

## Review article

### The Role of Transcranial Magnetic Stimulation as a Diagnostic Tool for Multiple Sclerosis

Muhannad M. Alsharidah<sup>1</sup>, Sarah S.Alseneidi<sup>1</sup>, Afnan A. Alkharan<sup>2</sup>, Ali Hamza<sup>3</sup>, and  
Shahid Bashir, PhD<sup>4\*</sup>

<sup>1</sup> College of Medicine, King Saud University, P O Box 2925, Riyadh 11461 and Saudi Arabia.

<sup>2</sup> College of Medicine, Princess Nourah Bint Abdulrahman University, Riyadh, Saudi Arabia.

<sup>3</sup> Department of Electrical Engineering, National University of Computer and Emerging  
Sciences, Lahore, Pakistan

<sup>4</sup> Neuroscience center, King Fahad Specialist Hospital – Dammam, Saudi Arabia

#### \*Corresponding author

Dr. Shahid Bashir

Neuroscience center, King Fahad Specialist Hospital – Dammam, Saudi Arabia

Contact number: +966-538152268

E-mail address: sbashir10@gmail.com

## Abstract

Multiple sclerosis (MS) is an immune-mediated, chronic inflammatory disease of the central nervous system (CNS), characterized by demyelination, axonal degeneration, and cognitive impairment. It also has an important impact on the quality of life of patients and their family members. An estimated 2,500,000 people in the world have multiple sclerosis.

Neurophysiological parameters, like sensitivity to demyelination and the strength of excitatory and inhibitory synaptic interactions in the cerebral cortex, can be identified through transcranial magnetic stimulation (TMS) in patients affected by multiple sclerosis (MS). These parameters can be valid and objective parameters that can be correlated with the progression of MS, and can provide reliable indices for the severity of illness and the efficacy of drugs used to treat it.

The discovery of specific and detailed neurophysiological parameters as surrogate end points for disease activity could represent an important step in clinical trials. Changes in cortical connectivity have already been demonstrated in MS, but in clinical practice, other measures are usually used to evaluate disease activity. We speculate that TMS may be more effective in identifying disease progression that leads to long-term disability, compared to standard surrogate markers, due to the fact that it represents a direct measure of synaptic transmission(s) in MS.

### Key words:

MS: Multiple sclerosis, TMS: transcranial magnetic stimulation, Evoked Potentials;

## Introduction:

Multiple sclerosis (MS) is an immune-mediated, chronic inflammatory disease of the central nervous system (CNS), characterized by demyelination, axonal degeneration, and cognitive impairment. It also has an important impact on the quality of life of patients and their family members. MS is the leading cause of non-traumatic neurological disabilities in young adults, affecting 0.1% of the general population in Western countries [1, 2]. Several innovative new drugs are currently in advanced stage of development for MS. The principal clinical measures of disease activity, used to assess the efficacy of MS in clinical trials for new drugs, such as the Expanded Disability Status Scale score, and CNS magnetic resonance imaging, present some limitations [3]. Numerous studies have investigated changes in cortical excitability with TMS in MS and correlated it with disabilities of the illness [4, 5]. TMS could therefore represent a valid instrument that could be used to obtain an objective and reliable marker and potential surrogate end point for the progression of MS.

Transcranial Magnetic Stimulation (TMS), a safe, inexpensive and non-invasive neurophysiological technique, has detected abnormalities in MS patients and is significantly correlated with the severity of clinical manifestation, as well as the brain and spinal cord MRI lesion load [6, 7]. If validated, TMS could be used as a surrogate marker of disease activity and could represent a suitable measure of drug efficacy in MS clinical trials, possibly reducing the duration and costs of these trials. The use of neurophysiological techniques in MS clinical trials might shorten their duration, reduce their costs compared to MRIs, allow greater accessibility to the majority of clinical institutions, and provide more reliable data on their efficacy in preventing long term disability [8]. Thus, this technique could contribute to the development of improved treatments for the millions of individuals currently affected by MS around the world.

