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Milestones in Clinical Neurophysiology

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Abstract

Over the last 25 years, clinical neurophysiology has made many advances for the understanding, diagnosis and even treatment for different movement disorders. Transcranial magnetic stimulation has been the biggest technical advance. Progress in pathophysiology includes improved knowledge about bradykinesia in Parkinson's disease, loss of inhibition and increased plasticity in dystonia, abnormal startle in hyperekplexia, and various features of psychogenic movement disorders that can aid diagnosis. Studies have been done looking at the use of non-invasive brain stimulation for therapy, but effects are generally small.

Keywords

transcranial magnetic stimulation; EEG; EMG; Parkinson's disease; Dystonia

The past 25 years has seen enormous interest in central motor control and the insights that it can bring to disorders of movement. As in many fields the advances in investigation as well

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as the directions that they have often been driven by new technologies and increasing computer power or by greater insights into basic mechanisms from new data in animal experiments.

Technology

The basic tools of clinical neurophysiology, EMG and EEG, remain the same now as 25 years ago; new insights have come in the main by exploiting the ready availability of powerful computers. In the early 1980s, computers were commonly used for averaging, but were rarely able to achieve more complex processing without hours of calculation. In terms of motor control the major early advance of the late 1960s and 1970s had been development of "backaveraging" since this could reveal activity in the brain that had preceded (and perhaps caused) an EMG event in the periphery. It was a major advance that had produced not only the extensive literature on the Bereitschaftspotential,[1] but also had made major impact in the study of myoclonus where it produced the standard classification of cortical, subcortical and spinal subtypes.[2] In the past 25 years, this work has been augmented by increases in computational power that allow easy analysis of signals in the frequency rather than temporal domain. In this work, EEG and EMG signals are first split into their individual frequency components which are then analyzed separately for changes in power or coherence between spatially separate sites. This reveals additional information content in the signal and has been critical to our current understanding of the link between activity recorded from deep brain electrodes in the basal ganglia and symptoms of movement disorders.

The main technological breakthrough of the past 25 years for clinical neurophysiology has been the development of non-invasive methods of brain stimulation, beginning with Merton & Morton's description of transcranial electrical stimulation (TES) of the motor and visual cortices in 1980 (Figure 1).[3] This was the first time that it had been possible in conscious individuals to stimulate directly motor pathways in the brain, and this revitalized studies of central motor control. However, TES only gained limited acceptance because the stimulus produced a strong contraction of scalp muscles which many individuals experienced as uncomfortable. It was only when transcranial magnetic stimulation (TMS) was introduced in 1985 that studies of central motor pathways began to increase exponentially.[4] TMS is virtually painless and is accepted readily by participants. It was used in a large number of different disorders of movement to study cortical excitability accompanying movement, and in paired pulse designs to study intracortical mechanisms in the motor cortex or connectivity between motor areas. Repetitive TMS (rTMS), which has lasting after-effects on the cortex, has also become mainstream with many centers using it to explore synaptic plasticity in the motor cortex, or even therapeutically to ameliorate symptoms of Parkinson's disease or dystonia or to improve the response to physical therapy after stroke. The re-introduction of transcranial direct current stimulation (tDCS) in 2000 brought another method into wide circulation.[5] In movement disorders, it is used as a tool to study brain excitability, but perhaps will eventually be used primarily as a therapeutic method to influence brain excitability or plasticity.

Deep brain stimulation also deserves to be mentioned even though it is only applicable to small numbers of people. For example, recordings from the electrodes have boosted interest in the idea that changes in the rhythmic activity of neural populations in basal ganglia and connected structures are an important element in bradykinesia of Parkinson's disease whereas the effects of stimulation through the electrodes on the activity of other distant motor structures has given novel insights into the pathophysiology of Parkinson's disease and dystonia.[6]

Not all advances have been driven by technology. In several cases, new insights have come about using methods that were available in the later 1970s and early 1980's; the reason they were not explored at the time lay in lack of knowledge, not of equipment. For example, the discovery in animal experiments of plateau potentials in spinal motoneurons led to development of methods to explore the phenomenon in humans by looking at recruitment and derecruitment of single motor units using needle electrode recordings.[7] These in turn fuelled speculation that plateau potentials might have an important role in production of spasticity. Another example is the current use of the startle reaction to probe reticulospinal circuitry.[8, 9] In this case, early work on forms of reticular myoclonus[10] which had identified the recruitment order and different spinal conduction velocity of presumed reticulospinal systems received a boost in the 1990s when a number of centers started to investigate hyperexplexias and their relation to the normal startle pattern. The startle is now used to probe reticulospinal contributions to movement.[11, 12]

