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The use of F-response in defining interstimulus intervals appropriate for LTP-like plasticity induction in lower limb spinal paired associative stimulation

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HIGHLIGHTS

- We suggest a method for estimation of appropriate ISIs in lower limb spinal PAS.
- F-response and MEP latencies allow defining ISIs that lead to LTP-like plasticity.
- This method can be useful for clinical applications of PAS for lower limbs.

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ABSTRACT

Background: In spinal paired associative stimulation (PAS), orthodromic volleys are induced by transcranial magnetic stimulation (TMS) in upper motor neurons, and antidromic volleys by peripheral nerve stimulation (PNS) in lower motor neurons of human corticospinal tract. The volleys arriving synchronously to the corticomotoneuronal synapses induce spike time-dependent plasticity in the spinal cord.

For clinical use of spinal PAS, it is important to develop protocols that reliably induce facilitation of corticospinal transmission. Due to variability in conductivity of neuronal tracts in neurological patients, it is beneficial to estimate interstimulus interval (ISI) between TMS and PNS on individual basis. Spinal root magnetic stimulation has previously been used for this purpose in spinal PAS targeting upper limbs. However, at lumbar level this method does not take into account the conduction time of spinal nerves of the cauda equina in the spinal canal.

New method: For lower limbs spinal PAS, we propose estimating appropriate ISIs on the basis of F-response and motor-evoked potential (MEP) latencies. The use of navigation in TMS and ensuring correct PNS electrode placement with F-response recording enhances the precision of the method.

Results: Our protocol induced 186 ± 17% (mean ± STE) MEP amplitude facilitation in healthy subjects, being effective in all subjects and nerves tested.

Comparison with existing method: We report for the first time the individual estimation of ISIs in spinal PAS for lower limbs.

Conclusions: Estimation of ISI on the basis of F and MEP latencies is sufficient to effectively enhance corticospinal transmission by lower limb spinal PAS in healthy subjects.

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1. Introduction

Paired associative stimulation (PAS) is a procedure where low-frequency transcranial magnetic stimulation (TMS) over the human primary motor cortex is paired with peripheral electrical nerve stimulation (PNS) of somatosensory afferents to alter neuronal excitability at the cortical level (Stefan et al., 2000). Spinal PAS targets the human spinal cord. In spinal PAS, orthodromic volleys induced by TMS in upper motor neurons and antidromic volleys induced by PNS in lower motor neurons are intended to arrive in a synchronous manner to the corticomotoneuronal synapses of the corticospinal tract (Taylor and Martin, 2009; Leukel et al., 2012; Cortes et al., 2011; Bunday and Perez, 2012).

PAS-induced changes in neuronal connectivity represent a form of spike timing-dependent plasticity (STDP) (Stefan et al., 2000). STDP can result in either synaptic long-term potentiation (LTP) or depression, depending on the timing of the pre- and postsynaptic stimuli (Dan and Poo, 2004). Accordingly, the crucial factor of PAS protocol is the interstimulus interval (ISI) between TMS and peripheral electrical stimulation. ISI determines whether plasticity is induced at the motor cortex (Stefan et al., 2000) or spinal cord (Taylor and Martin, 2009). Importantly, it also determines whether the protocol leads to synaptic potentiation, inhibition or has no effect (Taylor and Martin, 2009; Wolters et al., 2003).

PAS is an emerging potential rehabilitation strategy for stroke (Uy et al., 2003; Castel-Lacanal et al., 2007, 2009) and incomplete chronic spinal cord injury (Bunday and Perez, 2012; Roy et al., 2010) patients. In the population of neurological patients, the inter- and intraindividual differences in conductivity or length of neuronal tracts due to alterations caused by disease or injury are greater than in healthy subjects. Hence, for clinical applications of PAS it is important to develop methods enabling successful individual approximation of ISIs that will lead to induction of LTP-like plasticity.

