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Research paper

Omitting TMS component from paired associative stimulation with high-frequency PNS: A case series of tetraplegic patients

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ABSTRACT

Objectives: Earlier studies have shown how chronic spinal cord injury (SCI) patients have benefitted from paired associative stimulation (PAS), consisting of high-frequency peripheral nerve stimulation (PNS) and high-intensity transcranial magnetic stimulation (TMS). Since high-frequency PNS is poorly characterized, its therapeutic effect without TMS should be evaluated. We tested the effect of PNS combined with motor imagery in chronic SCI patients using the same parameters of PNS as in earlier PAS-based studies that also used TMS.

Methods: Five patients with chronic incomplete SCI and tetraplegia received a 6-week treatment of PNS combined with motor imagery to the weaker upper limb. Patients were evaluated with Manual Muscle Testing (MMT), hand function tests (Box and block, grip and pinch strength dynamometry), and spasticity.

Results: There was no significant change in hand function tests or spasticity. MMT values improved significantly immediately after the PNS period (0.59 ± 0.17, $p = 0.043$) and in the 1-month follow-up visit (0.87 ± 0.18, $p = 0.043$). However, improvement of MMT values was weaker than in chronic tetraplegic patients in a corresponding PAS study that used identical PNS stimulation but also included the TMS component omitted here (Tolmacheva et al., 2019a, Clin Neurophysiol Pract).

Conclusions: The lack of effect on functional hand tests with the protocol presented here suggests that the synergistic effect of PNS and TMS components is essential for the full therapeutic effect previously observed with PAS intervention. The moderate improvement of the MMT score suggests the possible usefulness of PNS and motor imagery for some of those tetraplegic SCI patients who have contraindications to TMS.

Significance: These results add to the understanding of the PAS therapeutic mechanism by highlighting the importance of dual stimulation for achieving the full therapeutic effect of long-term PAS with a high-frequency PNS component.

1. Introduction

Spinal cord injury (SCI) is an irreversible condition that leads to weakening of muscle activity in extremities, as well as bladder, intestinal and sexual dysfunction at varying degrees of severity. SCI treatment modalities are limited to maximizing the residual function and independence by rehabilitation, and minimizing the secondary complications (Harnett et al., 2020). As there is no cure for SCI, there is a need for experimental treatments that help SCI patients to improve muscle activity and increase independence. For tetraplegic patients, upper limb function is considered to have the highest priority (Anderson 2004).

There has been a considerable amount of interest in the use of different neuromodulation techniques for SCI rehabilitation (James et al., 2018). For example, paired associative stimulation (PAS) is a combination of transcranial magnetic stimulation (TMS) with peripheral nerve stimulation (PNS), capable of inducing a long-term potentiation (LTP)-like effect in the central nervous system (Stefan et al., 2000). The effects of various PAS protocols have been studied in numerous neurologic conditions both for diagnostic and therapeutic purposes (Suppa et al., 2017). We have recently shown in several works that a modified version of PAS, which consists of high-frequency (100 Hz) PNS and high-

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intensity TMS (Tolmacheva et al., 2019b), is a promising technique for improving muscle activity and function in chronic SCI patients (Shulga et al., 2016a, 2020; Tolmacheva et al., 2017, 2019a; Rodionov et al., 2019, 2020).

In our modified PAS protocol, we have used a combination of high-intensity TMS, high-frequency PNS, and motor imagery (Shulga et al., 2016a; Tolmacheva et al., 2019a, 2017; Rodionov et al., 2019). We hypothesize that simultaneous activation of upper and lower motor neurons by TMS and PNS, respectively, induces the therapeutic plastic response, presumably mainly at the cortico-motoneuronal synapse level. At the same time, motor imagery lowers the motor thresholds and possibly activates secondary motor areas, enhancing the effectiveness of the stimulation. It is important to investigate whether the effect of PAS that we have observed earlier (Shulga et al., 2016a, 2020; Tolmacheva et al., 2017, 2019a; Rodionov et al., 2019, 2020) is indeed based on the combination of all three components, or whether the same therapeutic effect can be achieved with lighter intervention. While the TMS component of PAS is safe and noninvasive, it has some contraindications, such as epilepsy or pacemaker (Klein et al., 2015). On the other hand, the PNS component is safe (Eldabe et al., 2016), relatively cheap and easy to administer after short familiarization, and has fewer contraindications.