### 1. Historical context

Although many people had observed and described the pathological changes and symptoms of MS previously, Jean-Martin Charcot [9] is generally credited as the first person to comprehensively characterize MS as a distinct disease. During a series of lectures entitled 'les scleroses en plaques disseminate' presented in the Salpêtrière Hospital in Paris, Charcot described a condition occurring in younger adults, who at autopsy were noted to have greyish and reddish plaques of variable contours and sizes scattered through the CNS. Charcot gave an account of their clinical features, delineating the cerebral, spinal and mixed cerebrospinal structures with vivid descriptions of the clinical pathogenesis and pathophysiology. He identified

the discrepancy between lesions and symptoms, and established the link between axonal loss and clinical disability [10].

### 1.1 Prevalence and incidence

MS affects between 1 and 2.5 million people worldwide. Prevalence and incidence rates vary considerably across the globe, with a strong north to south gradient defined by an increasing disease frequency with distance from the equator [11]. The effects of aging on the clinical course of MS are not well understood and the detection of MS may be made more difficult by the existence of co-pathologies. There is strong evidence that the incidence of MS at an advanced age indicates a shorter interval to higher rates of motor disability [12]. Nevertheless, death is attributed to MS in two-thirds of cases. The high national prevalence rate and the long-term nature of the disease place a significant financial burden on the economy of the Kingdom of Saudi Arabia (KSA) [13, 14].

### 1.2 Diagnosis

For most people, the clinical course of MS begins with episodes of neurological dysfunction followed by complete recovery [15]. MRI is the 'gold standard' for diagnosing MS and monitoring the course of the disease [16, 17]. However, although MRI scans can reveal multiple lesions distributed throughout the white and grey matter of the CNS [18], diagnosis of MS with MRI is frequently confounded by the differential diagnosis of other diseases characterized by demyelination of the optic nerves (neuritis), severe myelopathy with extensive spinal cord lesions, or even a normal MRI with abnormalities typical to MS [19]. Therefore, cerebrospinal fluid (CSF) analysis is often employed to confirm the diagnosis. A persistent and consistent presence of oligoclonal banding (OCB) exists in the CSF of MS patients; thus a positive CRF analysis requires only two lesions, identified by MRI, in order to confirm the diagnosis of MS [20,21].

Lesions typically affect the optic nerve, brainstem, cerebellum, spinal cord or cerebral hemispheres [22]. However, if white matter abnormalities are detected by MRI at clinically unaffected sites, the probability of a future positive diagnosis increases from 50% within 2 years, to 82% within 20 years [22].

### 1.3 Classification of MS

A confirmed diagnosis of MS requires evidence of characteristic, neurological lesions in the CNS that have occurred in both time and space, and exclusion of alternative diagnoses [16].

### 1.3.1 Etiology

Epidemiological studies of MS indicate a complex etiology in which unidentified environmental factors trigger the disease in genetically susceptible individuals [23]. MS is linked to alleles of the major histocompatibility complex (MHC). Although the exact mechanisms are unknown, the human leukocyte antigen HLA-DRB1\*1501 gene is the strongest genetic factor identified to date that influences susceptibility to MS [24]. This gene may also determine the balance between disease susceptibility and resistance [23, 24]. MS has a familial recurrence rate of about 17.3% [25]. When both parents have MS, the risk increases to about 30% [25]. However, thus far, investigations into the recurrence of familial MS and studies relating to monozygotic and dizygotic twins have provided no conclusive evidence of the presence of hereditary genetic traits [26].

### 1.3.2 Demyelination:

Myelin is formed from the extending plasma membrane of oligodendrocytes, creating spiral segments of sheathing that wrap around axons and envelop bundles of axonal segments. The insulating and protective properties of the myelin sheath are largely due to its structure, thickness, low water content, and its richness in lipids. Myelin sheath thicknesses and internodal lengths vary according to axonal caliber [27]. The number of wrappings around an axon can vary between 10 and 160 [28]. Depending on the subtype of the oligodendrocyte, 10 or more axons can be myelinated at one time [29]. As a consequence, inflammatory damage to a single oligodendrocyte has the potential to affect multiple axons.

### 1.3.3 Remyelination

Remyelination is associated with functional recovery in MS, although some individuals have demonstrated extensive remyelination without signs of functional improvement [30]. However, the extent of remyelination between individuals, or even within specific MS lesions, is highly variable [31].

