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Resetting tremor by single and paired transcranial magnetic stimulation in Parkinson's disease and essential tremor

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HIGHLIGHTS

- Single- and paired-pulse transcranial magnetic stimulation (TMS) provide a useful opportunity to test non-invasively tremor pathophysiology in Parkinson's disease (PD) and essential tremor (ET).
- The tremor-resetting index (RI) differentiated the functional roles of primary motor cortex (M1) and supplementary motor area (SMA) in PD vs. ET tremor.
- M1-TMS resulted in a higher RI in PD than ET, suggesting a stronger M1 involvement in PD resting and postural tremor than ET postural tremor.

ABSTRACT

Objective: The pathogenesis of tremor in Parkinson's disease (PD) and essential tremor (ET) is not fully understood. This study tested the role of primary motor cortex (M1), supplementary motor area (SMA) and cerebellar cortex on PD and ET tremor by single- and paired-pulse transcranial magnetic stimulation (TMS).
Methods: Ten PD patients with resting tremor, six of them also with postural tremor, and ten ET patients with postural tremor were studied. Randomized single- and paired-pulse TMS with an interstimulus interval of 100 ms were delivered over M1, SMA and cerebellum. TMS effects were evaluated by calculating a tremor-resetting index (RI).
Results: Single- vs. paired-pulse TMS showed no difference. M1-TMS and SMA-TMS but not by cerebellar TMS induced a significant RI in PD and ET. M1-TMS resulted in a significantly higher RI in PD than ET. Furthermore, M1-TMS in PD but not in ET resulted in a significantly higher RI than SMA-TMS.
Conclusions: Findings suggest a stronger involvement of M1 in resting and postural tremor in PD than postural tremor in ET.
Significance: RI provides a useful marker to explore the differential functional role of M1, SMA and cerebellum in PD vs. ET tremor.

1. Introduction

The pathophysiology of resting tremor in Parkinson's disease (PD) and postural tremor in essential tremor (ET) remains not fully understood. Accumulating evidence suggested that PD resting tremor may primarily involve the basal ganglia-thalamocortical (BGTC) circuit and ET postural tremor may be mainly associated with the cerebellothalamocortical (CTC) circuit (Schnitzler et al., 2006; Muthuraman et al., 2012; Raethjen and Deuschl, 2012;

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Helmich et al., 2013). However, the pathogenesis of the two tremor types can be complex. For instance, pathological interactions between the BGTC and the CTC circuit may eventually develop in PD tremor (Helmich et al., 2013).

Transcranial magnetic stimulation (TMS) can induce a transient perturbation in physiological and pathological neurocircuits, therefore providing a good opportunity to study tremor pathogenesis. Single-pulse TMS over the primary motor cortex (M1) activates corticospinal neurons largely transsynaptically (Hallett, 2007). Previous studies showed that postural tremors in both PD and ET were modulated by single-pulse TMS of M1 (Britton et al., 1993; Pascual-Leone et al., 1994; Ni et al., 2010). These findings suggested a common central mechanism, probably through M1, in PD and ET postural tremor. However, a typical tremor manifestation in PD patients is resting tremor instead of postural tremor. A simultaneous comparison of PD resting tremor, postural tremor and ET postural tremor may further clarify the role of M1 in the tremor pathogenesis. The supplementary motor area (SMA) and the cerebellum are the other two important motor-related brain areas linked to the BGTC and the CTC circuits, respectively. Investigating whether and how TMS of the SMA and the cerebellum can modulate typical PD and ET tremor can be helpful in further understanding the pathophysiology of tremor in these two conditions. One previous study demonstrated that cerebellar TMS reset postural but not resting tremor in PD, suggesting that the CTC circuit is involved in postural but not resting tremor in PD (Ni et al., 2010).

TMS activates cortical inhibitory interneurons in addition to the corticospinal neurons. Paired-pulse TMS with a specific interstimulus interval can assess function of the inhibitory interneurons (Valls-Sole et al., 1992; Kujirai et al., 1993; Wassermann et al., 1996; Ziemann et al., 1996). The long-interval intracortical inhibition (LICI), i.e. inhibition of the test motor evoked potential (MEP) by a suprathreshold conditioning TMS at interstimulus intervals of about 50–200 ms, is impaired in patients with PD (Berardelli et al., 1996; Chu et al., 2009). LICI is very likely mediated by γ-aminobutyric acid (GABA) type B ($GABA_B$) receptors (McDonnell et al., 2006). Recent studies revealed that GABA is involved in ET pathophysiology (Paris-Robidas et al., 2012; Helmich et al., 2013; Chuang et al., 2014). GABAergic agents such as gabapentin, alprazolam, clonazepam or ethanol are usually therapeutically effective (Zesiewicz et al., 2013). In this exploratory study, we applied a LICI-inducing paired-pulse TMS to investigate whether tremor resetting by TMS is altered on the influence of LICI. The hypothesis is that while tremor is modulated with a similar pattern by single- and paired-pulse TMS, the TMS-induced tremor modulation could be mainly contributed from the corticospinal neurons *per se* instead of the co-activated inhibitory interneurons. If there are significant differences of the modulation patterns between single- and paired-pulse TMS, a functional role of the inhibitory interneurons on the TMS-induced tremor modulation has to be further considered.