Reflex studies of spinal cord were also well developed in the early 1980's but in this case one of the drivers to further advances was the increasingly influential model of spinal networks of the Lundberg group in Sweden.[13] This led to the exploration of reciprocal inhibition and presynaptic inhibition in patients with dystonia, revealing one the first of many examples of disordered inhibition in this condition.[14, 15] Another example of this is the work on the propriospinal system that was built on basic studies of C3-C4 propriospinal neurons of the cat by the group of Lundberg in Sweden. Pierrot-Deseilligny and colleagues proposed a series of H-reflex and other methods to study this system in humans and then went on to show that this pathway might become overactive in patients with lesions of the corticospinal system, perhaps as an attempt to compensate for lack of motor drive to the spinal cord.[16]

In some instances, older insights were simply revived. In a series of very careful papers, Colebatch extended the original work of Bickford and colleagues on sound and tap evoked reflexes in neck muscles.[17] This formalized the paradigm of the vestibular evoked myogenic response (VEMP) which is now widely used diagnostically in vestibular disorders. Galvanic vestibular stimulation is also an old method that activates vestibular nerve afferents and has been employed very successfully to test vestibular contributions to balance control.[18]

Pathophysiology advances

Parkinson's disease

One of the physiological puzzles about Parkinson symptoms has been the slowness of reaction time. This was difficult to study until the development of TMS which allowed assessment of the excitability of the motor cortex during the reaction time. The main finding was that the beginning of a change in excitability started normally quickly, but that it took a longer time to build up the excitability enough to "trigger" the movement.[19] Hence, the abnormality of akinesia appeared similar to the abnormality of bradykinesia, and might be described as a reduction of normal motor energy. "Failure of energy" also seems responsible for the progressive reduction in movement speed in sequential movements.[20] This feature of Parkinson disease is not responsive to dopaminergic treatment.[21]

The physiology of how the basal ganglia dysfunction leads to bradykinesia has not been clear. Observations of cellular and local field potential (LFP) activity in various basal ganglia nuclei at the time of surgery (for lesions or deep brain stimulation) have opened up a new area of investigation.[6] Cellular activity in the basal ganglia nuclei is not typically synchronized and LFPs do not show prominent oscillations. In Parkinson's disease, there is synchronization and oscillations in both the subthalamic nucleus and globus pallidus in 10–

30 Hz (beta) range (Figure 2).[22, 23] The origin of this beta rhythm is not completely clear, but it correlates with bradykinesia and decreases with dopaminergic therapy.[24]

Dystonia

There have been great strides in the pathophysiology of dystonia. While it was known from early physiological observations that there is an overflow of movement into the antagonist and extraneous muscles, there was no clear understanding of how that might occur. An important set of observations which initiated a large series of studies was that there is failure of blink reflex inhibition[25] and spinal reciprocal inhibition in patients with dystonia.[14] The idea that a lack of inhibition might lead to excessive movement made sense, and subsequently other inhibitory mechanisms were investigated. In addition to a deficit of spinal and brainstem inhibition, there is also a deficit of cortical inhibition.[26] Studies of cortical inhibition were facilitated by development of TMS as a physiological tool. Multiple intracortical inhibitory circuits were identified and many of these are abnormal in dystonia. Reciprocal inhibition was also abnormal at the cortical level.[27, 28] The functional consequence of loss of inhibition was recognized by the identification of a loss of surround inhibition in voluntary movement, the failure to inhibit muscles not needed for the task.[29]

Somewhat surprising, a mild loss of sensation was found in patients with dystonia, both in the spatial and temporal domains.[30–32] There were problems also with kinesthesia[33] and the vibratory illusion of movement.[34] These abnormalities were found to be due to failures of surround (or lateral) inhibition in both spatial[35] and temporal domains.[36]

