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The Triple Stimulation Technique: An Advanced Neurophysiological Method to Assess Motor Function in Multiple Sclerosis

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Abstract

The triple stimulation technique (TST) is a collision method enabling study of motor conduction within the central nervous system. By combining transcranial magnetic stimulation of the cortex to peripheral nerve stimulation, this method markedly improves the evaluation of the corticospinal pathways. In multiple sclerosis (MS) and other disorders affecting central motor conduction, it allows accurate detection and quantification of the proportion of normally conducting axons and of motor conduction failures caused by conduction block, neuronal or axonal lesions.

This review aims to (1) describe briefly the TST, its yield, strengths and limitations, (2) summarize the observations made in MS to date, (3) discuss the potential of the method.

The TST is non-invasive and safe. Its practicability has been optimized by use of efficient software. Several studies have demonstrated that it is suitable to explore corticospinal conduction in MS, that its findings mirror the disability and clinical neurological signs of patients, and that it is reliable to evaluate follow-up and responses to treatments, including during the critical early stages of MS. We believe that the method is ready to be implemented to research and to routine clinical acquisitions. It should demonstrate useful to evaluate new therapies, monitor achievement of "no evidence of disease activity" (NEDA) and eventually to better understand neurodegeneration and repair in MS.

Keywords: Collision technique; Corticospinal tract; Magnetic and electrical stimulation; Motor evoked potentials; Transcranial magnetic stimulation

Abbreviations: CIS: Clinically Isolated Syndrome; CMAP: Compound Muscle Action Potential; CMCT: Central Motor Conduction Time; MEP: Motor Evoked Potential; MS: Multiple Sclerosis; NEDA: No Evidence of Disease Activity; P-MS: Progressive Multiple Sclerosis; PP-MS: Primary Progressive Multiple Sclerosis; RR-MS: Relapsing-Remitting Multiple Sclerosis; SP-MS: Secondary Progressive Multiple Sclerosis; TST: Triple Stimulation Technique

Introduction

Transcranial magnetic stimulation eliciting motor evoked potentials (MEP) is a non-invasive method that enables investigating the function of central motor pathway. Conventional MEP provide mainly the central motor conduction time (CMCT, i.e., time taken by the action potential to travel from cortex to the peripheral motor neuron of brainstem or spinal cord). In MS, while CMCT is of great interest in detecting subclinical slowing of conduction [1,2], conventional MEP disclose only gross failures of conduction since the size of MEP is smaller than the response to peripheral stimulation and varies markedly and unpredictably among normal subjects, and from one stimulus to the next [2-5]. The triple stimulation technique (TST) improves conventional MEP by circumventing the phenomena that cause their small size and variability [6]. This allows precise detection and quantification of corticospinal conduction failures in patients [7]. Furthermore, contrary to slowing of motor conduction that may remain clinically silent, conduction failures parallel the motor disability experienced by patients. Thus it can serve as objective evaluation of the motor disability of MS patients. The TST has provided new insights into normal and pathological corticospinal tract conduction. It improved evaluation of the disorders that compromise corticospinal conduction through conduction block, axonal or motor neuron lesions.

TST: The Method

The TST to study central motor pathways has been described in healthy subjects [6] and in patients presenting with various disorders of the central nervous system [7]. Figure 1 summarizes its principle. In brief, TST is preceded by transcranial and peripheral nerve stimuli that allow calculation of the CMCT, measurement of the size of the MEP and compound muscle action potential (CMAP). This part of the study serves also to calculate the delays required for the collision technique. CMCT is calculated by subtracting the peripheral conduction time from the total latency from cortex to target muscle. This is done using the formula: CMCT=MEP latency-(Fwave latency+$CMAP_{distal}$ latency-1)/2 [8].