The objective of this study was to examine the effects of PNS without TMS, combined with motor imagery in SCI patients with chronic tetraplegia, in order to further investigate the therapeutic mechanism of PAS by examining the effect of high-frequency PNS independent from TMS. We applied this stimulation to five patients with incomplete tetraplegia. We omitted the TMS component, but otherwise the parameters and duration of stimulation were identical to our recent PAS study (Tolmacheva et al., 2019a).

2. Methods

2.1. Patients

The study was approved by the Ethics Committee of Medicine of Helsinki University Hospital. Five patients (2 males, aged 36–68) were recruited using the national spinal cord injury register. Inclusion criteria were chronic incomplete SCI of the cervical region over 18 months since injury, and impaired muscle function in upper limbs. Patient characteristics are listed in Table 1. Conventional rehabilitation continued without any changes throughout the stimulation period. Patient 2 used transcutaneous electrical nerve stimulation (TENS)-treatment irregularly for neck and shoulder pain management, but otherwise no electrical stimulation was used in conventional rehabilitation. Patient 4 used pregabalin for sciatica for two weeks during the stimulations (weeks 4–5 of stimulation), but otherwise no changes in medication were made during the stimulation period. After the stimulation period, neuropathic pain medication for patient 2 was changed from amitriptyline to duloxetine, unrelated to the research project. Patient 3 received a botulinum toxin injection to the spastic right pectoralis major muscle during week 6 of stimulation, unrelated to the research project.

2.2. Study design

Each patient received a total of 22 treatment sessions during the 6-week period: five times a week for the first two weeks, and three times a week for the next four weeks (Table 2). The hand with the lower motor score was selected for treatment. The stimulation lasted 20 min per nerve (240 PNS trains, see below). Three nerves were stimulated during one session (60 min in total). During stimulations, the patients were instructed to imagine the movement produced by the stimulated nerve in the same manner as in our previous PAS studies (Tolmacheva et al., 2019a, 2017; Rodionov et al., 2019). The patients imagined extending the wrist and fingers in radial nerve stimulation, spreading fingers and flexing IV-V fingers in ulnar nerve stimulation (10 min per movement), and opposing I-II-III fingers in median nerve stimulation.

2.3. Peripheral nerve stimulation

PNS was given with a Dantec Keypoint® electroneuromyography device (Natus Medical Inc., Pleasanton, CA) using surface electrodes (Neuroline 720; Ambu A/S, Ballerup, Denmark). Median, radial and ulnar nerves were stimulated. In radial nerve stimulation, the electrodes were pressed against the skin to ensure contact between electrodes and nerves. In patient 5, the radial nerve stimulation was administered anteriorly to the lateral epicondyle of the elbow, while in the other patients the radial nerve was stimulated proximally to the lateral epicondyle. The median nerve was stimulated at the palmar wrist (carpal tunnel) and ulnar nerve at the wrist proximally to the Guyon canal. Anatomically, the stimulation sites were identical to our earlier PAS studies (Shulga et al., 2016a; Tolmacheva et al., 2019a, 2017; Rodionov et al., 2019). Each nerve was stimulated with a pair of electrodes placed along the anatomical course of the nerve, with the cathode placed distally and anode proximally. The electrode adhesive area was 461 mm^2 and gel area 95 mm^2; the distance between the active centers of the electrodes was approximately 24 mm (2 mm between the edges). The stimulus was current controlled.