There have been a number of hints that there is a derangement of plasticity in dystonia. Particularly, in focal hand dystonia it is clear that repetitive activity is a trigger of the disorder. Physiological evidence for this was identified with the use of a TMS technique, called paired associative stimulation (PAS), where a median nerve stimulus is paired with a cortical stimulation to create either an increase or decrease in excitability similar to long-term potentiation (LTP) or long-term depression (LTD).[37] This was shown to be abnormal in dystonia (Figure 3).[38]

Tremor

The physiology of tremor remains surprisingly obscure. We have learned some new information, however, that moves our understanding forward. One area is the relationship of the normal 8–12 Hz central oscillation, often playing a role in physiological tremor and the abnormal oscillation of essential tremor. Can the essential tremor oscillator be a manifestation of dysfunction of the normal 8–12 Hz oscillator? Following two patients at risk for essential tremor over 10 years showed that essential tremor developed without any prior manifestation of the 8–12 Hz oscillator, suggesting that the two phenomena differ.[39]

It does seem likely that there is a network of structures responsible for the generation of tremor, rather than a single oscillator. For essential tremor, this has been demonstrated using MEG and network analysis. The network included contralateral primary motor cortex, premotor cortex, thalamus, brainstem, and ipsilateral cerebellum.[40] In this regard, more evidence is being accumulating suggesting that the cerebellar dysfunction plays a role in essential tremor. Quantitative physiological testing shows that movements in patients with essential tremor show mild cerebellar dysfunction.[41, 42]

Myoclonus

While hereditary hyperekplexia was thought to be an exaggeration of the startle reflex, this had not been formally demonstrated.[43] The EMG pattern for startle was identified, and it

was shown convincingly that patients with hyperekplexia show an exaggeration of this pattern, particularly including deficient habituation.[8, 9]

The concept of propriospinal myoclonus was developed because of a unique pattern of EMG activity in the axial muscles suggesting the slow spread of excitability from midthoracic region up and down the spinal cord.[44–46] The EMG pattern can be used in diagnosis. There needs to be caution with this type of myoclonus, however, since the EMG pattern can be mimicked voluntarily,[47] and some patients have been described where the disorder is psychogenic.[48]

Psychogenic movement disorders

The nature of psychogenic movement disorders is somewhat obscure. Current thinking still is dominated by the idea that most patients have a conversion disorder, where a psychiatric symptom is converted to a somatic symptom. Physiological studies including neuroimaging have begun to reveal features of the disorder. These physiological findings are noted below in the section on diagnosis, but they can be summarized by the concept that many aspects of the physiology are similar to normal voluntary movements, yet the patients believe that they are involuntary. The EMG underlying the movement and the EEG correlate are similar to those seen with voluntary movement.[49] There is evidence for emotional influence in the generation of psychogenic movement disorders, such as an abnormal affective modulation of the startle reflex.[50]

Restless legs syndrome

A frequent feature seen in restless legs syndrome is periodic limb movements in sleep (PLMS). Studies of this movement disorder show that this likely arises as a hyperexcitability of flexor reflexes in the spinal cord.[51]

Spasticity

Spasticity is a complex phenomenon that is caused both by changes in muscle/tendon properties as well as by reflex alterations within the spinal cord.[52] Work in the past 25 years has documented reduced Ia reciprocal inhibition onto ankle plantarflexors, reduced presynaptic inhibition and reduced Ib inhibition. Changes in motoneuronal properties may also be important. In the rat, very low chronic spinal section leads to spasticity of the tail, and correlative observations of single motoneurones show an increased propensity to develop depolarizing plateau potentials.[53] These may increase reflex excitability as well as sustain muscle spasms. However, whether they exist in human spasticity is uncertain: during induced spasms, motor units need significantly less synaptic drive to sustain firing than they do at the onset of a spasm, which would be consistent, but not proof of a role in spasticity.[54]

Diagnosis

Parkinson’s disease

Sometimes there is difficulty in deciding whether a patient has idiopathic Parkinson’s disease or a Parkinson-plus condition. In some of the Parkinson-plus conditions there is a prolongation of central motor conduction time as demonstrated with TMS.[55] Another useful physiological test is the startle reflex; while normal in Parkinson’s disease, it is markedly depressed in progressive supranuclear palsy.[56] A prospective study of 41 patients with atypical parkinsonism showed a sensitivity of 100% and specificity of 95% for the diagnosis of progressive supranuclear palsy using the startle reflex together with the acoustic blink reflex and electro-oculography.[11]