In summary, even in the progressive forms of MS, compensatory mechanisms have been observed that respond to inflammatory injury in the neural circuits. In some cases this allows for

partial or complete restoration of neural function [30]. However, there are many disturbances to which the CNS cannot respond, and where the insult and injury may be of such intensity that any natural response is inadequate [32].

#### 1.3.4 Cellular abnormalities

Traditionally, axonal degeneration has been regarded as the major cause of neurological deficits and irreversible disability in pulse-width modulation [33]. However, while it is acknowledged that the symptoms of MS are generally attributable to the interruption of myelinated tracts in the CNS [34], recent studies have shown that a certain proportion of neurodegeneration is independent of demyelination [2, 31]. Indeed, the current view is that the entire CNS appears to be involved in the disease [35]. Inflammatory processes within the CNS can trigger a cascade of events that profoundly affect synaptic density, neurotransmitter concentrations, signal transmission mechanisms, mitochondrial density, and disrupt the microtubule transport systems critical to the normal functioning and survival of neurons [36]. The extent of MS-related symptoms and disability is determined by the intrinsic ability of the CNS to retain the integrity and compliance of the central mechanisms and neural pathways [37].

#### 1.3.5 Glutamate

Glutamate is the principal fast excitatory neurotransmitter in the CNS. Glutamate-dependent signaling is required for all sensory and motor processing and glutamatergic receptors contribute significantly to synaptic plasticity, and learning and memory [38]. During inflammatory episodes, microglia and leukocytes release substantial amounts of glutamate into the extracellular space [39]. N-methyl- D-aspartate (NMDA) receptors consist of a complex pharmacology with multiple modulatory sites. They are key components in long-term potentiation (LTP) of neuronal pathways, memory formation and synaptic plasticity [40]. A- amino- 3- hydroxy- 5- methylisoxazole- 4- propionic acid (AMPA) receptors desensitize quickly, strongly influencing neuronal output, and are responsible for the majority of fast excitatory transmissions and enhanced synaptic plasticity in the human brain [41]. Recently, confocal microscopy has revealed that MS causes a significant decrease in excitatory synapses and mRNA proteins encoding AMPA, NMDA and Metabotropic glutamate receptor (mGlu) receptors [42]. Moreover, a significant reduction in their respective synaptic binding proteins within the hippocampi of post-mortem MS brains has been reported [42, 43].

### 1.3.6 GABA

Gama-aminobutyric acid (GABA) receptors and glycine are the principal inhibitory transmitters in the CNS that, when activated, can generate membrane hyperpolarization and reduction in dendritic excitatory activity that strongly inhibits action potential firing [44]. GABA as well as GABAergic receptors has been found to be significantly elevated in MS demyelinated hippocampi, suggesting that GABA exerts a powerful inhibitory influence in MS [45].

### 1.4 Medication

Disease modifying therapies for MS are still at a relatively early stage of development. Drugs have been shown to be effective in reducing relapse rates in the early forms of the disease with a 30% reduction in frequency of new episodes over 2 to 3 years, and to a certain extent slowing clinical progression during relapsing-remitting episodes [46]. However, studies have shown no useful effects of drug therapies on the secondary- progressive phase, except in rare cases of progressive forms of the disease with continuing high relapse rates [47]. Long-term observational studies assessing the validity of drug interventions have suffered from the lack of patients' willingness to participate, or in some cases, loss to follow-up, or death [48]. Initially, there appears to be a high level of compliance and adherence to medications, but discontinuation rates have been reported as high as 50% within 2 years of drug initiation [48].

### 1.5 Summary

MS presents as a complex, unpredictable, changeable and heterogeneous disease affecting the CNS, causing moderate to severe disability in the majority of those affected by it. Symptoms can change without warning, leading to an unpredictable level of dysfunction and recovery [49]. The fluctuating and progressive nature of this disease can present confusing pictures to clinicians, complicating its management [50].

