Spinal Cord Injury: Lessons about Neuroplasticity from Paired Associative Stimulation

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Abstract

Paired Associative Stimulation (PAS) is a non-invasive neuromodulation method with rare cases of adverse effects for the patients with neurological injuries such as spinal cord injury (SCI). PAS is based on the principles of associative long-term potentiation and depression where the activation of presynaptic and postsynaptic neurons correlated in time, is artificially induced. Statistically significant improvement in motor functions after applying PAS has been reported by several research groups. With further standardization of the technique, PAS could be an effective treatment for functional rehabilitation of SCI patients. In this review we have summarized the methods and findings of PAS on SCI rehabilitation to facilitate the readers to understand the potentials and limitations of PAS for its future clinical use.

Introduction

Spinal cord injury (SCI) is a damage to the nerve cells of the spinal cord that relays signals ascending and descending of the spinal cord. Such injuries include bruising, compression, lacerations, and severance of the spinal cord (Kent 2006). While millions of patients are currently paralyzed due to spinal trauma worldwide (Alam and Zheng 2017); according to the World Health Organization (WHO) each year, there are between 250,000 to 500,000 new cases of SCI are addition to this number (World Health Organization 2013). SCI may lead to the loss of motor control and sensation of the body parts below the site of injury. If the injury is in the upper-cervical region, patients could be paralyzed on all four limbs resulting a quadriplegia or tetraplegia. A thoracic or lumbar injury, in contrast, results paralysis to the lower extremity of a patient is called paraplegia.

Based on the severity of injury, SCI are generally classified clinically as complete or incomplete. According to American Spinal Injury Association (ASIA), in a SCI if the brain's functional connections (sensory perceptions and volitional command to and from the brain) to the periphery are completely lost, it results in a clinically complete SCI; whereas if the injury leaves some sensory and/or motor functions below the injured level is defined as incomplete injury (**Figure 1**). According to a recent report, most frequently reported post-SCI neurologic category in the United States is incomplete tetraplegia (39.5%). Complete paraplegia accounts for 22.1%, complete tetraplegia for 21.7% and incomplete paraplegia for 16.3% (Mataliotakis and Tsirikos 2016). It is essential to note that a clinically complete SCI may not be pathologically complete cut of the spinal cord. It is likely due to the fact that the functional connection may have been disrupted by the injury; however, leaving a handful of dormant or non-functional connections around the lesion area. In a study of 88 clinically complete SCI

patients, 74 (84%) patients were found with some anatomical connections across their injury making them ~~incomplete~~ *discomplete* SCI (Sherwood and others 1992). Although, all these patients have been treated as complete paralyzed over the past years, with the advancement of new neuro-rehabilitation techniques there is a hope for them to regain functions (Taccola and others 2018).

A certain degree of recovery for incomplete SCI is possible through extensive physical rehabilitation (Harvey 2016; Wessels and others 2010) ~~exercises~~. Since some nerves remain undamaged, it is possible to strengthen their functionalities. However, some rare cases of recovery from complete SCI has also been reported recently (Choe and others 2013). Current functional rehabilitation treatments for SCI ~~recovery~~ mainly focus on incomplete injuries (Dietz and Fouad 2014; Nas and others 2015). Passive physical therapy has limited rehabilitation effect for patients. To enhance rehabilitation of SCI patients, various neurostimulation treatments, with different types of interventions and their target locations in the nervous system, have been proposed for post-acute treatment (Chari and others 2017). This report discusses about the usage, potentials and shortcomings of one specific modality, called paired associative stimulation.

Paired Associative Stimulation (PAS)

Paired associative stimulation (PAS) is a conjoint stimulation of different pathways or targets (Stefan and others 2000). PAS is based on studies of associative long-term potentiation (LTP) and long-term depression (LTD) (Bi and Poo 1998) where the activation of presynaptic and postsynaptic neurons correlate in time. LTP and LTD are factors affecting synaptic plasticity which play very important role on neuro-rehabilitation and neural repair. LTP and LTD can be artificially induced using PAS technique.

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已註解 [LJY[1]]: Reviewer 2: lack required references. It would be helpful to know what sort of rehabilitation measures were proven to beneficial for population with SCI and how PAS can add to the recovery profile.