In the laboratories of our group, transcranial magnetic stimulation uses a Magstim 200 stimulator with a circular (90 mm) or shape-of-8 hand-held coil (outside diameter 135 mm-Magstim Company, Spring Gardens, Whitland, Dyfed, UK). Recordings use Viking ENMG machines (Natus Neurology Incorporated, Pleasant View Road, Middleton, WI, USA). Other stimulators and ENMG apparatus may be used. For details concerning the stimulation of peripheral nerves, see the paragraph method in the respective articles that described the TST. Since its description, the procedure of the TST has been markedly simplified and automatized by use of software developed initially by the company Judex (Judex A/S, Hasserisvej 125, Aalborg, Denmark). This program is presently available on a number of different ENMG machines. A technical modification of the recording of ulnar innervated hand muscles has been implemented to account for the volume

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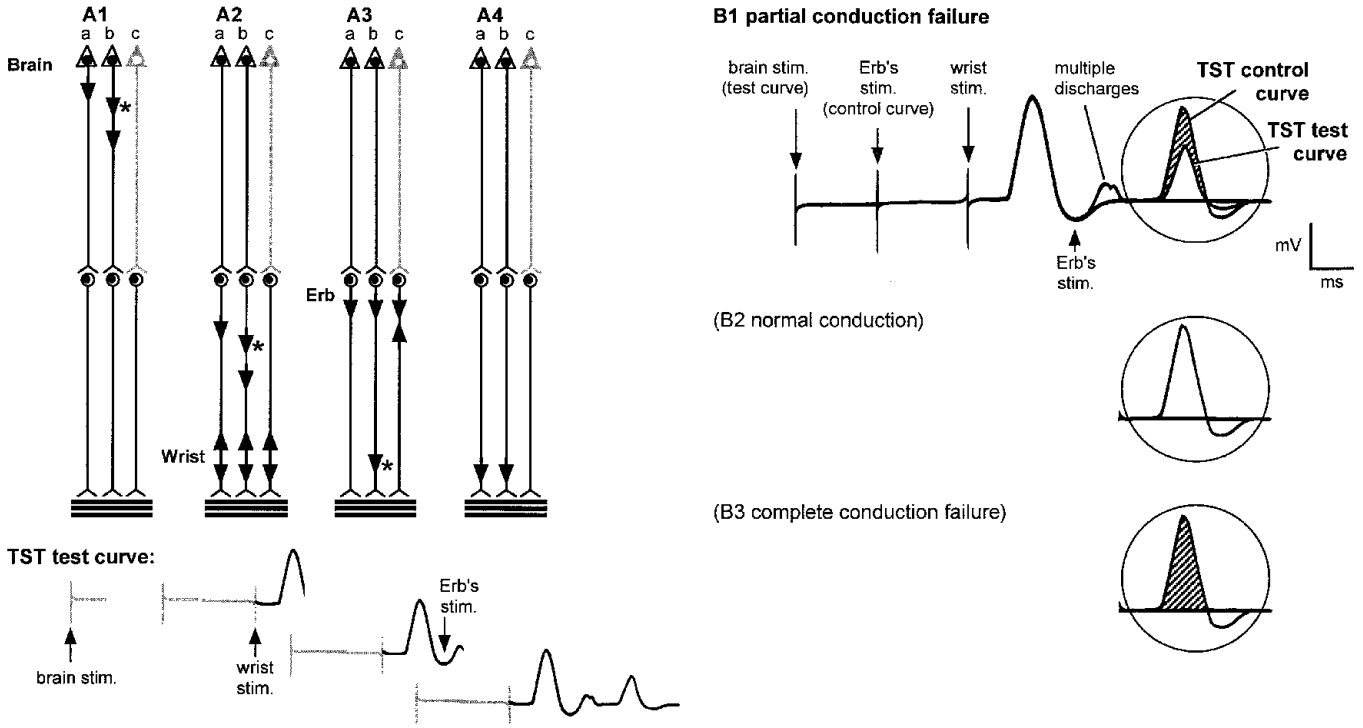

