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# Normative data and long-term test–retest reliability of the triple stimulation technique (TST) in multiple sclerosis

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HIGHLIGHTS

- The triple stimulation technique (TST) is an advanced technique to study neurophysiologic cortico-spinal tract integrity.
- Longitudinal methodological properties of TST measures were examined in multiple sclerosis (MS) patients. Additionally healthy controls were examined for derivation of normative data.
- TST values of MS patients were abnormal, highly reliable and stable during a long-term follow-up, supporting the diagnostic utility and methodological robustness of TST parameters.

ABSTRACT

*Objectives:* Transcranial magnetic stimulation is useful for the assessment of cortico-spinal tract integrity in multiple sclerosis (MS). An advanced approach is the triple stimulation technique (TST), utilizing a combination of central and peripheral stimuli, reducing individual response variability. Although TST measures have been implemented in longitudinal studies, basic methodological data on temporal properties of abnormal TST values in MS are sparse.
*Methods:* Normative TST data were obtained from 48 healthy participants. Longitudinal measures were derived from 17 MS-patients (relapsing–remitting: $N = 10$; clinically isolated syndrome: $N = 7$) prior to, three and twelve months following therapy initiation. Intraclass correlations were used to examine test–retest reliability. Complementary, patient ambulation and cognition were assessed.
*Results:* Patient TST parameters were abnormal, involving excellent test–retest reliability and stable mean values. Cognitive and motor performance improved.
*Conclusions:* Results are the first to show that abnormal TST values in MS, reflecting diagnostic utility, are highly reliable in a long-term follow-up. Methodological properties are adequate for a longitudinal implementation of TST. Parameters were insensitive to alterations in cognitive/motor functioning. Sensitivity may be verified in subgroups with different treatment regimes.
*Significance:* Results provide new normative data, support diagnostic utility of TST measures in MS, and confirm their long-term robustness.


## 1. Introduction

Fatigue and impaired motor capacity are common phenomena in multiple sclerosis (MS) and interfere strongly with everyday life functioning (Schwid et al., 1999; Krupp and Christodoulou, 2001; Burschka et al., 2012; Yusuf and Koski, 2013). Patients with such deficits are known to display abnormal activation in motor areas. A common finding in magnetic resonance imaging (MRI) studies is that MS patients display higher activation in motor areas during the performance of a motor task than healthy controls (Pantano et al., 2006; Colorado et al., 2012). A pattern of elevated activation has been found to correlate with tissue damage and may reflect compensatory neural mechanisms (Pantano et al., 2005). Congruent with this assumption, lesion burden often only shows a modest

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relationship with clinical symptoms (for recent reviews see Filippi and Rocca, 2011; Filippi et al., 2013). Functional brain changes in MS have hence been concluded to be dynamic in nature, and may be influenced by a variety of factors, including age, clinical course and the extent of impaired tissue (Pantano et al., 2006; Mezzapesa et al., 2008; Liu et al., 2012). Due to the fact that there may be considerable discrepancy between MRI data and clinical symptoms, complementary neurophysiologic methods have been utilized to support the process of diagnostics and monitoring in MS.

### 1.1. Triple stimulation technique (TST)

A useful technique in this context is transcranial magnetic stimulation (TMS; Kobayashi and Pascual-Leone, 2003). TMS is a non-invasive technique in which cortical motor areas are stimulated via electromagnetic induction and with which pyramidal tract conduction can be examined by monitoring motor output over target muscles (motor evoked potentials, MEP) in response to stimulation. Numerous studies involving TMS have shown that cortical excitability may be abnormal in MS (Caramia et al., 2004; Conte et al., 2009; Vucic et al., 2012), while evidence concerning more consistent associations between MS-related symptoms, such as fatigue and cortical excitability, is limited (Yusuf and Koski, 2013).

As a derivative of classic TMS, the triple stimulation technique has emerged (TST; Magistris et al., 1998, 1999; Bühler et al., 2001; Rösler et al., 2009; Scheidegger et al., 2012). TST is a collision technique by which trial-to-trial MEP variability can be reduced. It comprises transcranial magnetic stimulation of cortical motor areas, as well as two electric stimuli which are applied in the periphery along the motor nerve. Utilizing the collision of these impulses yields reduced inner-subject variability in response latency and magnitude, and as such provides a marker of corticospinal tract integrity characterized by high internal consistency. Based on this methodological advancement, TST measures have been successfully employed in various neurological disorders including multiple system atrophy (Eusebio et al., 2007), spinocerebellar ataxia (Sakuma et al., 2005), amyotrophic lateral sclerosis (Attarian et al., 2007), multifocal motor neuropathy (Deroide et al., 2007) as well as MS (Humm et al., 2003; Firmin et al., 2012).

