraphic recording of tremor by an experienced clinical physiologist can be very helpful. Although tremor is a remarkable sign to perform an accurate diagnosis during daily clinical practice, it is often underlooked. There are many biases and drawbacks, for example, the amalgam between tremor and senility, or the wrong idea that tremor is often associated with alcoholism (I recall the case of a waiter who was considered alcoholic, although he had in fact a severe ET that he tried to improve by drinking several glasses of wine before serving the guests).

When possible, the treatment of tremor depends primarily on the treatment of the condition causing the tremor (hyperthyroidism for example). However, this is exceptionally the case in most neurological disorders. In PD patients, tremor is rarely disabling, except in few forms of the diseases, and it is usually largely attenuated by the administration of levodopa provided the doses of the administrated

amino acid are high enough, which is not always possible. In most severe cases of parkinsonian tremor, the neurosurgical approach (high-frequency stimulation of the thalamus, thalamotomy) can be extremely helpful. Bilateral stimulation of the subthalamic nucleus has not only the advantage of abolishing the contralateral rest tremor, but also to markedly improve the most disabling akineto-rigid syndrome. In patients with ET, one has to clearly distinguish two clinical situations. In benign cases, when the symptom starts to bother the patient in his daily life, the administration of drugs such as beta-blockers or primidone is required provided there is no contraindication. In patients with severe ET, i.e., when the amplitude of the tremor is interfering with the most elementary gestures of daily life, the medical treatment becomes ineffective, and the best option, when acceptable, is neurosurgery. High-frequency stimulation of the Vim of the thalamus is the treatment of choice, but the destructive approach (thalamotomy) can be considered in fragile, aged, or non-cooperative patients.

These comments are obviously oversimplified and will be extensively developed in the book. Whether benign, needing a simple follow-up, or severe, implying a sophisticated treatment, the clinical aspects of the various types of tremor need to be perfectly identified as it is the only way to ensure an optimal management of patients. To become a good semiologist in the field of tremor is necessary, but it is not sufficient! One needs also to be an excellent physiologist. Nowadays, as the mechanisms of the different categories of tremor start to be understood, this is now possible. In this field, the practitioner needs to keep in mind three main ideas (1) tremor can result from the dysfunction of all parts of the nervous system: the cerebral cortex (rhythmic myoclonus), the basal ganglia (PD rest tremor), the brain stem (Holmes tremor), the cerebellum (ET), the spinal cord (in fact segmental myoclonus), and peripheral nerves (Charcot–Marie–Tooth diseases); (2) several groups of neurons are tremorogenic, giving rise to various rhythmic oscillations in the brain (12–14 Hz in the olive; 3–6 Hz in the basal ganglia); (3) there is no unique "center of tremor" explaining the rhythm, the speed, and the amplitude of tremor, which also depends on the tension of the implicated muscles. In most cases, even if the lesions are selectively confined in the brain, tremor results from the dysfunction of various neuronal circuits, thereby giving rise to different symptomatic aspects of tremor.

Why this new book then? The reason is that it provides an extensive state of the art of the available clinical and scientific knowledge related to tremor. The numerous chapters, provided by the best experts in the field, will allow the clinicians to base their diagnosis, prognosis, and treatment on an updated clinical and pathophysiological basis, with bridges between fundamental aspects and clinical approaches.

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Introduction

The field of tremor has dramatically widened since the publication of the books of Findley-Capildeo (1984) and Findley-Koller (1995). The Consensus Statement of the Movement Disorder Society is another key document for the history of research on tremor (Deuschl et al. 1998), suggesting a classification based on the distinction between rest, postural, kinetic, and "intention" tremor (tremor during target-directed movements). Additional data from a medical history and the results of a neurologic examination have been combined into one of the following clinical syndromes defined in the statement: enhanced physiologic tremor, classical essential tremor, primary orthostatic tremor, task- and position-specific tremors, dystonic tremor, tremor in Parkinson's disease, cerebellar tremor, Holmes' tremor, palatal tremor, drug-induced and toxic tremor, tremor in peripheral neuropathies, or psychogenic tremor.

A broad range of common neurological disorders manifest with rhythmic oscillations; this area of research has become increasingly productive both at the experimental and clinical level, and as a consequence, much new information has accumulated over the last years. Therefore, we thought that the quantity of novel knowledge was worthy of a comprehensive update. An example of the sprouting of knowledge is related to our current understanding of Essential Tremor. It is now accepted that this terminology covers several distinct disorders and that the symptomatology is much broader than initially thought. Interestingly, a better understanding of tremor mechanisms may bring new insights for fundamental brain mechanisms such as synchronization of neural networks, coordination and execution of movement.

Although apparently simple, tremor is a complex physiological and physiopathological phenomenon. Tremor may occur at any age and is often a cause of social difficulties, even if patients may not seek medical care, due to impairment of activities of daily life such as eating or writing. Ad hoc clinical rating scales of tremor are now complemented by functional evaluations and the use of motion transducers allow in particular the extraction of the amplitude and the frequency of tremor. Novel methods of assessment have emerged with their own advantages and limitations. Reliable and unobtrusive wearable sensors are available, so that a detailed monitoring and an accurate assessment of tremor can be performed. Such evaluation

can by itself contribute to a correct diagnosis of the underlying neurological disorder. Novel approaches in signal processing have also been developed. These methods are shared between several disciplines and research topics. In addition, many laboratories have developed their own tools and approaches to tremor assessment.

Tremor is intimately linked to the numerous interactions of the central and peripheral nervous system components tuning motor control, from the cerebral cortex up to the peripheral effectors. Activities of central generators, reflex loop delays, inertia, stiffness, and damping are all factors influencing features of tremor. This book discusses the pathophysiology of tremor including membrane mechanisms and rodent models, the advances in genetics and the musculoskeletal models pertinent to body oscillations. The main forms of tremor encountered during clinical practice are considered, taking into account neuroimaging aspects. The book covers recent advances in methodologies and techniques of assessment and provides practical information for the daily management. In addition to pharmacological treatments, neurosurgical approaches such as deep brain stimulation (DBS) and thalamotomy are discussed. Emerging techniques under development are also introduced. Future challenges are also presented.

This overview is intended for a large audience of scientists, clinicians including neurologists and neurosurgeons, internists, fellows, trainees, biologists, and biomedical and electrical engineers. The goal of this book is to provide both basic science information and detailed clinical approaches and to make recent developments accessible to this audience, in order to promote understanding and optimal care of patients suffering from tremor.

All the experts who have excellently contributed to this book have a direct experience in tremor. We are indebted to all of them for their efforts. We are also particularly grateful to Ann Avouris and Simina Calin for their commitment, continuous support, and professionalism.

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