Figure 1: From Magistris et al. 1999; with permission of Oxford University Press.
A) Principle of the TST. The motor tract is simplified to three corticospinal axons (a, b and c) with monosynaptic connections to three peripheral axons (this simplification does not account for the complexity of corticospinal connections). Horizontal lines represent the muscle fibers of the three motor units. One corticospinal axon (c) does not conduct due to a CNS lesion. (**A1**) After maximal transcranial stimulation, action potentials (shown as arrows) descend only in axons (a) and (b). Desynchronization of the two action potentials is assumed to occur within the corticospinal tract or possibly at spinal cell level). On axon (b), multiple volleys descend (*). (**A2**) After a delay, a second maximal stimulus is given at the wrist, leading to descending (orthodromic) action potentials causing a first negative deflection of the TST test curve, and to ascending (antidromic) action potentials in all three peripheral axons. Two of the ascending action potentials collide and cancel with the action potentials descending in axons (a) and (b). The sites of collision are different due to the desynchronization of the descending action potentials. The multiple volleys descending from the central motor neuron (b) cause a double discharge of the spinal motor neuron (b); the second discharge (*) on axon (b) is not cancelled and continues to descend. The action potential on axon (c) continues to ascend because no collision occurred. (**A3**) After a delay, a third maximal stimulus is given at Erb's point, evoking action potentials which descend on axons (a) and (b), while a collision occurs in axon (c). The second discharge (*) in axon (b) arrives at the muscle and causes a negative deflection. (**A4**) As a result, a synchronized response from the two axons (a) and (b) that were initially excited by the transcranial stimulus is recorded as a second main deflection of the TST test curve. The TST control curve is recorded by replacing the first stimulus at the cortex by a stimulus at Erb's point (succession of stimuli: Erb–wrist–Erb) with appropriate adjustments of the delays. (**B**) Possible TST results. In **B1**, **B2** and **B3**, three curves are superimposed (the TST test curve, the TST control curve and a response to wrist stimulation yielding a baseline). The three situations that may be encountered are illustrated in **B1**, **B2** and **B3**. (**B1**) Partial conduction failure, corresponding to the situation depicted in **A**. The size of the TST test curve is smaller than that of the TST control curve since (in this example) one of the three spinal motor axons innervating the ADM target muscle does not respond to the transcranial stimulus. The shaded area indicates the difference between TST control and test curves. (**B2**) Normal conduction is assumed if TST test and control curves are superimposed (all spinal motor axons innervating the ADM are brought to discharge by the transcranial stimulus). (**B3**) Complete conduction failure. The TST test trace is superimposed on the baseline (no spinal motor axons innervating the ADM respond to the transcranial stimulus).

conduction by the median nerve that is co-stimulated by stimulus performed in the suprascapular region (Erb's point). This is done by stimulating simultaneously ulnar and median nerves at the wrist using two small cathode electrodes fixed over the ulnar and median nerves and a large anode electrode fixed on the back of the wrist. For a detailed discussion of volume conduction in the TST [9].

Bühler et al. have adapted the TST to study the corticospinal pathways to the lower limbs [10]. They have provided normal values and thoroughly discussed the questions specific to the study of the lower limbs in healthy subjects and in patients (in particular the questions dealing with: desynchronization and multiple discharges to the lower limbs; facilitation required; proximal site of stimulation).

TST: Yield of the method

In healthy subjects, with appropriate intensity of transcranial stimulation, the TST amplitude ratio (amplitude of TST test curve to that of TST control curve) can reach 100%, indicating that a transcranial stimulus can excite all motor units leading to the target muscle. This intensity, variable among healthy subjects and among patients, is called "maximal stimulation". The TST circumvents also the varying influence of a number of motor units that may discharge more than once in response to a single transcranial stimulus. These multiple discharges, which influence the size of the MEP, do not interfere with the part of the TST curve of interest. They are recorded between the two main deflections of the TST (Figure 1). The TST upgrades transcranial cortical stimulation into a reliable tool to study the integrity of central motor pathways for clinical or research purposes (example in Figures 2 and 3). In patients with central motor conduction deficits the TST amplitude ratio is reduced in accordance with the magnitude of conduction block and/or axonal or neuronal lesions.