For the cortical level PAS, individually adjusted ISIs have been calculated using sensory evoked potentials (SEPs) (Kumpulainen et al., 2012; Mrachacz-Kersting et al., 2007; Muller-Dahlhaus et al., 2008). For spinal PAS involving the upper limbs, defining individual ISIs has been successfully implemented by means of measuring responses to cortical and cervical root stimulation (Taylor and Martin, 2009; Bunday and Perez, 2012). For spinal PAS involving lower limbs, the corresponding method would require lumbar root stimulation. The latency measured to the cervical root stimulation is a parameter that does reflect the overall peripheral motor conduction: even though it does not include the conduction time of spinal nerves in the spinal canal, this short conduction time is often negligible. However, the corresponding latency of response to stimulation at the lumbosacral neuroforamina does not reflect the overall peripheral motor conduction, because it does not include the conduction time of spinal nerves of the cauda equina in the spinal canal (Matsumoto et al., 2013). Moreover, lumbar root stimulation is more feasible to apply when patient is in prone position and is difficult to perform for neurological patients with restricted mobility.

An alternative way to measure conduction times in lower motor neurons is the F-response technique. F-responses are late responses obtained by supramaximal stimulation of motor and mixed peripheral nerves which are recorded over a muscle innervated by the stimulated nerve. F-waves are orthodromic responses produced by a pool of motoneurons which is antidromically activated upon peripheral nerve stimulation. Thus, F-waves reflect conduction to and from the spinal cord. F-response recording is a part of routine electroneuromyographic (ENMG) measurement in the clinic. F-waves are particularly useful for the diagnosis of polyneuropathies at early stage and for the diagnosis of proximal nerve lesions (Mesrati and Vecchierini, 2004).

We wanted to design a clinically feasible spinal PAS protocol for the lower limbs which would consistently induce LTP-like plasticity. To estimate appropriate ISIs on individual basis, we used motor-evoked potential (MEP) and F-response recordings.

2. Materials and methods

2.1. Subjects

8 healthy subjects (5 males; 1 left-handed; age 25–58 years, mean age 41 years) participated in the study (identified as A–H in Table 1). Our study included measurements of peroneal, femoral and tibial nerves. 2 subjects underwent measurements of all 3 nerves, 3 subjects measurements of 2 nerves, and 3 subjects of 1 nerve. If the subject was studied on two or three occasions, there was at least two days between experiments. The study was conducted as a part of clinical trial approved by Helsinki University Central Hospital medical ethical committee. An informed consent was obtained from each subject.

2.2. Estimating the correct timing of stimulation

2.2.1. Neurophysiological measurements

We aimed at obtaining measurements for the calculation of ISIs from exactly the same sites at which TMS and PNS would be given, to achieve maximal precision. Two pairs of identical surface electrodes (Ambu Neuroline 720, Ambu Ballerup, Denmark) for stimulation and recording were attached to the lower limb. Stimulating electrodes for the tibial nerve were placed at medial side of the ankle behind the medial malleolus; for the deep peroneal nerve at the frontal side of the ankle; and for the femoral nerve at the groin lateral to the pulsation of the femoral artery (Liveson and Dong, 1992). The muscles from which F-responses were measured are listed in Table 1. Using the same recording electrodes, we measured both MEPs to navigated TMS (see Section 2.3.2) from relaxed muscles elicited at 110% of resting motor threshold (RMT), and F-responses with a Dantec Keypoint® electroneuromyography device (Natus Medical Incorporated, California, USA). F-, M- and MEP-latencies were recorded (Fig. 1a). F-latency is the conduction time from the distal nerve stimulating electrode to antidromic propagation of activation to the spinal cord, and subsequent orthodromic propagation of activation from the spinal cord to the muscle (Fisher, 2007). Minimal F-latency (the shortest latency in a series of 10 measurements) at supramaximal stimulation (the stimulation intensity at which increasing the intensity does not further produce the increase in F-wave amplitude) was used. M-latency is the time from the stimulating electrode to direct activation of the muscle (Fisher, 2007). The latency of MEP, F-response or M-response was defined as the onset of the response where the signal deviated from the baseline; MEP amplitude was defined as peak-to-peak value.