Hebbian plasticity, a form of neuroplasticity, refers to the change in neural connection and strength of neural circuits through repeated sequential firing (Caporale and Dan 2008). The persistent pairing of the presynaptic and postsynaptic neurons leads to a strengthening of the synapse that outlasts the period of stimulation. This is also usually referred to as "those fire together, wire together". **Figure 2** illustrates the concept of the sequential firing. Neuron A repeatedly gives spikes which arrive at the synapse after the firing of neuron B, generating a lasting increase in synaptic strength which is also known as LTP. On the contrary, neuron C fires spikes which arrive at the synapse before neuron B, synaptic strength is therefore reduced, also known as LTD. The closer the pre- and post-spikes are to each other in time, the larger the effect of LTP or LTD. However, to initiate or strengthen the association between two neurons, the time between application of two stimuli should be precisely adjusted. The timing of the stimulation, which is also known as interspike interval (ISI), determines the plasticity and further defined as spike time dependent plasticity (STDP). PAS exploits the STDP principals to induce targeted neuroplasticity for functional repair after a neurological injury.

PAS has been applied to investigate several neurological disorders such as amyotrophic lateral sclerosis (Ceccanti and others 2018), stroke (Silverstein and others 2019), depression (Noda and others 2018), schizophrenia (Frantseva and others 2008; Wischnewski and Schutter 2016), etc. However, in this review we focus only on the technique for SCI. Current PAS techniques for SCI recovery can generally be divided into two categories: ***(1) brain and spinal cord stimulation****, and* ***(2) brain and peripheral nerve stimulation***. For the brain stimulation, non-invasive transcranial magnetic stimulation (TMS) is commonly used in human studies (Hallett 2000), while for animal studies intra-cortical or epidural electrical stimulation are used to achieve higher accuracy of targeted stimulation (Mishra and others 2017). For spinal cord and nerve stimulation, several invasive and non-invasive electrical

stimulation techniques are being utilized. Table 1~~Table 1~~ lists recent PAS studies and their target stimulations, parameters and utilized subjects.

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	Stimulation								Treatment Period	Subject	
Publication	Type	Target Limb / muscle	ISI*	Duration	Frequency	ES Magnitude	ES Position	Cortical Stimulation Magnitude			SCI Type
Mishra et al. 2017 (Mishra and others 2017)	• brain-spinal cord; • ES-; • epidural electrodes	Biceps brachii	- 10 ms	5 or 10 min (150 or 300 pairs)	0.2 ms biphasic pulse	1.8 ± 0.2 mA	dorsal root entry zone	ES: threshold for evoking MEP	Single session	Rats (12)	NA
Tolmacheva et al. 2017 (Tolmacheva and others 2017)	• brain-peripheral; • TMS and ES+; • transcutaneous	Upper Limb	customized	20 min per nerve (240 pairs)	50-Hz trains given at 0.2 Hz	Minimal value to evoke F-response	Median, radial and ulnar nerve	TMS: 100% SO	4 weeks (16 sessions)	Human (5)	Incomplete; chronic
Urbin et al. 2017 (Urbin and others 2017)	• brain-peripheral; • TMS and ES+; • transcutaneous	TA	customized	30 min (200 pairs)	200-µs pulses delivered at 0.1 Hz	150 % of M_{max}	CPN	TMS: 100% SO	Single session	Human (18 SCI patients + 23 healthy controls)	Incomplete; chronic
Dixon et al. 2016 (Dixon and others 2016)	• brain-spinal cord • TMS and ES	TA, SOL	customized	40 min (240 pairs)	0.1 Hz	customized	Nerves at thoracic 11 (T11) to lumbar 2 (L2)	TMS: lowest SO that induced repeatable MEPs	1 – 3 sessions	Human (19 healthy subjects)	NA
Shulga et al. 2016 (Shulga and others 2016)	• brain-peripheral; • TMS and ES+; • transcutaneous	Hand: APB, ADM and brachioradialis muscles Foot: AH, EDB/TA muscles	customized	1 hour per limb, i.e. 20 - 30 min per nerve	50-Hz trains of biphasic square-wave pulses for 100 ms	25 mA	• Hand: median, ulnar and radial nerves • Foot: CPN and TN	TMS: 90-100% SO	20-24 weeks	Human (2 SCI patients)	Incomplete; chronic
Bunday et al. 2012 (Bunday and Perez 2012)	• brain-peripheral; • TMS and ES+; • transcutaneous	First dorsal interosseous muscle	customized	17 min (100 pairs)	200-µs pulses delivered at 0.1 Hz	120% of M_{max}	Ulnar nerve	TMS: 100% SO	Single session	Human (19 SCI patients + 14 healthy subjects)	Incomplete; chronic
Roy et al. 2010 (Roy and others 2010)	• brain-peripheral; • TMS and ES+; • transcutaneous	TA	customized	10 - 12 min (120 pairs)	3 pulses at 100 Hz randomly delivered every 5–6 s (0.2 Hz).	customized	CPN and TN	TMS: 120% rest threshold (Mrachacz-Kersting and others 2007)	Single session	Human (22 SCI patients + 16 healthy controls)	Incomplete
Taylor et al. 2009 (Taylor and Martin 2009)	• brain-peripheral; • TMS and ES+; • transcutaneous	Biceps brachii	+ 3 ms	8 min (50 pairs)	0.1 Hz	100% maximal M_{max} (study	Brachial plexus	TMS: Study 1: 66 ± 13% SO;	Single session	Human (15 healthy subjects)	NA