The TST initially allowed demonstrating that (i) electrical and magnetic transcranial stimuli can achieve depolarization of all spinal neurons innervating a target muscle; (ii) two factors were obscuring the relation between MEP size and proportion of conducting central motor axons: 1) a shift in time of motor units discharge (desynchronization) is accompanied by phase cancellation that causes the small size of evoked

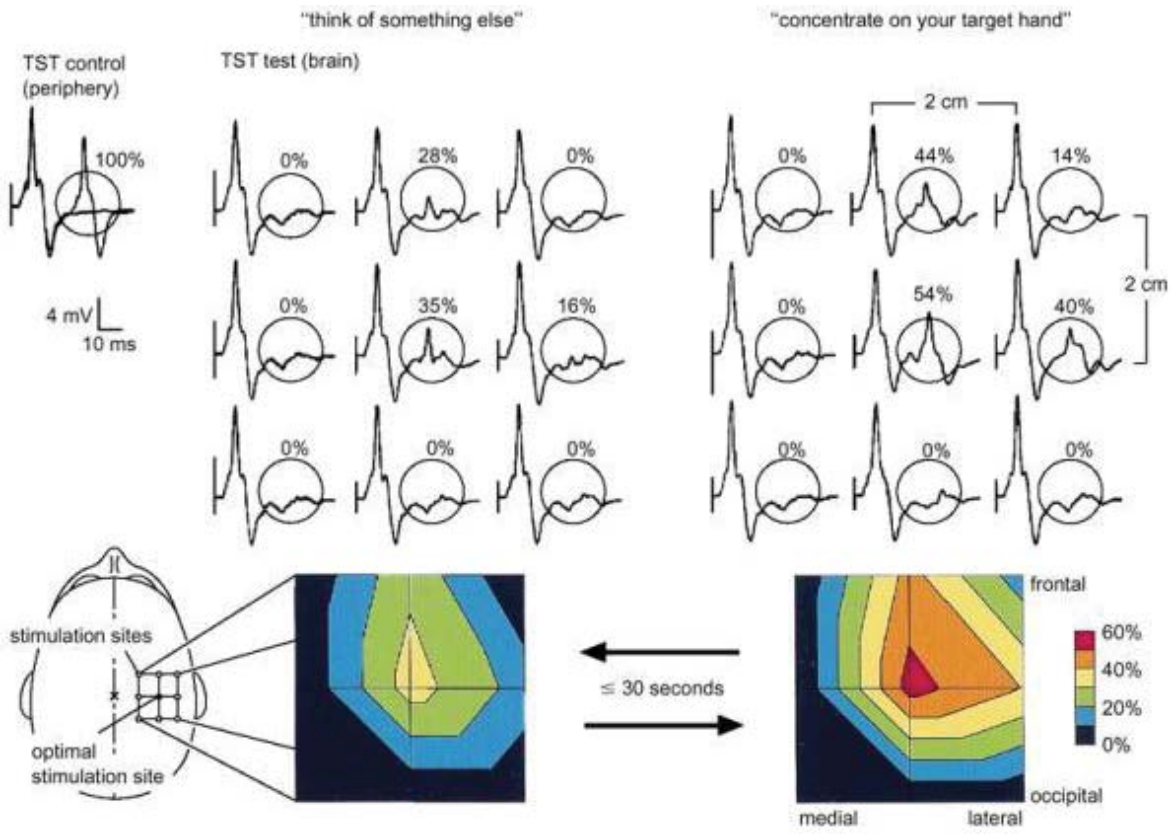

Figure 2: From Rösler et al. 1999; with permission of Wolters Kluwer Health, Inc.
Mapping result in one subject. The responses evoked over the nine stimulation sites during distraction (left panels) and target-hand concentration (right panels) are displayed. The triple stimulation response consists of a first negative deflection, which is not measured, and a second negative deflection (circled) which estimates the percentage of activated spinal motoneurons, as indicated by numbers next to the curves. The TST control curve (on left upper corner) calibrates the TST test curves and serves to indicate the response activated by 100% of the spinal motoneurons supplying the target muscle. The two bottom panels represent the interpolated isoamplitudes of the motor output maps.