2.2.2. Calculation of ISI

In most experimental systems, long-term potentiation is induced upon presynaptic spiking preceding the postsynaptic spiking within a specific time window, or upon simultaneous pre- and postsynaptic depolarization (Dan and Poo, 2004). In PAS protocols, the induction of LTP-like plasticity is manifested by the increase in MEP amplitude (Stefan et al., 2000). To test whether F-response recording is suitable for estimating the ISI appropriate for induction of MEP amplitude increase, we chose a protocol which aims at simultaneous pre-and postsynaptic depolarization. The conduction times for lower motor neurons (lCT) and upper motor neurons (uCT) were calculated on the basis of F-, M- and MEP-latencies (Fig. 1a and b). In the calculation of lCT we did not take into account the time for the spread of the activation in the spinal cord in F-wave measurement, since its exact value in humans has never been directly

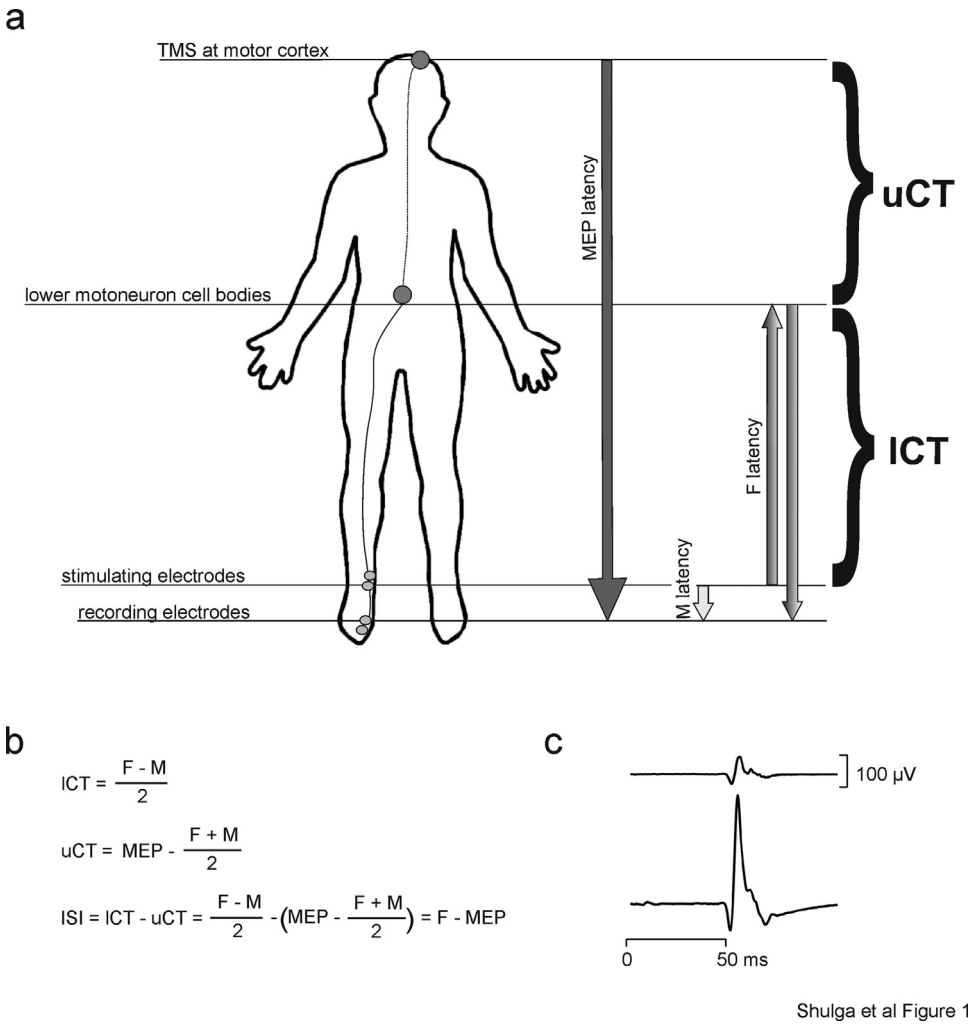

Fig. 1. (a) Schematic representation of the conduction times measurements which were done before paired associative stimulation protocol. Tibial nerve stimulation electrode placing is shown. The recording electrodes are placed over abductor hallucis muscle. uCT – upper motoneuron conduction time; lCT – lower motoneuron conduction time. (b) Calculation of the individual ISI for PAS protocol on the basis of measurements shown in (a). F – F-latency; M – M-latency; MEP – MEP-latency from cortical TMS. (c) Representative MEP before (upper) and after (lower) PAS protocol.