Stimulation intensity was selected individually by F-response parameters measured with single monophasic 1msec pulses (see 2.4). The stimulation intensity was defined as a minimal intensity required to produce repeatable F-responses to ensure that the stimulation reaches the spinal cord (Tolmacheva et al., 2017,

Table 1
Patient characteristics.

Patient	Gender	Age	Neurological level	AIS	Aetiology	Time since injury	Conventional rehabilitation	Medication affecting CNS, daily dose
1	female	68	C1	D	Intramedullar subependymoma at C1-5 level	6 y 4 mo	Physiotherapy 15x per year	None
2	female	67	C1	D	Intramedullar cavernoma haemorrhage at C1 level	1 y 7 mo	Physiotherapy 1 × week, occupational therapy 1 × week	Amitriptyline 75 mg
3	male	62	C4	D	Traumatic cervical spine injury	3 y 0 mo	Physiotherapy 1 × week, occupational therapy 1 × week	Pregabalin 300 mg, baclofen 75 mg, tizanidin 12 mg, donepezil 10 mg
4	male	36	C3	D	Traumatic cervical spine injury	14 y 8 mo	None	None
5	female	52	C1	D	Intervertebral disc prolapse at C6-7	1 y 11 mo	Physiotherapy 1–2 × week, pool therapy 1 × month	Pregabalin 300 mg

Table 2
Timeline and summary of stimulation protocol. PNS = Peripheral nerve stimulation.

Week 0	1	2	3	4	5	6	7	8	9	10	11
1. evaluation	PNS 5 times a week		PNS 3 times a week				2. evaluation	No stimulation			3. evaluation
	PNS: 20 min × 3 nerves, 100 Hz trains of 6 pulses given every 5 s, PNS intensity defined by F-responses										

2019a; Rodionov et al., 2019). The individual stimulation intensities are presented in Table 3. PNS was administered in 100 Hz trains consisting of 6 monophasic 1-msec square wave pulses, with the train delivered at 0.2 Hz. Earlier, we have used both 50 Hz and 100 Hz PNS in PAS for patients (Shulga et al., 2016a; Rodionov et al., 2020, 2019; Tolmacheva et al., 2019a, 2017), and we have recently shown that 100 Hz is more effective than 50 Hz PNS (Tolmacheva et al., 2019b; Mezes et al., 2020).

In patient 2, a visible muscle contraction was not seen during median nerve stimulation; in patient 5, contact with the radial nerve was challenging and required heavier manual compression which provoked transient pain to the lateral epicondyle area after stimulations. In all other cases, the stimulation caused a visible contraction in the innervated muscles, and adequate stimulation was verified by observing the muscle activation and movement.

The patients described the stimulations as slightly unpleasant during the first sessions, but adapted quickly. Patient 5 chose to use local anesthetic (EMLA) prior to stimulation (Shulga et al., 2016b), while all other patients did not find that necessary. Patient 4 had sciatica in the left lower limb unrelated to stimulations, but the stimulation protocol was executed as planned. The last session of patient 5 was cancelled due to the restrictions that arose from the covid-19 pandemic (in total, 21 of the planned 22 stimulations were done).

2.4. F-response measurements

F-wave minimal intensity was determined with the Dantec Keypoint device using surface electrodes (see above). Stimulating electrodes were placed as for PNS (see 2.3). The recording electrodes were placed on the abductor pollicis brevis (APB) muscle for the median nerve, on the adductor digiti minimi (ADM) muscle for the ulnar nerve, and on the extensor digitorum muscle for the radial nerve. The F-wave latencies and shapes were characterized with 0.2 msec pulses at supramaximal intensity (the intensity starting from which there were no additional increases in F-wave amplitude). Thereafter, the minimal intensity eliciting F-responses was identified using 1-msec pulses.