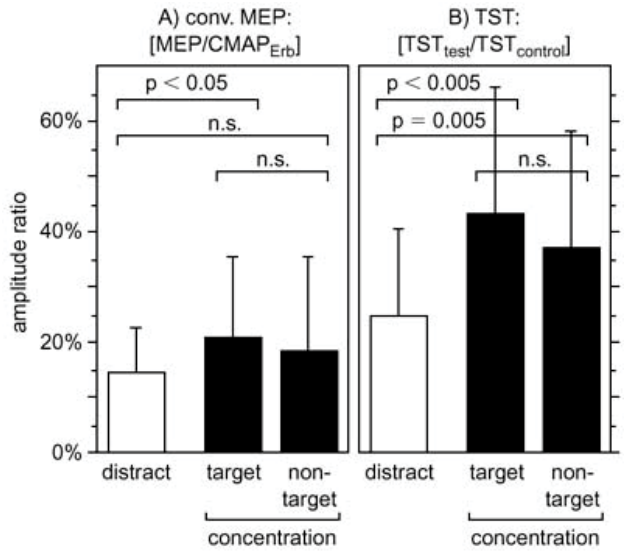

Figure 3: From Rösler et al. 1999; with permission of Wolters Kluwer Health, Inc.
Transcranial magnetic stimulation results in 11 healthy subjects after stimulation over the optimal stimulation site (hot spot=center of the motor map). Results compare responses obtained when subjects were distracted, concentrating to their target-hand, or to their non-target contralateral hand. (A) Study using conventional MEPs. (B) Same study using TST. Given are means +/- 1 SD and p values of the Wilcoxon test.

response; 2) this shift, and possibly the changing firing order of the motor units, varies from one stimulus to the next and from one subject to the other, provoking the variability in size of the MEP. The TST, by resynchronizing the discharge evoked by transcranial stimulation, avoids these influencing factors.

Whereas TST that uses "maximal" transcranial stimuli aims to assess the proportion of the functioning corticospinal axons, the TST that uses submaximal stimuli offers an avenue to study the normal and pathological variations of excitability of the corticospinal tract caused by various influences. With submaximal transcranial stimuli, the TST serves to avoid the unwanted variation in size of the evoked responses provoked by phase cancellation and occurrence of multiple discharges.

The TST has provided several new insights into the understanding of central motor conduction in healthy subjects and in several disorders affecting the central nervous system. The latter will only be briefly mentioned in this review that will mainly focus on the TST and its use in MS.

TST and conventional MEP

In 271 patients with a variety of central motor disorders, use of the TST increased the sensitivity to detect a central motor conduction deficit by a factor of 2.75 [7]. The TST to the lower limbs as well was 2.54 times more sensitive to detect central conduction failures than conventional MEP to lower limbs. Combining the TST to the lower

limbs with that of the upper limbs further increased the sensitivity to detect a conduction failure by 1.50 times [10]. It has been shown early on that the yield of conventional MEP increases if more target muscles are examined [12-14]. The same applies to the TST. It is noteworthy that prolonged CMCT were more frequent to the lower than to the upper limbs [10], as also reported by others [13]. The pyramidal tract to leg muscles thus appears particularly susceptible for conduction slowing. In patients, weakness of lower limbs correlated well with the deficit demonstrated by the TST to lower limbs. Central paresis and other clinical signs of pyramidal tract involvement were associated with reduced TST response sizes. This correlation, observed for the TST to both upper [7] and lower limbs [10], indicates that the TST measures a parameter of clinical relevance.