measured and is not known (Fisher, 2007). We adjusted ISIs on the basis of uCT and lCT for the depolarization to arrive simultaneously at the synapse between upper and lower motoneurons as shown in Fig. 1b. Positive ISI value means that peripheral electric stimulation precedes TMS (e.g., in case of 19-ms uCT and 25-ms lCT, the ISI is 6 ms, that is, peripheral stimulation precedes the TMS by 6 ms). It is to be noted that M-latency is irrelevant for the endpoint result, which reduces the impact of possible inaccuracies in measurements.

2.3. Stimulation protocol

2.3.1. Peripheral electric nerve stimulation (PNS)

We delivered PNS at the same electrodes that were used for stimulation of the F-responses, using Dantec Keypoint® electroneuromyography device (Natus Medical Incorporated, California, USA). Peripheral electric stimulation was delivered as 10 Hz trains of 1-ms square wave pulses for 500 ms to depolarize lower motor neurons' somata and dendrites by antidromic motor neuron volleys. The intensity was adjusted to produce a minimal motor response visually observable from muscle (stimulation intensity varied between 1.5 and 15.4 mA, mean 8.5 mA). This type of peripheral stimulation, when paired with TMS, has been shown to induce plasticity at the cortical level (Ridding and Taylor, 2001; McKay et al., 2002; Uy et al., 2003; Castel-Lacanal et al., 2007, 2009) and thus must also induce depolarization at the spinal cord level.

2.3.2. Transcranial magnetic stimulation

Prior to the experiment, the optimal site for cortical TMS was determined individually for each subject and each nerve based on the mapping of the precentral gyrus. The optimal site of stimulation of tibial, peroneal and femoral nerves was the spot by stimulation of which MEPs were most readily elicited from abductor hallucis, extensor digitorum brevis and vastus medialis muscles, respectively. The selected spots were registered in our MRI-guided navigation system (NBS navigation system, Nexstim Ltd, Helsinki, Finland). Navigated TMS (nTMS) displays a dynamic estimate of the stimulus-induced electric field on the patient's individual 3-D brain MRI reconstruction, and enables selection of localized stimulation targets from it. In prospective series of patients, comparison of the preoperative and intraoperative localization of hand motor cortex has given distances of 4–11 mm between nTMS and direct cortical stimulation (Forster et al., 2011; Picht et al., 2011; Krieg et al., 2012; Vitikainen et al., 2013). The navigation system ensured that the TMS stimulation target of the PAS protocol was the same as the stimulation site used for MEP latency and amplitude measurements. TMS was given at 56–100% of stimulator output (110% of resting motor threshold) with eXimia magnetic stimulator (Nexstim Ltd,

Table 1
Results of the measurements for each nerve. Subjects: A–E males. The numerical data is given as mean ± STE, range.

Nerve	Muscle from which MEP/F-response is recorded	Subjects involved	MEP latency before stimulation, ms	F latency, ms	ISI, ms	Peripheral stimulation intensity, mA	TMS intensity, % of stimulator output	MEP amplitude before stimulation, μV	MEP amplitude after stimulation, μV	MEP amplitude potentiation, %
Tibial	Abductor hallucis	A, B, C, D, F	47 ± 1	55 ± 3	8 ± 2	6 ± 1	76 ± 6	365 ± 106	688 ± 173	216 ± 48
			43–51	47–66	4–15	4–11	56–94	113–811	308–1304	132–374
Peroneal	Extensor digitorum brevis	A, B, E, F, G	43 ± 1	46 ± 1	3 ± 1	9 ± 1	72 ± 5	226 ± 36	426 ± 65	190 ± 15
			41–49	42–49	0–5	7–13	56–84	151–368	209–642	139–222
Femoral	Vastus medialis	A, C, E, F, H	27 ± 1	28 ± 1	1 ± 1	10 ± 2	94 ± 4	76 ± 14	117 ± 23	153 ± 12
			25–30	25–30	−2–5	2–15	83–100	49–110	57–175	116–198

Helsinki, Finland). Resting motor threshold was determined as minimal intensity required to produce a MEP over 50 μV in over 50% times in a series of 10 pulses.