已註解 **[LJY[2]:** Reviewer 2: mention the stimulus intensity (sometimes based on the MEP) that is used to stimulate the cortex.

						1: 75 ± 23 mA; study 2: 82 ± 27 mA)		Study 2: 70 ± 14% SO			
Stefan et al. 2000 (Stefan and others 2000)	• brain-peripheral; • TMS and ES+; • transcutaneous	ABP	- 25 ms	60 min (90 pairs)	200-µs pulse at 0.05 Hz	300% of perceptual threshold (6.0 ± 2.1 mA)	Median and digital nerve (wrist)	TMS: 44.4 ± 6.2% SO	Single session	Human (22 healthy subjects)	NA

***Table* 1** *Studies of paired associative stimulation. ADM: Abductor Digiti Minimi; AH: Abductor Halluces; APB: Abductor Pollicis Brevis; BR: Brachioradialis; CPN: Common Peroneal Nerve; EDB: Extensor Digitorum Brevis; ES+: suprathreshold electrical stimulation; ES-: subthreshold electrical stimulation; ISI: interspike interval; M_{max}: maximal compound muscle action potential; SO: stimulator output; SOL: soleus; TA: Tibialis Anterior; TN: Tibial Nerve; * cortical stimulation before peripheral stimulation is regarded as positive*

PAS timing

ISI determines the outcome of the stimulation. When presynaptic input arrives at the synaptic junction before the postsynaptic firing repeatedly, LTP occurs. In the particular case of sensorimotor recovery via neural plasticity after a SCI, LTP is desired. The ISI needed to be adjusted for each individual such that the afferent and efferent stimuli arrive at the synapse at the right time to induce LTP. Shulga and colleagues described a method to customize ISI for each subject such that the motor evoked potential (MEP) would be maximized for lower-limb rehabilitation (Shulga and others 2015). The derivation of the formula is illustrated in **Figure 3**.

Following equations are for brain-peripheral stimulation.

$$uCT = MEP - (M\ latency + F\ latency)/2$$

$$ICT = (F\ latency - M\ latency)/2$$

$$ISI = uCT - ICT = MEP - F\ latency$$

Here a positive value of ISI indicates stimulation at the cortex before peripheral. A similar approach was used by Dixon and colleagues (Dixon and others 2016) for calculation of ISI in brain-spinal cord stimulation. Instead of F latency, the time between the trans-spinal stimulation and the onset of evoked potential at the target muscle (TEP) was used. A time-constant of 1.5 ms was added to account for the time when signal travels from primary motor cortex (M1) to the corticospinal presynaptic terminal.