2.5. Evaluation of the patients

An experienced physiotherapist evaluated the manual motor scores (MMT), sensory score, spasticity and hand function. The physiotherapist was the same as in the Tolmacheva et al. (2019a) patient series, and was not informed that the patients did not receive TMS in this particular series. The physiotherapist was also blinded to the selection of the stimulated hand. F-responses were measured by a physician. Patients were also interviewed for pain, subjective changes in hand function or strength, and adverse effects. All measures were collected in three evaluations, except for F-response measurement, which was used for determination of PNS stimulation intensity before the first stimulation only. The first evaluation was done before the stimulation period, the second one immediately after the 6-week stimulation period, and the third evaluation 1 month after the stimulation period (Table 2). The follow-up measurement of patient 4 was delayed because of patient-related reasons, and was done approximately two months after the last stimulation.

Table 3
Individual intensities of PNS (median, ulnar, and radial nerve) defined by F-response measurement.

Patient	Stimulated Hand	PNS intensities, mA (med, uln, rad)
Patient 1	Right	3.5, 12, 7.5
Patient 2	Left	1.2, 5, 10
Patient 3	Right	3, 20, 8
Patient 4	Right	5.5, 3, 27
Patient 5	Left	5, 4, 6

2.5.1. Motor scores

Manual muscle testing was done for each muscle with a standard testing protocol that targets a single muscle at a time (Hislop et al., 2014). The full list of muscles evaluated in each patient is provided in Table 4. We evaluated the same muscles as in Tolmacheva et al. (2019a). If the MMT value of a muscle was 5/5 at the first evaluation, the muscle was left out from analysis; muscles with values of <5 were followed up. Average MMT scores of the followed muscles were calculated.

2.5.2. Box and block test

A Box and Block test was used for measuring hand function (Platz et al., 2005). The patient grasped one block at a time and moved the block from one compartment to the other for 1 min. The total number of transferred blocks was recorded.

Table 4
Muscles measured in manual muscle testing (MMT). MED = median nerve, ULN = ulnar nerve, RAD = radial nerve. Each muscle examined was given a value of 0–5, where 0 = no activity, 1 = muscle contraction, 2 = full range of movement with gravity eliminated, 3 = full range of movement against gravity, 4 = full range of movement against gravity and moderate resistance, 5 = full range of movement against gravity and maximal resistance.

Elbow	supination, m.supinator longus, m.biceps brachii	RAD
	m.brachioradialis	RAD
Wrist	flexion, m. flexor carpi radialis	MED
	m.flexor carpi ulnaris	ULN
	extension, m. extensor carpi radialis	RAD
	m.extensor carpi ulnaris	RAD
Fingers	PIP II-V m.flexor digit.superficialis	MED
	DIP II-III m.flexor digit.profundus I-II	MED
	DIP IV-V m.flexor digit.profundus IV-V	ULN
	extension, MP II-V m. extensor digitorum	RAD
	abduction, II-V mm. interossei dorsalis	ULN
	m.abductor digiti minimi	ULN
	adduction II-V mm.interossei palmares	ULN
	mm.lumbricales	ULN
Thumb	flexion, MP m. flexor pollicis brevis	MED-ULN
	IP m.flexor pollicis longus	MED
	extensio, MP m.extensor pollicis brevis	RAD
	IP m.extensor pollicis longus	RAD
	abduction, m.abductor pollicis brevis	MED
	m.abductor pollicis longus	RAD
	adduction; m.adductor pollicis	ULN
	opposition, m.opponens pollicis	MED

2.5.3. Grip and pinch strength dynamometry

Pinch dynamometry was performed with a Baseline® Mechanical Pinch Gauge (Fabrication Enterprises Inc., USA). Grip-force evaluation was performed with the Exacta™ Hydraulic Hand Dynamometer (North Coast Medical, Inc., USA). The patients were seated in a chair with their back straight, shoulder adducted, and elbow flexed at 90°. For the key pinch, the pinch gauge was placed on the proximal interphalangeal joint of the index finger and tip of the thumb. For the tip pinch, the gauge was in between the tips of the index finger and thumb. For 3-finger pinch, the gauge was placed between the tip of the thumb and tips of the index and middle fingers. The grip strength was also performed in a free position where patients could generate the best possible grip force, in addition to the standard position. Both hands were tested, and for each test the best result out of three attempts was recorded.