2.3.3. Dual stimulation protocol

We tested our protocol by delivering spinal PAS over three large lower extremity nerves: peroneal, femoral and tibial. Both peripheral stimulation and TMS were triggered by Presentation® software (Neurobehavioral Systems Inc., Albany, USA) to guarantee the adjusted ISI. The peripheral electric stimulation train was delivered once every 5 s, each train synchronized with single-pulse TMS, for 20 min. ISIs were calculated for the correct synchronization of TMS with the first pulse of peripheral train. All experiments were applied to left motor cortex/right lower limb. In the experiments which concerned peripheral stimulation alone, no sham TMS was used.

2.3.4. Data analysis

For each experiment, 15 MEPs were recorded before and immediately after the stimulation from relaxed muscles and averaged offline. MEPs amplitude was defined as peak-to-peak value. Statistical significance was evaluated by Wilcoxon signed ranks test or paired samples *t*-test on IBM SPSS Statistics 21 software.

3. Results

After spinal PAS protocol was applied for 20 min, MEP amplitudes were significantly increased compared to the values before the stimulation. Mean MEP amplitudes measured from abductor hallucis muscle were increased to 216 ± 48% of baseline (before stimulation) amplitude ($P = 0.043$ by Wilcoxon signed ranks test; mean ± standard error; $n = 5$ subjects) after PAS involving tibial nerve. Mean MEP amplitudes measured from extensor digitorum brevis muscle were increased to 190 ± 15% ($P = 0.043$ by Wilcoxon signed ranks test; $n = 5$ subjects) after PAS involving peroneal nerve. Mean MEP amplitudes measured from quadriceps femoris (vastus medialis) muscle were increased to 153 ± 12% ($P = 0.043$ by Wilcoxon singed ranks test; $n = 5$ subjects) after PAS involving femoral nerve. The detailed data for each nerve is presented in Table 1. To control the effect of PNS alone, two subjects to whom PAS protocol for peroneal nerve was applied, received on separate day only peripheral stimulation for peroneal nerve without concomitant TMS. After peripheral stimulation only, MEP amplitude in these subjects was 106% (subject A) and 73% (subject B) of the value before stimulation. The mean increase in MEP amplitudes across all PAS experiments was 186 ± 17% (mean ± STE; $n = 15$ experiments/8 subjects; $P < 0.0001$ by Wilcoxon signed ranks test or paired samples *t*-test; Fig. 1c). There were no non-responders: MEP potentiation was induced in all subjects and experiments. There was no significant effect of the PAS protocol on MEP latencies.

In neurological patients, upper and lower motoneuron conduction times can be delayed even by tens of milliseconds. To test what will happen if ISI is not correctly estimated and an error of 10 ms is allowed, we performed additional experiments involving peroneal nerve stimulation with different ISIs in subjects A, E and F. For each subject, we used the same settings (TMS and PNS intensity and site of stimulation) as in the experiments described above, and only ISI was changed. The average increase in MEP amplitude for these 3 subjects with simultaneous pre-and postsynaptic depolarization (calculated with formula F-MEP, Fig. 1) was 170 ± 17% (mean ± STE). If presynaptic stimulus was set to arrive 10 ms before postsynaptic (F-MEP−10 ms), the protocol caused MEP amplitude depression to 75–80% in 2 subjects and had no effect (103%) in one subject, the average MEP amplitude after stimulation in 3 subjects being 86 ± 9% ($P = 0.29$) of the value before stimulation. If presynaptic stimulus was set to arrive 10 ms after postsynaptic

(F-MEP+10 ms), the protocol caused MEP amplitude depression to 77–80% in two subjects, and had no effect in one subject (98%), the average MEP amplitude after stimulation in 3 subjects being $85 \pm 7\%$ ($P = 0.11$) of the value before stimulation.