$$ISI = MEP - (TEP + 1.5)$$

Depending on the severity of the injury and the number of neural tracts are intact, MEP might not be observable in some patients. Since both of the methods depend on the

recording of MEP, this leads to a potential problem in determining the appropriate ISI. However, there is no other method available which can accurately determine the ISI in SCI patients. This remains an area to be studied. It is worth noting that some early-day studies did not customize the ISI for each subject but still achieved statistically significant results of increased MEP, EMG or force output in short-term response (Stefan and others 2000; Taylor and Martin 2009). These studies carefully chose their ISI such that, given the subjects are healthy with more or less the same speed of action potential, the time of arrival of the presynaptic and postsynaptic stimuli could be roughly estimated. All other human studies reviewed in this report customized the ISI, especially those for SCI patients.

Stimulation Parameters

Since neuroplasticity occurs with repeated stimulation of the neuronal circuitry, it is necessary to repeat paired stimulation in order to induce the changes. One intervention typically consists of more than 100 pairs of stimulation over tens of minutes for each targeted nerve. An animal study showed that increasing the number/duration of PAS extends the time of increased MEP after the stimulation treatment (Mishra and others 2017). However, the claim lacks a solid statistical ground. Instead of using two-way ANOVA, this observation was made upon direct comparison between the percentage-change-against-time graphs of the two stimulation protocol (i.e. results of independent t-test comparing measurement at each time point with the baseline value). Nevertheless, from the Hebbian rule of neuroplasticity, it is expected that the longer the stimulation duration, the longer-lasting the change in neural circuits.

Electrical stimulation (constant current) was used in all the studies listed in Table 1~~Table 1~~. Two popular choices of stimulation pulses are (1) 200-μs duration of pulses delivered

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at 0.1 Hz and (2) 50-Hz trains of biphasic pulses. Both types of pulse were effective in triggering motor response in the subjects. Although no study on pulse shape specifically for PAS has been reported. Deprez and colleagues suggested that interphase gap of stimulation increases stimulation efficiency in rat's brain (Deprez and others 2018). Future studies are required to examine if this increased efficiency can also be observed in SCI patients.

Stimulation intensity varies across studies. The most common practice is to refer to the maximal compound action potential (M_{max}) evoked in the target muscle. Electrical stimulation at 100%, 120% and 150% of M_{max} was used in the experiments reported by Taylor, Bunday and Urbin, respectively (Bunday and Perez 2012; Taylor and Martin 2009; Urbin and others 2017). Tolmacheva and colleagues preferred to use the minimal stimulation magnitude that can evoke F-response (Tolmacheva and others 2017). In contrast, Stefan and colleagues referred to the subject's perception threshold rather than the motor threshold (Stefan and others 2000). In a study, instead of customizing the stimulation intensity for each subject, Shulga and colleagues set a fixed current magnitude of 25 mA for all the subjects (Shulga and others 2016). To the best of our knowledge, there has not been a study comparing the advantages or drawbacks of these stimulation parameters of PAS.

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Brain-Spinal Cord Associative Stimulation

PAS in the form of brain and spinal cord stimulation induces neuroplasticity in healthy human subjects and animals. After repetitive PAS in rat's brain and spinal cord, increase in MEP amplitude and decrease in spinal threshold were observed for at least 30 minutes and 40 minutes, (Mishra and others 2017) (**Figure 4**a-c). With the appropriate ISI, Dixon and colleagues found significant decrease in motor threshold and increase in MEP amplitudes via transspinal-transcortical PAS (Dixon and others 2016).

When paired brain and spinal cord stimulation is performed on rats, MEP increases the most when the stimulation electrodes are put on the dorsal root entry zone (DREZ), contralateral to the side of cortical stimulation (Mishra and others 2017) (**Figure 4**d,e). Positioning of surface electrodes in human subjects is unlikely as precise as in small animals due to the size of regular recording electrodes. This is a disadvantage if a specific structure (for example, the DREZ) is the target of stimulation and surrounding nerves are to be avoided. However, using a larger electrode would ensure the nerve in interest is covered by the electrode and is stimulated. Hence, Dixon and colleagues used a patch electrode of 10 x 5 cm^2 to cover the spine from T11 to L2 with equal coverage on both sides of the vertebrae (Dixon and others 2016).

