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Clinical short communication

Superconditioning TMS unmasks latent voluntary innervation in MND – A case report

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ABSTRACT

Motor neuron disease (MND) includes both ALS and Progressive Muscular Atrophy (PMA) as variants. Abnormalities in brain excitability and upper motor neuron (UMN) function are characteristic of ALS, but by definition are absent in PMA. Transcranial magnetic stimulation (TMS) may be useful in demonstrating UMN pathology, but loss of muscle responsiveness with disease progression limits its usefulness in later stages of MND. We have developed a novel form of TMS comprised of 4 stimulating pulses that can enhance MEPs in target muscles already responding to traditional TMS inputs, in some cases even restoring MEPs in target muscles rendered unresponsive by the disease. An example of restored MEPs in response to this superconditioning TMS pattern (TMSsc) in a person with PMA is described, along with an unexpected finding. Despite a prolonged (> 5 year) history of movement paralysis in his right tibialis anterior (TA), immediately after cessation of TMSsc delivery the subject could now easily contract and relax this muscle; the presence of a latent pathway for voluntary innervation of his right TA was revealed. This modulation of central motor functional connectivity in response to TMSsc suggests a further, clinically-significant benefit of this form of noninvasive brain stimulation beyond its ability to enhance MEPs to traditional TMS inputs.

1. Introduction

Transcranial magnetic stimulation (TMS) for noninvasive modulation of motor cortex excitability has proven to be a valuable tool for studying central motor function. The original model used a single rapidly varying magnetic pulse [1]. Dual pulse TMS emerged when the output of two stimulators was coupled through a device that allowed independent adjustment of each stimulator's intensity and the interpulse interval (IPI) between the two pulses. With this dual pulse variant, intracortical inhibition and facilitation could be selectively studied using an appropriate conditioning-test (C-T) paradigm. Pulse #1 of the pair (the *conditioning* pulse) uses a stimulus intensity that – on its own – is *subthreshold* for eliciting a motor evoked potential (MEP), and pulse #2 (the *test* pulse) is *suprathreshold* for an MEP. Very short (1–5 ms) C-T intervals inhibit the resultant MEP, compared to the test MEP alone: this effect has been termed *short interval intracortical inhibition* (SICI) [2]. Slightly longer C-T intervals (10–25 ms) tend to cause facilitation of the test MEP, dubbed *intracortical facilitation* (ICF) [3].

We recently described a novel TMS protocol utilizing *three* subthreshold pulses followed by a single suprathreshold test pulse (i.e. 4 pulses in total). In healthy subjects, this *superconditioning* TMS (TMSsc) protocol enhanced the effectiveness of dual pulse TMS for both inhibition and facilitation [4].

The advantages of TMSsc for enhancing dual pulse TMS effects extend to persons with motor neuron disease (MND) [5]. In the majority of MND patients, both upper and lower motor neurons are impacted, causing weakness and paralysis in muscles of the limbs or face, depending on the disease phenotype. In cases of recent MND diagnosis, thresholds to single pulse TMS may be lower [6] or unchanged [7], but with disease progression it's common for thresholds to increase [8,9] to the point where muscles are unresponsive to TMS [10,11]. In this case report, we show an example of markedly enhanced MEPs – followed by restored voluntary movement – in response to a brief course of TMSsc delivery in a subject with MND.

2. Material and methods

The subject of this case report was a 59 year-old male with a 14-year history of distal lower limb onset weakness, diagnosed with progressive muscular atrophy (PMA), a subset of MND. Spinal muscular atrophy

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was ruled out [12]. At his most recent clinical evaluation, he did not meet the Revised El Escorial diagnostic criteria for ALS [13]. Clinical evaluation showed bilateral foot drop with diffuse lower limb areflexia and severe atrophy in his right TA. EMG needle examination showed chronic neurogenic changes in the left TA with markedly reduced recruitment and no active denervation changes. Recruitment was completely absent in his right TA, with decreased insertional activity. His ALSFRS-R score on the day of testing was 40, and he was not taking Riluzole.

Responses to TMSsc inputs in a healthy control subject (58 year old female) are included for comparison. Both subjects provided written informed consent to the protocol that had been approved by Upstate Medical University's IRB.