There are some patients who are thought to have early Parkinson's disease, but who turn out not to have dopamine deficiency on neuroimaging studies. These patients are called SWEDDs, and are known not to advance to more severe typical Parkinson's disease with time. Distinguishing these patients clinically can be difficult. One possible method is using PAS, which is abnormally exaggerated in these patients similar to the result in organic dystonia.[57]

Tremor

While the underlying physiology has been known for some time, it is becoming more frequent in physiology laboratories to use methods to separate exaggerated physiological tremor from essential tremor.[58] This can certainly be useful in ambiguous cases. Exaggerated physiological tremor, generated by peripheral mechanisms, will show a reduction in frequency with weighting, whereas essential tremor, generated centrally, will not show a change in frequency with weighting.

Psychogenic movement disorders

The diagnosis of a psychogenic movement disorder is often difficult. Criteria have been largely clinical and sometimes a subjective decision has been necessary to judge whether an involuntary movement is organic or not. Clinical neurophysiological assessment has proven to be very useful in this regard, particularly with myoclonus and tremor. This may justify modifying the criteria to include a "laboratory supported" diagnosis with increased certainty.

While the EMG burst duration is often useful in the diagnosis of myoclonus, only epileptic myoclonus can be ruled out with this assessment alone. Psychogenic myoclonus can have EMG burst durations in the same range as some types of organic myoclonus.[49] The EEG analysis might be more revealing. In psychogenic myoclonus, very frequently a normal looking Bereitschaftspotential can be recorded, similar to what might be present prior to a voluntary movement.[59] This is not present in any type of organic myoclonus. Evidence of the utility of this method was recently demonstrated in a series of patients with idiopathic spinal myoclonus.[60]

The latency of reflex myoclonus can be studied, and in organic myoclonias the latencies are about 40–50 ms. In psychogenic reflex myoclonus, the latencies are similar to, and never faster than, the fastest voluntary reaction time, 100 ms or longer depending on the type of sensory stimulus. [61, 62] Moreover, like voluntary reaction times, the latencies are rather variable.

Organic tremors have a slightly different frequency in different body parts. The explanation for this is not clear, but the generators of both essential tremor and Parkinson tremor must be somehow fractionated. There are some uncommon exceptions such as orthostatic tremor. On the other hand, psychogenic tremor almost always has the same frequency in different body parts.[63] This includes simultaneous changes in frequency when they occur. Entrainment testing is a very valuable technique for showing this. This is done by measuring tremor of one hand and performing voluntary tapping with the other hand at a series of different frequencies. The clearest abnormality is when the tremor frequency changes to match the voluntary frequency, but it is also possible that the tremor will stop or change to some other frequency.[64] A nice way of demonstrating entrainment is with coherence analysis (Figure 4).[65] However, it is important to note that not all psychogenic tremors entrain.[66]

Another method to see if voluntary movement interferes with the tremor is the ballistic movement test. The tremor is quantified upon making a quick movement of another body part. Tremor will transiently stop for a psychogenic tremor, but that this does not happen for either Parkinson tremor or essential tremor.[67]

Psychogenic dystonia has proven to be difficult. In a comprehensive study with a variety of physiological tests, patients with psychogenic dystonia had similar abnormalities to patients with organic dystonia.[68] The explanation for this has not been clear. There has now been a report suggesting that PAS is normal in psychogenic dystonia, where it is abnormal in organic dystonia as noted earlier.[69]

Cerebellar disease

There is a TMS method that can identify whether there is a cerebellar abnormality or dysfunction of cerebellar outflow pathways.[55] Stimulating the cerebellum should lead to a reduction of MEP size produced by stimulating the motor cortex at an interval of about 5–7 ms.[70] This is deficient with cerebellar disease.[71] This method can be used to detect subclinical cerebellar dysfunction, as in progressive supranuclear palsy, for example, and this might also be useful in diagnosis.[72]