Although promising, no study of paired brain and spinal cord stimulation on SCI patients has yet been reported. Although similar studies were performed on healthy subjects, their results still have impact on SCI patients. As the studies have shown induction of LTP by paired stimulation of brain and spinal cord, it is expected that the same potentiation can be induced in the residual neural circuitry of SCI patients. As the MEP in patients are likely weaker than the healthy subjects, it may take longer time before the potentiation could be observed.

Brain-Peripheral Nerve Associative Stimulation

Most PAS utilizes brain and peripheral nerve stimulation. Bunday and colleagues conducted a study to show the difference between SCI patients who receive PAS with (1) cortical stimuli which arrive at synapses before peripheral stimuli (STDP group); and (2) peripheral stimuli arrive at synapse before cortical stimuli (control group) (Bunday and Perez 2012). Enhancement in corticospinal transmission and improvement in voluntary motion was only observed in the STDP group (**Figure 5**).

Table 2~~Table 2~~ shows a summary of both long-term (multiple treatment sessions) and short-term (single treatment sessions) effects of brain and peripheral nerve stimulation on several electrophysiological and functional outcome measures. The different measures of treatment outcomes and the results achieved by different research groups are described in this table.

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		Upper-Limb	*Lower-Limb*
Short-Term	MEP	Increased (Bunday and Perez 2012; Stefan and others 2000)	Increased (Roy and others 2010; Urbin and others 2017)
	EMG	Unchanged (Stefan and others 2000) Increased (Bunday and Perez 2012; Taylor and Martin 2009)	Increased (Urbin and others 2017)
	Force	Increased (Bunday and Perez 2012; Taylor and Martin 2009)	
	Functional Test	Improved (Bunday and Perez 2012)	
Long-Term	MEP	Increased (Shulga and others 2016)	Increased (Shulga and others 2016)
	EMG	Increased (Shulga and others 2016)	Increased (Shulga and others 2016)
	Force	Increased (Shulga and others 2016)	Increased (Shulga and others 2016)
	Functional Test	Improved (Shulga and others 2016)	Improved (Shulga and others 2016)
	Motor Scores	Increased (Shulga and others 2016; Tolmacheva and others 2017)	Unchanged (Tolmacheva and others 2017) Increased (Shulga and others 2016)
	Sensory Scores	Unchanged (Shulga and others 2016; Tolmacheva and others 2017)	

Table 2 *Short-term (single treatment session) and long-term (multiple treatment sessions) effects of paired brain and peripheral nerve associative stimulation on motor evoked potential (MEP), electromyography (EMG), and several functional outcomes including force, motor and sensory scores.*

Stefan and colleagues demonstrated one of the very first results of human motor cortex plasticity under PAS via median and digital nerves (Stefan and others 2000). TMS-induced MEP was increased, similar to that observed in brain-spinal cord PAS. A study carried out by Bunday and colleagues on ulnar nerve produced similar results (Bunday and Perez

2012). MEP elicited by both TMS and TES significantly increased within the first 30 minutes after PAS in SCI patients. Increase in MEP was also observed in stimulation targeted at tibialis anterior (TA) muscle (Roy and others 2010; Urbin and others 2017). Long-term of increased MEPs in both upper-limb and lower-limb were observed in a previous study. (Shulga and others 2016). PAS in each limb lasted for at least 10 weeks in the two chronic SCI patients. Increase of MEP could be observed from week 5 to the end of the treatment period. In the follow-up session, 1-month after the last stimulation session, MEP either further increased or remained unchanged. One limitation of this study was, however, that no statistical analysis was done on the results.

According to Setfan and colleagues, single-session PAS with 90 pairs of pulses does not induce any change in the muscle potential caused by voluntary contraction (Stefan and others 2000). Contrary to their study, other studies found increase in voluntary force and EMG in heathy subjects after PAS targeted at the upper arm (Bunday and Perez 2012; Taylor and Martin 2009). Study in the TA muscle in SCI patients also showed increase in EMG of voluntary motion (Urbin and others 2017). This contradiction in the literature has not been explained. However, since the stimulation protocols used in these studies were different in many ways (see Table 1~~Table 1~~ for comparison), it is difficult to conclude which factor contributed to this discrepancy.