Methods of EMG recording and TMS delivery have been published [4]. Briefly, EMG was recorded from abductor pollicus brevis (APB) and tibialis anterior (TA) with surface electrodes (Cleartrace; Conmed). Signals were amplified and filtered (20 Hz – 2 kHz), digitized (5 kHz sampling), and stored for analysis (Spike2; Cambridge Electronic Design). Single pulse, dual pulse, and 4 pulse TMS was delivered from a set of 4 Magstim 200 magnetic stimulators and 3 Magstim BiStims. A flat round coil was used for testing APB, whereas an angled double-cone coil was used for TA.

Resting MEP thresholds to single pulse (RT_1) and 3-pulse (RT_3) TMS were established, based on an MEP exceeding ~20 μV (peak-to-peak) to at least 3 of 5 identical trials. The intensity of the test pulse was set to 120% of the RT_1 value (i.e. $1.2{\cdot}RT_1$). For dual pulse TMS, the conditioning pulse intensity was set to $0.8{\cdot}RT_1$. For TMSsc, the superconditioning (SC) pulses were set to an intensity of $0.75{\cdot}RT_3$, while the test pulse was unchanged at $1.2{\cdot}RT_1$. The intervals between SC pulses and between the last SC pulse and the test pulse were systematically varied [4].

Before MEP testing, we asked subjects to make a brief (~ 2 s) maximal voluntary contraction (MVC; isometric) in each target muscle. We believe this measure better reflects the functional integrity of the entire CNS motor pathway to a target muscle, compared to a compound muscle action potential obtained from supramaximal median or common peroneal nerve stimulation. Next, we collected MEPs, typically delivering 5 trials of each condition, with 5–8 s between each pulse or pulse train. EMG was offset to zero volts, rectified, and averaged. Mean response magnitude (RMS) between cursors was measured, hence values are independent of time.

3. Results

Fig. 1 shows representative MEPs to single pulse, dual pulse, and four pulse (i.e. superconditioning) TMS inputs from the left APB of a control subject. The MEP to single pulse TMS (A) had a magnitude of 164 μV. Dual pulse TMS with intensities and IPI shown for SICI (Fig. 1B) resulted in a reduction of the test MEP to only 33 μV (20.1% of the test MEP in 'A'). TMSsc with parameters as shown (Fig. 1C) caused slightly stronger inhibition of the test MEP (25 μV) compared to the SICI-specific input in 'B'. Dual pulse TMS to cause ICF resulted in a much larger MEP (Fig. 1D) (237 μV) compared to the test MEP alone. Finally, a superconditioning TMS input optimized for facilitation (Fig. 1E) resulted in the largest MEP (501 μV) seen from the L APB in this subject.

Fig. 2 illustrates the effect of TMSsc in a subject with MND. During MVC measures he showed good strength and recruitment in his left TA, but no visible or palpable contraction in his right TA (Fig. 2A). Single pulse TMS at 75% intensity failed to evoke any MEP from his right TA (data not stored), and he asked that we not try anything stronger. We therefore concentrated on his left TA for MEP testing, but continued to monitor EMG from both TAs. His RT_1 was 60% for his left TA, so we used a test pulse intensity of 72% (i.e. $1.2{\cdot}RT_1$). His left TA to single pulse stimulation was well defined (Fig. 2B; 37.5 μV). Undetected by us during original data collection, signal averaging showed this subject *did* have a small MEP in his right TA to 72% single pulse TMS (Fig. 2B; 2.9 μV). However, during left TA testing with superconditioned TMS optimized for facilitation we saw that in addition to a large MEP from his left TA (Fig. 2C; 118.4 μV), his *right* TA was now responding with a short latency MEP (28.7 μV). Immediately after delivering the 5 TMSsc trains causing the response shown in Fig. 2C, we interrupted our normal protocol and asked this subject to repeat MVC efforts in his right TA. As shown in Fig. 2D, there was now clear EMG recruitment during 2 successive contraction attempts, coinciding with visible dorsiflexion of his right ankle. His ability to stop and restart the EMG activity on command told us this was unquestionably a *voluntary* contraction, rather than a spasm or burst of fasciculations. Further evidence for the voluntary nature of this contraction comes from the co-activation of 1–2 motor units in his *left* TA muscle for the first contraction attempt (Fig. 2D). In our experience, such co-activation of contralateral muscles is common in persons with limb paresis who attempt maximal contractions in isolated muscles [14].