Here we investigated to what extent resting tremor in PD and postural tremor in ET were modifiable by single-pulse TMS and LICI-inducing paired-pulse TMS of M1, SMA and cerebellum. We suppose that the findings can help clarify the mechanism of the TMS-induced tremor modulation.

2. Methods

2.1. Subjects

Patients were screened by taking a detailed medical history and clinical examination, surface electromyography (SEMG) recordings, neuroimaging studies and the TMS Adult Safety Screening Questionnaire (Keel et al., 2001) before they were enrolled into this study. For PD patients (Gibb et al., 1990), we recruited exclusively patients with a significant resting tremor (>grade 3 of the UPDRS tremor score) at their forearms. Those patients with advanced PD severity (modified Hoehn & Yahr stage IV and V) were excluded because it would have been difficult for them to discontinue medication. For ET patients, all patients fulfilled the consensus diagnostic criteria for classical ET (Deuschl et al., 1998) with a prominent postural tremor (grade 2–4 on the Fahn, Tolosa, Marin tremor rating scale) at their forearms. At least two movement disorder expert neurologists confirmed inclusion and exclusion criteria during patient recruitment. In case the patients took regular anti-parkinsonian or anti-tremor medications, they were requested to discontinue these medications for at least 24 h prior to the measurements of this study. Ten PD patients (6 men, aged 62.7 ± 11.4 years) and ten ET patients (5 men, aged 64.3 ± 13.2 years) with significant tremor amplitude at the extremity of the recording muscle were studied (Table 1). All of the patients gave their written informed consent prior to participating in this study, which was conducted in accordance with the latest revision of the Declaration of Helsinki. Approval by the local ethics committee of the China Medical University Hospital was obtained (DMR100-IRB-263).

2.2. Procedures

2.2.1. Determination of resting motor threshold (RMT), MEP1mV, $LICI_{50\%}$ and cortical silent period duration

The patients were seated in a comfortable chair with their arms and hands relaxing on armrests. MEP was recorded by SEMG from the hand or forearm muscles that showed maximal tremor activity in the preceding SEMG recordings at screening. The SEMG was amplified by a D360 (Digitimer Ltd., UK), filtered from 5 Hz to 2.5 kHz, digitized (sampling rate 2 kHz), processed with the CED 1401 plus (Cambridge Electronic Device, UK) and stored on a laboratory computer for off-line analysis (Spike2 for Windows, version 3.05, CED). The resting motor threshold (RMT) was determined in the M1 contralateral to the SEMG recording site (i.e. RMT_{M1}) by using two different stimulation coils, a figure-of-eight coil (diameter of each wing, 70 mm) and a double cone coil (diameter of each wing, 110 mm). Either coil was connected to two single-pulse magnetic stimulators with monophasic current waveforms (Magstim Co., Ltd.) through a BiStim module (BiStim, Magstim Co., Ltd.). RMT_{M1} with the figure-of-eight coil was used for M1 stimulation and RMT_{M1} with the double cone coil for SMA and cerebellar stimulation. Since SMA and cerebellum are located deep from the scalp, a double cone coil stimulates these areas more effectively than a figure-of-eight coil. The figure-of-eight coil was held tangential to the scalp over the M1 contralateral to the recording site with the handle pointing backwards and ~45° away from the midline, i.e. inducing a current in M1 directed from lateral-posterior to medial-anterior. The double cone coil was held with the handle upward from the scalp and the junction of the coil was also rotated ~45° away from the midline to induce a current direction from lateral-posterior to medial-anterior in M1. The optimal coil position ('hot spot') was determined as the site where TMS at a slightly suprathreshold intensity produced consistently the largest MEPs at the target recording muscle. RMT was determined to the nearest 1% of maximum stimulator output (MSO) as the lowest stimulus intensity that elicited small MEP (>50 μV peak-to-peak amplitude) in at least five of ten consecutive trials, using the relative frequency method (Groppa et al., 2012). MEP_{1mV} was determined as the stimulus intensity that elicited MEP of on average 1 mV in peak-to-peak amplitude in the resting target muscle. LICI was measured by a paired-pulse protocol using a suprathreshold conditioning TMS stimulus (TMS1) followed by a test TMS stimulus (TMS2). The interstimulus-interval between TMS1 and TMS2 was