2.5.4. Sensory scores

Sensory scores were done by blinded physiotherapist. Sensory testing of light touch and pin-prick was performed for the upper limbs on C5-T1 dermatomes using the American Spinal Cord Injury Association Impairment Scale (AIS) classification.

2.5.5. Spasticity

An experienced physiotherapist evaluated spasticity with the Modified Ashworth Scale (MAS) from elbow and wrist (extensors and flexors). The MAS scale has been shown to have satisfactory inter-and intra-rater agreement (Meseguer-Henarejos et al., 2018).

2.6. Statistical analysis

Wilcoxon signed-rank tests were performed with IBM SPSS statistics 25 software. The test was selected based on the number of patients. If all post-values are higher than pre-values in five patients, the Wilcoxon signed-rank test inherently produces $p = 0.043$.

3. Results

3.1. Manual muscle testing

After the 6-week period of peripheral nerve stimulation, the average MMT score of the treated hand was higher in all five patients: 0.59 ± 0.17 points (average ± standard error, $p = 0.043$). This increase in motor scores was sustained one month after the last session, and the average increase was 0.87 ± 0.18 points, $p = 0.043$ (Fig. 1; individual MMT values are presented in Supplementary Table 1). The corresponding data for PAS-treated patients in Tolmacheva et al. (2019a) was 1.44 ± 0.37 points ($p = 0.043$) immediately after PAS, and 1.57 ± 0.4 points ($p = 0.043$) at the 1-month follow-up.

In the non-stimulated hand, three of the five patients had abnormal motor scores; the non-stimulated hand showed an increase in MMT score in two out of these three patients (average increase 0.64 post-PNS and 0.67 at the 1-month follow-up).

3.2. Box and Block, grip and pinch strength dynamometry

In all grip strength and pinch tests, as well as the Box and Block test, all five patients had worse values in the stimulated hand compared to the non-stimulated hand. After the 6-week period of PNS, no significant changes at the group level were observed in hand strength or functional tests, neither immediately after PAS nor after the 1-month follow-up. Individual values are presented in Supplementary Table 2. In a corresponding series where the patient received PAS (Tolmacheva et al., 2019a), there were significant increases in all of these test results, except for grip in fixed position, at 1-month follow-up. The results and the comparison to the PAS case series are shown in Table 5.

3.3. Sensory scores

All five patients had diminished values in stimulated hand sensory score at baseline. After the stimulation period, there was no significant change in sensory scores (total light touch sensory score C5-T1 average in stimulated hand: baseline 10.2, post-PNS 9.2, $p = 0.78$; 1-month follow-up 9.6, $p = 0.334$). This is not different from our PAS studies, where we also did not detect significant changes in sensory scores (Tolmacheva et al., 2017; Rodionov et al., 2020).

3.4. Spasticity

Total elbow and wrist extension and flexion MAS scores (0–4 each) were evaluated. There was no major change in spasticity after the PNS period (total MAS score ± 0 in three patients, and +1 in two patients) or in the 1-month follow-up (±0 in two patients, +1 in three patients). There were no significant changes in MAS scale scores in the earlier PAS works either (Tolmacheva et al., 2017; Rodionov et al., 2020).

3.5. Pain

Three out of five patients had posttraumatic chronic pain after SCI. Pain intensity (numeral rating scale 0–10), characteristics and duration per day were obtained by interview before the stimulation period, after the stimulation period, and at the 1-month follow-up. Patient 5 reported slight worsening of pain at the 1-month follow-up in terms of more painful hours per day; this was subjectively related to paused (after the stimulation period and unrelated to the research project) conventional rehabilitation. There was no change in pain intensity or pain characteristics in the other patients after the PNS period. Interestingly, six out of seven patients with neuropathic pain in our earlier PAS works reported that PAS diminished or abolished neuropathic pain or milder unpleasant sensations (Shulga et al., 2016a, 2020; Tolmacheva et al., 2017; Rodionov et al., 2019, 2020).