4. Discussion

Different ISIs in a PAS protocol can result in synaptic potentiation, depression or no effect (Taylor and Martin, 2009; Wolters et al., 2003). We were able to effectively induce LTP-like plasticity by spinal PAS in lower limbs in every experiment in every subject by estimating ISI with F and MEP response recordings using the formula F-MEP for the calculation of ISI. Our protocol induced LTP-like plasticity in the corticospinal tract in all subjects, making it suitable for further development of clinical applications of PAS for lower limbs. Importantly, the protocol was successfully applied to different nerves. To our knowledge, the use of F-response measurement in adjustment of PAS protocol, as well as individually tailored lower limb spinal PAS protocol have not been reported before. We also report for the first time the possibility to apply PAS for the femoral nerve, which can be useful for the future studies of clinical applications of PAS protocols.

Compared to the magnetic spinal root stimulation (Matsumoto et al., 2013), F-response measurement takes into account the conduction time of spinal nerves of the cauda equina in the spinal canal. It is also a more commonly used procedure. An optimal performance of spinal root magnetic stimulation requires a special TMS coil and trained personnel (Matsumoto et al., 2013). Transcutaneous electrical spinal stimulation technique (Troni et al., 2011) enables measuring the conduction times of lower limb nerves at the level of the lumbosacral enlargement and thus could be an alternative to F-response measurement. However, one advantage of the F-response technique is that it allows using the very same electrodes for the F-response and MEP measurements as well as for the subsequent peripheral electrical stimulation. This possibility adds precision to the ISI calculations as well as ensures the correct placing of electrodes for MEP measurement and for the peripheral electrical stimulation during PAS protocol. It also enables easy evaluation of the integrity of the nerve of interest just before the stimulation.

There is an intraindividual variability of F-wave latencies (Fisher, 2007). However, the latency for any particular motor unit potential F discharge is stable (Mesrati and Vecchierini, 2004). We consistently used in all subjects the minimal F-latency which most likely represents fastest conducting motor fibres (Mesrati and Vecchierini, 2004).

It is not completely clear whether conduction velocities in the F-wave are fully representative of the motor nerve as a whole, since it reflects the activity of only a small proportion of motor units. Several studies have suggested that there is no bias in the selection of motor units in the F-wave and that motor units of all sizes do produce F-waves. However, there is a possibility that largest and fastest conducting fibres generate F-waves more readily than the smaller fibres (Fisher, 2007; Mesrati and Vecchierini, 2004). On the other hand, smaller fibres are more excitable than the larger fibres (Watras, 2004) and thus could be more readily activated by TMS upon MEP recording. Even if F-response and MEP recordings do activate different fibres in lower motoneurons, the involvement of faster fibres in F-wave than in MEP would drive the outcome of the (F-MEP) formula towards a smaller value, that is, towards an earlier TMS pulse. It is also possible that while the arrival of ortho- and antidromic volleys occurs simultaneously at the synapses belonging to the fastest lower motoneurons, the postsynaptic depolarization of the slower-conducting lower motoneurons occurs several milliseconds later than presynaptic. LTP-like plasticity is induced either by simultaneous pre- and postsynaptic activation, or by presynaptic depolarization preceding postsynaptic depolarization within a specific time window (Dan and Poo, 2004). Even if a small deviation towards earlier TMS pulse occurs in our method, it is plausible that it fits within this time window allowing the synaptic potentiation to occur. Moreover, if the spinal root magnetic stimulation was used, there would be no guarantee that peripheral nerve conduction velocity elicited by magnetic stimulation matches precisely the conduction velocity elicited by PNS.

5. Conclusions

Although cervical root stimulation has been successfully used for calculation of individualized ISIs in spinal PAS protocols designed for the upper limbs, the lumbar root stimulation is not an optimal procedure as a corresponding technique for the lower limbs, since it does not take into account the conduction time of spinal nerves of the cauda equina in the spinal canal. We show that F-response technique, which is clinically feasible also for neurological patients with impaired mobility, combined with MEP latency recording, provides information sufficient to estimate ISIs that will induce LTP-like plasticity in lower limb spinal PAS. Our results in healthy subjects justify further research of clinical applications of PAS protocols for lower limbs in neurological patients.

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