TST to study rapid changes taking place in corticospinal conduction

In addition to the conduction failures that may be detected and measured by the TST, the method may be used to study rapid changes of excitability occurring within the central nervous system [11,15]. Rösler et al. in a study that mapped the responses to transcranial stimuli delivered to healthy subjects, showed that the TST enables detection of rapid changes occurring within the central nervous system in response to the mental task studied (Figure 2) [11]. The TST proved notably superior to the conventional MEP in detecting these changes (Figure 3).

TST for follow-up studies

The test-retest reliability has been studied and considered excellent in healthy individuals and thus well suited for follow-up examinations of central motor conduction failures [16]. A thorough recent study performed in healthy subjects and MS patients has confirmed the excellent test-retest reliability of the TST [17].

TST and MRI

MRI is irreplaceable to disclose images of lesions within the central nervous system and to observe the changes that may occur over time. However, is not always correlated to the deficit experienced by patients. At times, worrisome images may not be accompanied by any symptom, or patients may recover a normal function, while abnormal MRI images remain unchanged. It is thus reasonable to combine methods that assess function, such as the TST, with MRI that proposes images of lesions. Comparison of the information provided by functional MRI and neurophysiology is promising and remains to be evaluated.

TST: Strength of the method

The TST caused no adverse side effects. The procedure is not unduly time-consuming. TST to both upper limbs may be performed in less than 30 min by an experienced examiner. Variability of the responses being limited, averaging is avoided, thus number of transcranial stimuli are notably less numerous than with techniques requiring averaging. During follow-up, the TST that studies a ratio of MEP to peripherally evoked CMAP avoids the differences that can be caused by minor changes of placement of the recording electrodes over the target muscle.

TST: Weaknesses and limitations

Discomfort caused by electrical stimuli may be problematic to a number of subjects. Whereas electrical transcranial stimulation [18] was painful, mainly due the excitation of scalp muscles and nerve terminals, magnetic transcranial stimulation [19] is painless. Peripheral nerve stimuli used in the TST, that excites both motor and sensory axons, are unpleasant and mainly so for proximal stimuli performed at Erb's point. As for any nerve conduction studies, this has to be explained to the patient and few stimuli using progressively increased intensities should be given prior to perform the test itself. In our experience, the subjects tested hardly ever declined serial testing. Nevertheless, the TST may not be suitable for the examination of children or pusillanimous adults.

The TST, that detects and quantifies non-propagation of action potentials within the central motor pathways, is unable to distinguish between inexcitability to stimulation, conduction blocking, axonal and/or neuronal loss, thus use of the term "conduction failure" [7]. This is unless a repeated study discloses a rapid improvement typical of the alleviation of conduction block. A limitation of the technique is that proximal limb muscles may not be tested. In such recordings, the two main deflections of the TST curve would not be sufficiently separated in time.

Conventional evoked potentials in MS

Evoked potentials, whether visual, auditory, somatosensory or motor, are no longer essential to establish the diagnosis of most MS patients. Nevertheless, they may be useful to demonstrate the spatial multiplicity of lesions within the central nervous system, at times to disclose sub-clinical dysfunctions and to monitor disease progression, in particular when results of the different modalities are combined [20].

TST in MS

A number of studies have shown that the TST, which is an advanced neurophysiological method that refines conventional MEP, may help studying MS patients, not only at time of diagnosis but also during the course of the disease.

MS patients investigated with the TST were reported initially by Magistris et al. [7]. Out of 271 patients examined for the suspicion of a corticospinal deficit, 126 were MS patients (94 definite, 14 probable and 8 suspected MS according to Poser's criteria [21]). In these patients, abnormal motor clinical findings (weakness, pyramidal signs, or both) were observed in 39% (of the 221 right and left sides studied) whereas abnormal electrophysiological findings were detected in 51%. These abnormal findings consisted in prolongation of CMCT as sole abnormal electrophysiological finding in 3%; conduction failure in 29%; both conduction slowing and failure in an additional 19% of sides. Interestingly in this series, (i) conduction failure (48%) was 2.2 times more frequent than conduction slowing (22%); (ii) TST tests detected 2.9 times more conduction failures than conventional MEP and (iii) accurately measured the percentage of functional axons to the target muscle tested in each MS patient. Subsequently, several studies have used the TST in MS.