### 1.2. Test–retest reliability of TST measures in multiple sclerosis

Due to the apparent utility of TST for uncovering pathological functional processes, it has been suggested that TST parameters might be usable as outcome measures in intervention studies involving MS patients (Humm et al., 2006). However, to our knowledge, from a basic methodological perspective, long-term follow-up assessments focusing on test–retest reliability of TST parameters in MS have never been conducted. Consequently, it is difficult to interpret putative changes in TST parameters in the context of intervention studies. This issue is aggravated by the fact that even for healthy individuals, availability of information on test–retest reliability of TST measures is limited. Humm et al. (2004) examined test–retest characteristics of TST parameters in healthy participants across two assessment sessions, separated by 3–4 weeks. The authors provide information on what they refer to as *test–retest repeatability*, i.e., the extent to which the common TST parameter (TST amplitude ratio in percent) changed from the first to the second assessment session. The results revealed that changes in mean TST values were small (approximately 3%), warranting the conclusion that test–retest repeatability was excellent. However, it should be noted that the authors' analytic approach focused on putative shifts in mean TST amplitude ratios and that such an approach cannot entirely address the characteristic of *test–retest reliability*. Test–retest reliability does not solely refer to changes in mean values across measurement points, but addresses the issue of systematicity of variance, i.e., rank-ordering of subjects' values over time (for examples of applications in neurophysiologic research see Gasser et al., 1985; Allen et al., 2004). As such, it provides information about the consistency of temporal alterations/temporal stability within a sample.

### 1.3. Purpose of the current study

To our knowledge, a corresponding methodological exploration of TST parameters focusing on MS patients is lacking. We regard such an examination as important for several reasons. Firstly, given the dynamic nature of neurophysiologic changes in MS, basic methodological characteristics of TST parameters require verification in a longitudinal design. Sufficient long-term test–retest reliability of abnormal TST values would provide further support for TST measures as reliable parameters, aiding the diagnostic process. Secondly, reliability of TST measures in MS needs to be established with regards to intervention studies. Humm et al. (2006) reported immediate improvements in TST measures following high-dose steroid therapy in MS patients with acute exacerbation of motor deficits. Improvements were attributed to a reduced central motor conduction block. Despite these promising findings, the authors did not provide information on test–retest reliability, limiting the possibility to interpret these findings.

The major goal of the current work hence was to obtain original data on test–retest reliability of abnormal TST measures in MS patients. In order to examine whether patient TST values were indeed abnormal, reflecting diagnostic utility, they were compared to additionally gathered, normative data of healthy controls.

In a secondary, exploratory analysis, it was verified whether potentially improved motor and cognitive functioning during basic immune-modulating therapy, might also be accompanied by changes in TST values, resembling putative effects of high-dose steroid therapy, as reported by Humm et al. (2006).

## 2. Methods

### 2.1. Participants

Patients were recruited in the Department of Neurology, Klinikum Bayreuth GmbH, Germany, and were eligible to participate if they had been diagnosed with relapsing remitting multiple sclerosis (RR-MS; illness duration <10 years; age range 18–60 years), or had suffered an initial episode (clinically isolated syndrome, CIS). Suitable participants were approached during the routine clinical process, and had an indication to receive immune-modulating therapy. In sum, 17 patients (RR-MS: 10; CIS: 7) who met inclusion criteria completed the TST assessment sessions at baseline (Time 1), after three months (Time 2), and after twelve months (Time 3). Demographics and clinical characteristics are displayed in Table 1.

Healthy participants for normative TST values ($N = 48$, 24 female, mean age: 30.54, SD = 8.50) were examined once, with the same TST protocol as the patients, involving derivations from hand and foot muscles. In case of all healthy participants, a history or presence of neurologic disease, hypertension or other disease influencing neural function was ruled out by physical examinations and interviews. It was further ensured that healthy participants were not taking any drugs known to influence neural function (analgesics, psychopharmacological drugs). Two additional healthy participants were excluded from the analysis because only three extremities could be included during the stimulation procedure. In one participant, due to anatomical problems involving a very short neck, stimulation at Erb's point on one side