3.6. Adverse effects and subjective gains

Patient 5 had transient pain after stimulations because of the heavier manual compression that was required for radial nerve stimulation. Otherwise, no adverse effects were observed. Patient 3 reported a slight subjective functional gain in terms of improved ability to use the stimulated hand in daily life, and patient 5 reported slight subjective improvement in hand strength. Other patients did not report any major subjective changes during or after the PNS.

4. Discussion

This study documented a slight increase in MMT values following PNS-treatment, which was sustained during the 1-month follow-up period. However, there was no significant change in functional hand tests (Table 5).

With the exception of omitting TMS from the protocol, this study used exactly the same setup and settings as in the study of Tolmacheva et al. (2019a); PAS with a 100 Hz PNS component and motor imagery was administered to five SCI patients in 22 sessions over the course of 6 weeks. We aimed at recruiting a group of patients with similar age and time since injury characteristics.

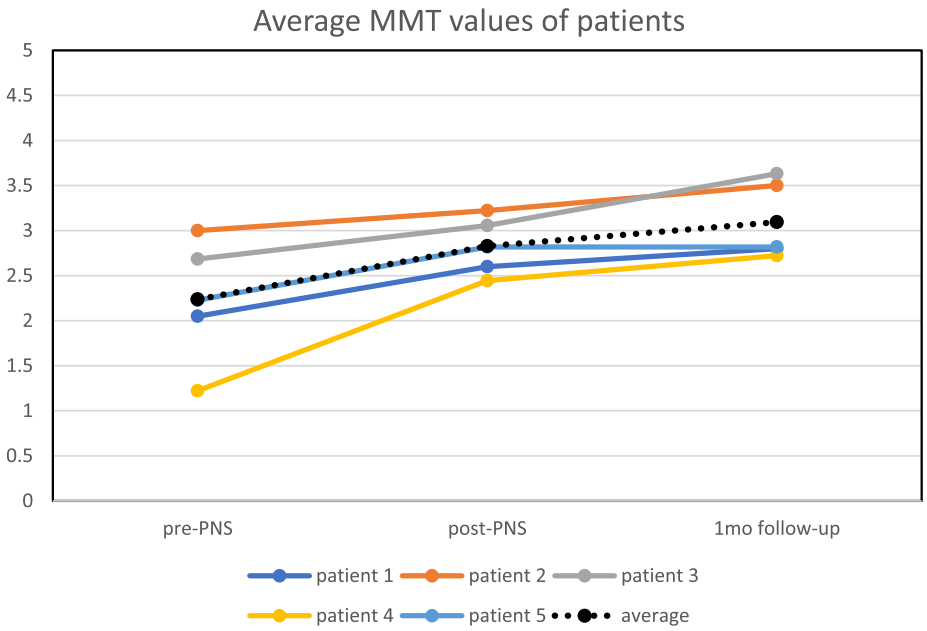

Fig. 1. The average MMT score of all evaluated muscles having a score of <5 at initial evaluation. The average pre-PNS value is 2.23, post-PNS 2.6, and 1-month follow-up 3.09.

Table 5
Stimulated hand average change in % ± standard error (SE) post-PNS and 1-month control. Corresponding values from Tolmacheva et al. (2019a) patient series are provided for comparison.

	Post-PNS average % change (±SE)	Corresponding values from Tolmacheva et al. (2019a)	1 month average % change (±SE)	Corresponding values from Tolmacheva et al. (2019a)
Box and Block	7 (±10)	12 (±2) *	4 (±5)	18 (±4) *
Index pinch	69 (±62)	43 (±16)	136 (±59)	59 (±12) *
Key pinch	−2 (±11)	29 (±9) *	11 (±10)	32 (±10) *
3-finger pinch	55 (±62)	66 (±36) *	102 (±103)	76 (±38) *
Grip, free position	49 (±28)	92 (±45)	47 (±66)	81 (±30) *
Grip, fixed position	25 (±21)	13 (±13)	14 (±30)	10 (±14)

*Designates significant result ($p < 0.05$).