Bühler et al. studied, among other disorders of the central nervous system, 26 MS patients (27 sides to the lower limbs; 25 sides to the upper limbs) [10]. The increase of sensitivity of the TST to detect a conduction failure as compared with conventional MEP was largest in MS patients, 3.75 times, thus larger than in ALS, 3.0 times, or in myelopathies patients, 1.88 times. Even when the CMCT was taken into account together with the conventional MEP amplitude ratio, MS showed the largest increase in sensitivity, 1.89 times, in comparison with ALS, 1.33 times, and myelopathies, 1.25 times.

In a work by Rösler et al. studying the effect of the discharge desynchronization occurring to transcranial stimulation, it was observed that MEP were smaller than TST responses in all subjects, and under all stimulating conditions, confirming the marked influence of desynchronization on the size of MEP [22]. These authors showed that desynchronization reduced the MEP amplitude on average by one third, though with marked and unpredictable inter-individual

variations. Somewhat surprisingly, the MEP size reduction was similar in healthy subjects and in MS patients, in whom frequent slowing of central conduction was expected to influence this finding.

Humm et al. studied 141 MS patients, 90 patients with acute relapsing-remitting MS (RR-MS) and 51 patients with chronic primary or secondary progressive MS (P-MS) [23]. The TST indicated conduction failure in presence of a clinical motor deficit, without significant difference between RR-MS and P-MS when patients with similar clinical motor deficit were compared. The CMCT, which was not related to the clinical motor deficit in either RR-MS or P-MS, was frequently normal or only slightly abnormal in RR-MS, whereas it was often markedly prolonged in P-MS. The prolongation of the CMCT in P-MS was not explained by differences in disease duration or severity, spinal cord involvement or by the target muscle used. Thus, it was considered that it possibly relates to a pathophysiologic difference between the disease types.

Humm et al. have used the TST to quantify temperature-induced changes (=Uhthoff phenomenon) in central motor conduction and their relation to clinical motor deficits in 20 MS patients [9]. This study showed that Uhthoff phenomena (classical, when cooling improves motor conduction, or paradoxical, when it aggravates it) are due to varying degrees of conduction block and are associated with slowing of central motor conduction. In contrast to conduction block, CMCT is not notably affected by temperature. However, patients with central motor conduction slowing are particularly vulnerable to develop temperature-dependent conduction blocks. This finding suggests that the same type of myelin disturbance that causes conduction slowing renders conduction vulnerable to temperature changes.

In contrast to what is observed at the level of the peripheral nerve, where a stimulus generates one impulse, transcranial excitation generates several impulses, observed as D (direct) and I1, I2, I3 (indirect) waves. The summation of these potentials is probably required to cause the spinal motor neuron to discharge. It is possible that these groups of impulses, separated in time by few milliseconds, are more susceptible to develop frequency dependent conduction blocks. This may explain some particular features of MS such as its sensitivity to changes in body temperature.

Humm et al. have tested the central motor conduction deficit of MS patients using the TST before and after treatment of acute exacerbation by methylprednisolone in 41 MS patients (24 RR-MS; 8 SP-MS; 9 PP-MS) and 4 subjects with isolated optic neuritis [15]. They observed that in RR-MS and SP-MS the treatment was followed by a prompt increase in conducting central motor neurons paralleled by improvement of force that most probably reflected partial resolution of central conduction block. The lack of similar clinical and neurophysiological changes in PP-MS corroborates previous clinical reports that showed limited efficacy of methylprednisolone in this patient group, and points to pathophysiological differences underlying exacerbations in PP-MS. It is noteworthy that the CMCT, which was significantly more prolonged in SP-MS and PP-MS compared with RR-MS, did not vary for any patient group at any time.