## 2. Neurophysiological Measures

### 2.1 Transcranial Magnetic Stimulation

TMS is a well-established, non-invasive technique used to examine the integrity and excitability of the corticospinal-neuromuscular pathway in both healthy and neurologically impaired populations [51]. The following sections describe the technical principles underlying TMS, and the methodological considerations and safety issues that influence the design of TMS experiments [6]. A single stimulus evokes multiple descending volleys in corticospinal motor neurons producing a contralateral, synchronous muscle response, also known as a motor evoked potential (MEP) [52]. Surface electromyography electrodes are placed on the target muscles to be stimulated and once positioned, the magnetic coil is fired and MEPs are recorded by surface EMG electrodes [7]. The repetitive discharge of spinal motor neurons represents the natural excitability of the corticospinal-neuromuscular muscular pathway in response to the magnetic pulses of the TMS [53].

## 2.2 MEP variability

The MEP is influenced by intrinsic factors relating to the excitability of the corticospinal pathway, such as the number of motor neurons recruited by the magnetic pulse, the number of motor neurons discharging more than once in response to the stimulus, and the synchronization of the motor neuronal discharges [54, 55]. The stimulus-response relationship varies considerably between subjects, and between muscles in the same individual, even those in close anatomically proximity, such as hand muscles or upper leg muscles [54]. Extrinsic factors that are implicated in MEP variability are the role of the coil and its position on the scalp. Furthermore, MS-related conduction block, conduction impedance, and slowing of signal velocity may modify the MEP [56].

## 2.3 TMS measures and motor threshold

The TMS measures most commonly used in the analysis of motor data are resting motor threshold (MT; the minimal TMS intensity required to evoke an MEP), latency (the time from triggering the pulse to the start of the MEP), amplitude (baseline to peak or peak to peak value) and area (measured as root mean squared, or as the area under the line of the rectified signal) [57]. MT is the lowest stimulus intensity of TMS that elicits a recordable MEP in the target muscle [58]. Obtaining accurate resting MTs requires a systematic search for the optimal coil position (hotspot) above the motor area corresponding to the target limb or muscle [59]. When the coil is directly over the hotspot, it is a general practice to obtain 5-10 MEPs of 50  $\mu$ V in at least 50% of successive



trials [60]. MTs are generally recognized as a measure of the integrity and excitability of the neural pathway, at both the cortical and spinal level [61].

#### 2.4 Central motor conduction time

The latency of an evoked potential is the time interval between triggering the stimulus at the motor cortex and the start of the MEP [62]. The time required for a volley generated in the motor cortex to travel through the spinal cord is known as the central motor conduction time [63]. It can be determined by comparing the difference between the latency of a cortically stimulated MEP, and the latency of a TMS pulse at the spinal roots, or the latency of the response to electrical or magnetic stimulation at a point on the motor nerve [64].

#### 2.5 The cortical silent period

The cortical silent period (CSP) is characterized by an interruption of the EMG signal after the TMS is delivered at the motor cortex during a tonic contraction [65]. It is defined as the time between the end of the MEP and the return of the EMG signal [66]. CSP requires an individual to contract the target muscle at ~20-30% of maximal voluntary force [67]. The duration of the CSP is dependent upon the percent of stimulator output, yet appears to be unaffected by the intensity of the MVC [68]. The resulting CSP lasts for only ~100 ms, with considerable variability in duration between subjects [69]. The initial portion (40-50 ms) of the CSP is generally believed to be a response to spinal inhibitory mechanisms that follow motor neuron excitation, namely hyperpolarization and recurrent inhibition. Inhibitory mechanisms at the spinal level are known to mediate the CSP during its latter stages [69].

### 3. Innovation and Significance

Neurological diseases frequently show typical patterns of cortical excitability, which are likely to change during the progression of the illness [70]. Our working hypothesis is that altered pattern of excitability tend to regress to normal activity under effective therapeutic approaches. The discovery of specific and detailed neurophysiological parameters as a surrogate end point of disease activity could represent an important step in clinical trials, providing reliable indexes of severity of illness and efficacy of drugs.

Changes in cortical connectivity have been already been demonstrated in MS, but in clinical practice other measures are usually used to evaluate disease activity. We speculate that TMS may be more effective in signaling disease progression leading to long term disability, compared to standard surrogate markers, because it represents a direct measure of synaptic transmission(s).

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