Average age in this study was 57 yrs (36–68yrs) *vs* 56.2 yrs (42–68yrs) compared to Tolmacheva et al. (2019a), and time since injury was on average 5.5 yrs (1 y 7mo–14y 8mo) *vs* 7.1 yrs (1y 3mo–15y 4mo). All patients in both studies had AIS D classification. All hand function tests reported in Table 5, except for grip in fixed position, showed significant improvement at the group level in five patients after PAS at the 1-month follow-up in the earlier study, but such significant increase at the group level was not seen in this study. Also, MMT improvement was smaller in this study than after PAS, both immediately after the stimulation (0.59 ± 0.17 *vs* 1.44 ± 0.37) and in the 1-month follow-up (0.87 ± 0.18 *vs* 1.57 ± 0.4), i.e. under similar conditions, PAS was 184–237% more effective in the earlier study.

This study included two traumatic and three neurologic SCI patients, whereas all five patients in the Tolmacheva et al. (2019a) study were neurologic. However, the MMT values of the two traumatic patients improved 0.39 and 1.22 post-PNS, and 1.00 and 1.50 at the 1-month follow-up. Since the average improvement of these patients was higher than the group average of this patient series, it is unlikely that SCI aetiology could explain the result.

We have previously shown that PAS induced better and more long-lasting improvement than PNS in a study where patients were receiving PAS to one hand, and PNS to the contralateral hand, with the hand selected randomly and evaluated blindly (Tolmacheva et al., 2017). However, in such setup it is impossible to evaluate the effect of PNS alone, since stimulation of one hand might have an effect on the other hand through neurophysiological and behavioral mechanisms. Indeed, in the Tolmacheva et al. (2019a) case series, we have observed some improvements in the unstimulated hand after PAS of the contralateral hand. The comparison of the PNS case series obtained in this work with the PAS case series from Tolmacheva et al. (2019a) yielded similar results as in Tolmacheva et al. (2017), where PNS had similar but much weaker effects than PAS. The difference between PAS case series (Tolmacheva et al., 2019a) and this case series is especially clear in the 1-month follow-up results (Table 5). This is fully consistent with Tolmacheva et al. (2017), where we observed the significant difference between PAS and PNS-treated hands after one month: only the PAS-treated hand group kept improving after the stimulation, while the PNS-treated hand did not. This indicates that PAS, but not PNS alone, can produce stable durable plastic changes in the corticospinal pathway.

Peripheral electrical stimulation in spinal cord injury has been studied more in the form of neuromuscular electrical stimulation (NMES), or more specifically, functional electrical stimulation (FES) which activates muscles performing certain functions. In SCI and tetraplegia, there is preliminary evidence that FES can reduce disability (Patil et al., 2014) and improve muscle strength (de Freitas et al., 2018). However, PNS is different from NMES/

FES, as PNS is set to stimulate the peripheral nerves and results in a mass activation of innervated muscles, as well as antidromic neuronal impulses from stimulation site, which in our protocol is set to reach the spinal cord and corticomotoneuronal synapse (Shulga et al., 2016a; Rodionov et al., 2020, 2019; Tolmacheva et al., 2019a, 2017). The effect of different kinds of PNS variants has been studied in chronic pain management (Nayak and Banik 2018), in post-stroke motor impairment (Carrico et al., 2016) and foremost, in subacute stages of SCI where PNS has been found to be useful in one study (Lee et al., 2015). However, we have been using new PNS parameters in our PAS studies, where pulses are given at 50–100 Hz and the intensity is adjusted individually based on minimal intensity inducing F-responses to ensure the activation of the motor nerves (Shulga et al., 2016a, 2016b; Rodionov et al., 2020, 2019; Tolmacheva et al., 2019a, 2017). This type of PNS has not been previously evaluated for SCI patients on its own.