Rico et al. studied 22 patients presenting with a clinically isolated syndrome (CIS) [24]. The study concerned mainly conventional MEP parameters, namely the amplitude ratio (MEP:$CMAP_{distal}$) and the CMCT obtained from MEP to 44 upper and lower extremities. TST was applied to 12 subjects (12 sides). The authors evaluated the amplitude ratio as abnormal in 50% of patients. CMCT was abnormal in 18% of subjects. TST was abnormal in 3 patients out of 12; all 3 had abnormal clinical pyramidal signs, whereas the 9 patients with normal TST did not. TST in this work may not be compared to the conventional MEP, as studies were too few and derived from only one side per patient. The high proportion of abnormalities disclosed in CIS by the ratio MEP:$CMAP_{distal}$ is surprising. It deserves to be reconsidered because several studies, including our own, have on the contrary observed in healthy subjects and in various disorders including MS, that this ratio has a rather low sensitivity [4,6,7,22]. During the early stages of MS, when uncertainty and unpredictability prevail, reliable data is needed.

Scheidegger et al. studied fatigue and compared the results obtained in 23 MS patients with those observed in 13 healthy subjects [25]. During the fatiguing exercise, the decline in central motor conduction was significantly less pronounced in MS patients than in healthy subjects, although the reduction of force was slightly more in MS patients. This unexpected finding led to interesting hypotheses, such as that impaired intracortical inhibition and/or recruitment of additional or "latent" corticospinal motor neurons could have taken place in MS following functional and structural reorganization of sensorimotor cortex.

Hofstadt-van Oy et al. studied 10 RR-MS and 7 CIS patients prior to, then three and twelve months following initiation of immunomodulatory treatment, and compared them to the results obtained in 48 healthy subjects [17]. They showed that abnormal TST responses in MS were highly robust in the long-term follow-up, thus confirming that TST is adequate for diagnostic and longitudinal studies.

Discussion

The TST complements and notably improves conventional MEP obtained by transcranial stimulation of the cortex. The method is non-invasive and usually well tolerated by patients, although proximal peripheral stimuli are unpleasant. Thanks to the commercially available TST software the procedure is not unduly time consuming. It is suitable to assess central motor dysfunctions and studies performed to date have shown that it is a powerful advanced neurophysiological tool in MS. We were astonished to observe that the recording of few muscles yielded a large amount of results pertinent to the clinical experience of patients. This is all the more surprising as the TST evaluates only the central motor tract. This high sensitivity is probably explained by (i) the large size of the motor tract within the central nervous system; (ii) the length of the pathway studied, that extends from cortex to spinal motor neurons; (iii) possibly to the spatial dispersion within the central nervous system of axons conducting to a given group of muscles. Obviously the multiple lesions of MS also plays a role, however it is probably in its own not a sufficient explanation, because the same impression arose from studying MS patients early during the disease, and also from the study of other disorders of the central nervous system.

In MS, the TST is a powerful tool allowing detecting and quantifying dysfunctions of central motor conduction. Although a single TST test showing conduction failure does not distinguish conduction blockade from axonal and/or neuronal loss, repeated testing may provide a clue. A rapid improvement of function will speak for conduction block, or for some plasticity, whereas objective measurement disclosing no change will show either that a drug was unable to alleviate blocking or that axonal/neuronal lesion impedes rapid improvement. The method is suitable to participate in the diagnosis and in the follow-up of treatment. It should improve clinical trial designs and has potential prognostic value that has to be evaluated further in CIS, early stages of MS, and in monitoring achievement of "no evidence of disease activity" (NEDA). Eventually it may provide new insights and understandings in the mechanisms of neurodegeneration and repair occurring in MS.

At the time of explosion of new therapies in MS, it would be crucial

to objectify whether treatment improves the function, in which MS group, when and which drug should be started, or stopped. The TST might help achieve these goals, and by providing immediate assessment of function in individual patients, without having to wait for long-term clinical outcomes in large cohorts of patients.

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