Balance Disorders

In the past the mainstays of vestibular testing were the caloric reflex and eye movements provoked by passive movements of the head. These have now been supplemented by the vestibular evoked myogenic potential (VEMP), which tests otolith function, particularly that from the saccule. They can be used to assess the severity of peripheral vestibular damage in conditions such as Ménière's disease, vestibular neuritis, and vestibular schwannoma. VEMPs can also be used to document vestibular hypersensitivity to sounds (Tullio phenomenon).[17]

Therapy

Physiological studies over the last decades have clearly shown that the brain is highly plastic, and that this plasticity underlies, for example, the ability to learn motor skills. It should then be possible to improve some motor disorders with either physical training or with non-invasive modulation or combinations. This type of strategy has been employed extensively in the area of stroke. Rehabilitation with extensive practice, perhaps augmented with robots or constraint of the good limb, is clearly helpful. Brain stimulation with rTMS or tDCS that increases brain excitability can be helpful and works synergistically with training.[73, 74] Training can also be useful after spinal cord injury. A frequent goal of patients with spinal cord injury is to be able to walk again. This has been difficult to achieve, but has been thought to be possible since a locomotor generator is thought to reside in the spinal cord. Rehabilitation techniques that employ extensive gait training have shown that it is possible to get the isolated human spinal cord to walk. This has been accomplished with robotic training, initially with unloading of the body and then gradual loading.[75]

Parkinson's disease

There has been great success with the invasive techniques of brain lesions and deep brain stimulation. This has inspired work with non-invasive brain stimulation. Since this type of stimulation cannot be given continuously, however, the goal has been different, that of leading to a plastic change that might be more permanent. Physical therapy with motor training, by itself, can certainly be useful. Recently in this regard, there has been interest in dance therapy.[76] However, almost any exercise training has positive benefits.[77]

A number of studies have employed either TMS or tDCS. Early studies used single sessions of 5–10 Hz stimulation of the motor cortex and showed short term improvement of motor tasks and the UPDRS.[78–80] More substantial and long lasting effects may well come from repeated sessions over weeks. Studies of 5 Hz rTMS delivered daily for 10 days[81] and of 25 Hz with 8 sessions of 25 Hz over four weeks,[82] both showed increasing benefit with

multiple sessions and endurance of some effect for at least a month after the sessions were finished.

Dystonia

Since there is a deficiency of inhibition in dystonia, it is reasonable to try to increase inhibition as therapy. Slow rates of rTMS can increase inhibition and this method has shown modest benefit over the motor cortex[83] and premotor cortex.[84] Another approach has been rehabilitation training to improve surround inhibition or somatosensory discrimination. For example, patients with writer's cramp have been trained to write with individual fingers.[85, 86] Patients have also been trained to read Braille with each finger of the hand hoping to improve sensory discrimination as well as motor control.[87, 88] Improvements with these methods have been modest and, interestingly, are not sustained after the training is finished.

Other movement disorders

Physiological methods have been tried in other conditions with small numbers, but without great successes as yet.

Future

Predicting the future is a notoriously dangerous pastime: 25 years ago who would have envisaged that it would be possible to investigate and interact with processes of synaptic plasticity in the human cerebral cortex, or that transcranial brain stimulation would become such a common methodology in cognitive neuroscience? Thoughts on some possible areas for technological development in the future are noted below; however it may be useful to start by considering which research areas have been consistently ignored in the past 25 years, and which therefore should be ripe for intellectual harvest if and when our technology allows.

The clinical neurophysiology of Parkinson's disease has made advances in understanding the causes of bradykinesia; but we have made less progress in understanding the origin of rigidity or the many problems of balance and gait such as festination and freezing. Gait freezing is now being actively investigated.[89–91] Bloem et al.[92] highlight the latter particularly well in their video of a patient with severe gait disorder who nevertheless could cycle to hospital for his appointments. How motor output can see-saw so quickly between pathology and normality is a mystery ready to be solved.

Tremor is ubiquitous in health and disease, yet our knowledge of its mechanisms and the relationship between different types of tremor is rudimentary.[93–95] Current understanding is that tremor emerges from disordered activity in neural circuits; but do different tremors represent disorders of different circuits, or different disorders of the same circuit? Advances in understanding the behavior of populations of neurons using coherence analysis and more complex techniques might help solve these questions in the future.