This study has a small sample size. While MMT scores of the stimulated hand improved after the stimulation in all patients, no statistically significant improvement was observed in hand function or grip and pinch-strength tests. MMT as an indicator might be more sensitive than hand function tests, as MMT reflects the sum of all stimulated muscles, whereas the grip-strength test evaluates a few muscles at a time. The improvements in muscle strength and function were modest and variable, and thus in a small sample size study this has led to a statistically significant result only in the more sensitive test. Also, spasticity, pain and joint stiffness could have had more effect on hand function tests than on MMT.

The moderate improvement in MMT could be a result of several different factors. First, PNS results in repetitive muscle contraction, which may lead to muscle force improvement in injured patient. In studies of NMES stimulation for SCI patients there has been improvement in stimulated muscle strength (de Freitas et al., 2018). Even though the settings in PNS are different from NMES, PNS could also improve MMT values through the same mechanism as NMES, activating the muscles innervated by the stimulated nerve.

Second, there is some evidence to suggest that in SCI, function of peripheral motor axons below the level of the SCI is also compromised (Lin et al., 2007), and peripheral nerve dysfunction may limit the muscle function and response to rehabilitation in addition to the SCI itself (Van De Meent et al., 2010). Short-term peripheral nerve stimulation has been shown to ameliorate axonal dysfunction after SCI in a subacute stage, and it was suggested that peripheral nerve stimulation enhances the responsiveness of motor axons to other rehabilitation therapies by improving the biophysical properties of axonal membrane (Lee et al., 2015). However, in a multicenter study of 345 SCI patients there was no reduction of peripheral motor axon compound muscle action potential (CMAP) amplitude in AIS D incomplete SCI patients after injury, even though CMAP amplitude was decreased in AIS A-C groups (Van De Meent et al., 2010). In this study, all patients were AIS D.

Third, the combination of motor imagery, which is capable of activating M1 (Carrillo-de-la-Peña et al., 2008), with high-frequency PNS might produce a weaker but similar effect as our PAS protocol, leading to synchronous activation of upper and lower motor neurons, respectively. Since the type of PNS that we use does not require exact adjustment of the interstimulus interval between TMS and PNS (Shulga et al., 2016b), it might promote weaker plasticity in the corticomotoneuronal synapse even when combined with motor imagery alone. However, upper motor neuron activation by motor imagery is neither as precisely timed nor as specific as the combination of TMS and PNS where motor cortex stimulation sites and interstimulus intervals are defined precisely (Shulga et al., 2015) and individually. Motor imagery is impossible to monitor continuously in a therapy setup, and it is strongly affected by inter-individual differences in performance. On the other hand, TMS activates M1 predictably and reliably, without any effort required from the patient.

Neither TMS nor PNS components alone have been able to potentiate motor-evoked potentials (MEPs) in our earlier studies in healthy subjects (Shulga et al., 2016b; Tolmacheva et al., 2019b). Although MMT scores improved slightly with PNS alone, direct comparison with other peripheral non-invasive stimulation techniques, such as FES, is needed to establish whether high-frequency PNS without TMS is of clinical value e.g. for those patients with contraindication to TMS.

In summary, even though precise comparison of PAS and PNS would require randomized setting, this study together with our previous results (Tolmacheva et al., 2019a, 2017) suggests that the effect of PAS on upper limb strength and function in chronic tetraplegic SCI patients is superior to PNS alone.

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Declaration of interest

Authors have nothing to disclose.

Author contributions

SA; AJ; PM: Design of research. PM: performed stimulations and drafted manuscript. PM & SA interpreted results. SS: performed measurements. SA and AJ revised and edited manuscript. SA, AJ, PM, SS approved final version of manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cnp.2021.01.004.

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