When asked if he could feel any movement in his right ankle, he responded "A little bit." We were able to reproduce these findings in two subsequent testing sessions, separated by ~3 month intervals, but

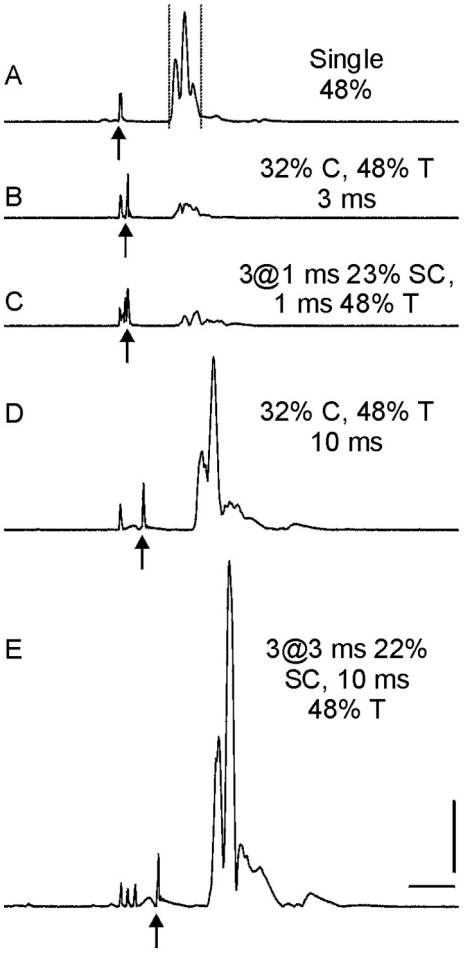

Fig. 1. MEPs from the left APB of healthy control subject. A) MEP to single pulse TMS. Cursors for defining onset/offset are included in this trace only, for reference. MEP onset was typically easy to define, but offset timing tended to be less well defined, because response durations to superconditioning inputs tended to be more prolonged than to single pulse stimulation. B) MEP to SICI input. C) MEP to superconditioning input optimized for inhibition. D) MEP to ICF input. E) MEP to superconditioning input optimized for facilitation. Note the slight difference in superconditioning pulse intensity with 1 ms IPI (23%; 'C') and 3 ms IPI (22%; 'E'). The IPI differences reflect slight differences in the target muscle's RT_3 value when using IPIs of 1 ms (RT_3 = 32%) and 3 ms (RT_3 = 30%). For all panels: vertical arrow at time of test MEP; vertical bar = 250 μV; horizontal bar = 20 ms.