A last challenge will be to understand the grey area between physiology and psychiatry that is so important in conditions such as Tourette's syndrome or psychogenic movement disorders. How can production of movement be divorced from its awareness?[96] What link is missing here and what is its anatomical-physiological counterpart?

Future technologies may or may not be able to address these questions. One current development may be useful if it proves safe and practical. Ultrasound stimulation of deep brain structures was recently demonstrated in rat brain.[97] It has been known for some time that pulsed ultrasound of the appropriate frequency can activate nerve axons, and this paper shows that the same is true for activation of brain. Given that ultrasound can be focused this

opens the possibility of stimulation of deep brain structures. The main problem will be demonstrating safety since ultrasound can cause cavitation and physical damage.

A second area of development that is attracting interest is more sophisticated signal analysis of EEG (or MEG). It is clear that the brain operates in networks, and these networks can be identified by looking at coherence between regions. Overall descriptions of the networks can be done with graph theory.[98] It is already clear that there are disturbed patterns in Parkinson's disease that may have some explanatory power for behavioral disorders.[99, 100]

Multimodality studies may yield more information than using one modality at a time. The combined use of TMS and EEG, TMS and neuroimaging, and EEG and neuroimaging are all possible, and have been used to produce new results. For example, the combined use of rTMS and raclopride PET studies in patients with Parkinson's disease show patterns of dopamine release differ on the two sides correlating with the severity of symptoms.[101]

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Figure 1.

First public demonstration of transcranial electrical stimulation of the human motor cortex. Seated is P.A. Merton, one of the two developers of the method.[3] He is directing attention to his left hand which would twitch when the stimulus was given. Holding the anode of the stimulator on the scalp is R.H. Adrian. The electrical circuit diagram is on the blackboard, showing the power source (the black box on the table beside Dr. Adrian), a capacitance (visible on the table as a free standing cylinder) and a switch (a Morse key being pressed by the right hand of Dr. Adrian). The audience is a group of 3rd year preclinical medical students. April, 1980, Cambridge, Physiology Lecture Theatre.

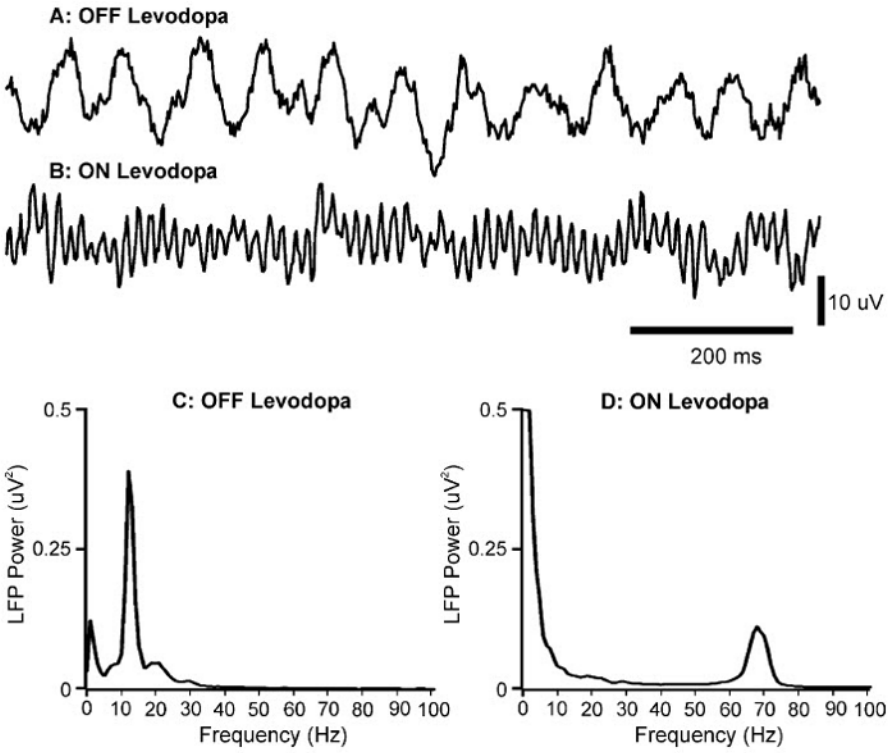

Figure 2.