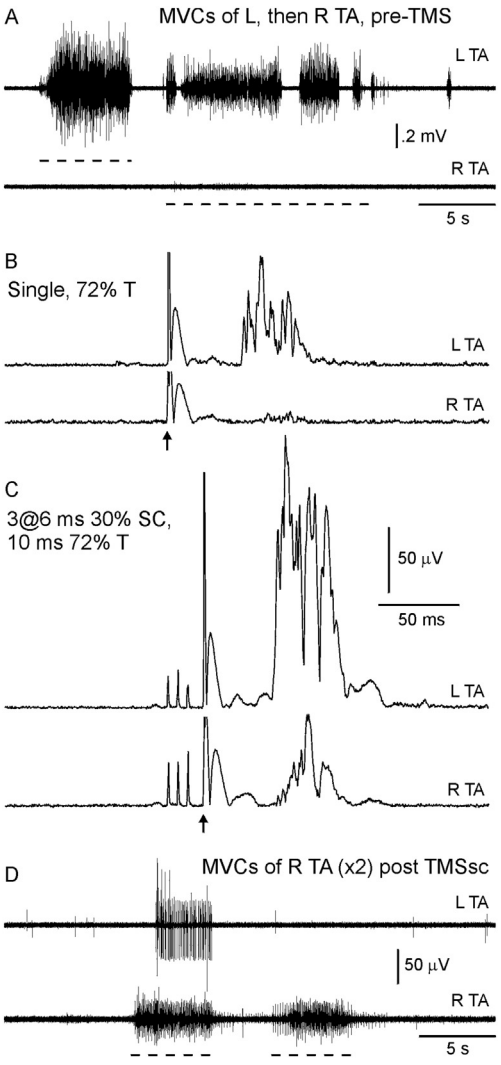

Fig. 2. From a subject with MND. A) MVC attempt in his left TA (upper) and right TA (lower). Time of contraction effort indicated by dashed line under each EMG record. B) MEPs to strong (72%) single pulse TMS while we were targeting the subject's left TA. The right-side response went unrecognized at the time of testing. C) MEPs to TMSsc optimized for facilitation (i.e. 10 ms interval between final superconditioning pulse and the test pulse). D) Immediately after completing the trials giving rise to the records in 'C', we asked the subject to attempt two brief MVCs in his right TA; the delay from the last TMS delivery in 'C' to the first MVC effort was ~ 18 s. Calibration bar values are labeled for 'A' and 'D'; the bars embedded in 'C' apply to both 'B' and 'C'.

were unable to ascertain for how long this post-TMSsc effect on his right TA voluntary contraction persisted. The subject has since passed away.

4. Discussion

Compared to dual pulse TMS, the most obvious effect of a superconditioning train on the test MEP is greater modulation – either inhibitory or excitatory, depending on the test interval – of motor cortex excitability. This suggests a mechanism of *temporal summation* between intracortical interneurons and those upper motor neurons giving rise to the MEP. For TMSsc patterns optimized for facilitation, a direct consequence is that MEPs can still be followed in some persons with central motor deficit who are no longer responsive to strong, single pulse TMS. Also, in persons with elevated thresholds to single pulse TMS, testing could be accomplished with weaker TMS test pulse intensities, making repeated studies more feasible, by lowering the risk of subject dropout.

An important point worth emphasizing is that the intensity of the test pulse was always the same as that used for single and/or dual pulse inputs, whereas the intensity of the *superconditioning* pulses was always less than that of the single conditioning pulse used for traditional dual pulse inputs. These SC pulses, which on their own were *much* weaker than a test muscle's RT_1 value, were clearly still able to recruit both excitatory and inhibitory interneuron populations acting on UMNs, since both facilitation and inhibition of the test TMS pulse was possible, depending on the test pulse interval.

The original report of neuromodulation following repeated four pulse trains of high frequency (1.5 ms IPI) TMS pulses (i.e. 'Quadropulse TMS') described a long-lasting enhancement of MEP amplitude in hand muscles of control subjects, surpassing the effect of dual pulse TMS [15]. In a similar manner, we described a functionally significant effect of 'Quadropulse' TMS in a subject with incomplete spinal cord injury: her walking speed markedly increased after receiving 250–360 'Quadropulse' TMS trains [16].

In one regard, the effect of TMSsc in the MND subject featured herein is even more surprising, in that he had been all but paralyzed to voluntary movement of his right TA for at least 5 years. Were his pathology restricted exclusively to his lower motor neurons (LMN), it's hard to explain how certain strong TMS inputs could fail to recruit lower motor neurons, while other equally strong inputs – but now preceded by a train of *much weaker* cortical stimuli – *were* able to cause LMN recruitment. This finding points to a role of cortical involvement in this individual – whether in upper motor neurons, cortical interneurons, or elsewhere – in spite of an absence of clinical signs, such as pathological reflexes and pseudobulbar affect. Findings to this effect have appeared elsewhere [12,17,18]. One group in particular, after following a large cohort of patients with PMA over time, concluded "… PMA should be considered a form of ALS." (page 1686) [19].

One obvious question is how long did the functional improvement in this subject's right TA muscle illustrated in Fig. 2 persist? We can't answer that question: shortly after generating the records illustrated in Fig. 2, the subject asked that we end the test session, due to fatigue. We noted very small MEPs to single pulse TMS in this subject's right TA during 2 subsequent test sessions, suggesting a lasting effect of TMSsc. However, we can't exclude the possibility that we were now more vigilant for even tiny MEPs, knowing they occurred with TMSsc inputs.

Overall, the potential in persons with CNS motor dysfunction of persistent and beneficial effects of superconditioning TMS on muscle voluntary contraction cannot be addressed based on our findings herein. We believe this question is worthy of further investigation, especially since TMSsc inputs require fewer high-intensity stimulus pulses, hence are better tolerated by persons with central motor deficits.

Declarations of interest

None.

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