Local field potential (LFP) from the subthalamic nucleus in a patient with Parkinson's disease. (A) LFP after overnight withdrawal of medication. (B) LFP after subsequent levodopa challenge. (C) Power spectrum LFP after overnight withdrawal of medication (140 s record). (D) Power spectrum LFP after subsequent levodopa challenge (140 s record). Note the peak at around 13 Hz off medication and that at around 70 Hz after levodopa. From Brown and Williams 2005[22] with permission.

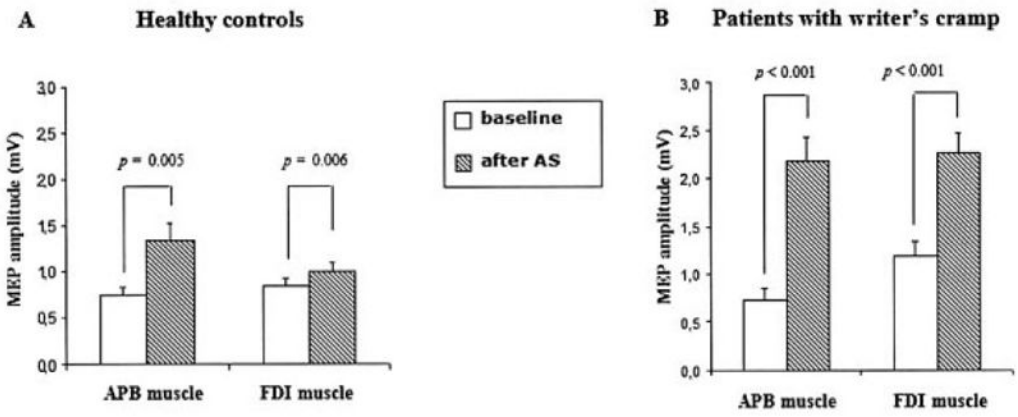

Figure 3.

Effect of paired associative stimulation (PAS) on the size of motor evoked potentials (MEPs) of the right APB and FDI muscle in 10 healthy controls (A) and 10 patients with writer's cramp (B). The bar charts illustrate the mean peak-to-peak amplitude (mV) of MEPs recorded at rest before (open columns) and after (shaded columns) associative stimulation. Each error bar equals SEM. PAS led to an increase in MEP size in patients and controls. However, the facilitatory effect was significantly stronger in patients. Modified from Quartarone et al. 2003[38] with permission.

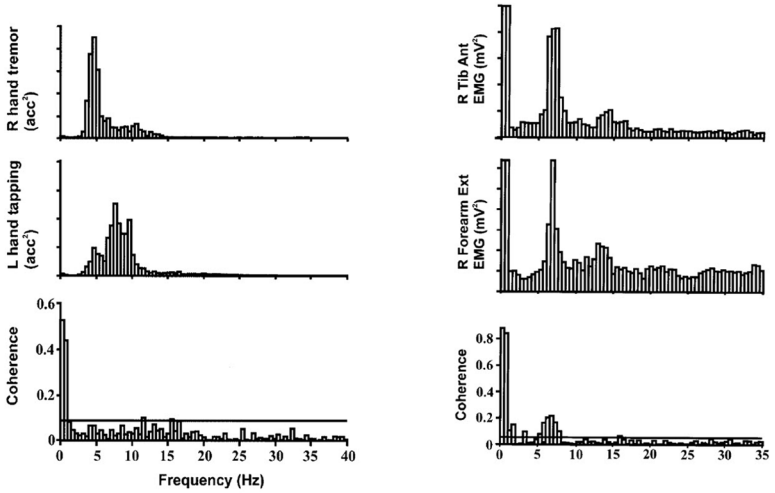

Figure 4.

Coherence entrainment test using frequency analysis of a dystonic tremor (left side) and a psychogenic tremor (right side). For the dystonic tremor the test is negative, but it is positive for the psychogenic tremor. The left side shows ongoing right hand tremor and simultaneous voluntary tapping movements of the left hand, both measured with accelerometry, without any coherence. The right side shows ongoing right foot shaking and simultaneous right hand voluntary tapping, both measured with EMG, with significant coherence. Modified from McAuley and Rothwell 2004[65] with permission.