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Most studies reported here, followed the International Standards for Neurological Classification of SCI (ISNCSCI) worksheet designed by the American Spinal Injury Association (ASIA) for the scoring for motor function. In the upper limb, improvement in motor scores has been observed ipsilateral to the stimulated nerves (Shulga and others 2016; Tolmacheva and others 2017). PAS gives more significant improvement compared to just peripheral nerve

stimulation (PNS) in chronic patients with motor-incomplete SCI (Tolmacheva and others 2017). No improvement was found in the neck, trunk and lower limbs (Tolmacheva and others 2017), which is reasonable as the treatment was targeted at the upper–limbs only.

In a long-term study of Shulga and colleagues, voluntary motion and EMG was not observable in the SCI patients in the beginning. After several weeks of PAS, voluntary movements were restored and EMG signals were observed in previously paralyzed muscles in both upper-limbs and lower-limbs (Shulga and others 2016). These functions were preserved in the follow-up session, 1-month after the last stimulation session. It was also reported that robust improvements were observed in muscles that were not innervated by the stimulated nerves (Shulga and others 2016).

The scoring for sensory function followed the ISNCSCI Worksheet, which access the subject's sensation level to light touch and pin-prick in different muscles (Association 2015). No significant improvement in sensory perceptions has been found even in long-term studies (Shulga and others 2016; Tolmacheva and others 2017). This, however, does not conclude whether sensory recovery is possible with treatment period longer than 24 weeks.

Limitations and Future Directions

There are still a lot to be done in optimizing and standardizing the protocol for electrical stimulation before PAS can be more widely applied as a clinical practice for SCI rehabilitation (**Figure 6**). As mentioned in this review, stimulation pulse forms and intensities vary across studies. This would create confusion for those who want to apply the treatment. Although some studies may not involve a control group, the functional improvement in patients can be considered as a treatment effect of PAS. Recovery after SCI generally occurs in the first three months after the injury, with occasional cases of further improvement

maximum up to 1.5 years (Fawcett and others 2007). All SCI studies mentioned in this report involved chronic SCI patients of one or more years' post-injury. Spontaneous recovery is considered extremely unlikely for these subjects.

In the study of Roy and colleagues SCI patients were grouped into responders (with MEP increase >20%) and non-responders (with MEP increase <20%) according to their response to a single-session PAS treatment (Roy and others 2010). The authors believe that the problem lies in the "weak activation of the motor cortex by the spared ascending sensory pathways". However, they did not verify the hypothesis with proof from clinical assessments of the injury. Whether increasing the magnitude of electrical stimulation can trigger increase in MEP response remains a question. As shown in the study of Shulga and colleagues, it may take some weeks of treatment before improvements can be observed in the patients (Shulga and others 2016). Whether the non-responders would improve with long-term stimulation is a key question. If the difference between the responders and the non-responders could be found, we will be able to tell which group of patients are more likely to benefit from PAS. It is worth noting that not all studies found PAS successful in inducing MEP response. Besides intrasubject variability, failure could also be due to operation errors in targeting the muscle and inattention of the subject (McGie and others 2014).

One reason for the lack of sensory improvement could be explained from the anatomy and the nature of SCI. Since the impact is usually from the posterior side, disruption to sensory neurons are more severe than that to motor neurons. Ascending sensory neurons are disconnected from their cell bodies in the dorsal root ganglion, hence gradually degenerate through phagocytosis by macrophages (Thuret and others 2006). Sensory signals therefore cannot be passed to the brain. Electrical stimulation, which only strengthen the neural

connections between neighbouring neurons, does not help in regeneration of the sensory axons. On the other hand, motor function can benefit from rerouting of interneurons, which forms new connections between cortical neurons and motor neurons (Thuret and others 2006). Thus, there is a difference between the motor and sensory recovery after PAS treatment.

Comparison between brain-spinal cord associative stimulation and brain-peripheral nerve associative stimulation could not be found in the literature. There are comparatively much less brain-spinal cord associative stimulation studies, no matter in human subjects or in animals. One possible reason could be that electrical stimulation targeting peripheral nerves are less likely to go off-target and stimulate other nerves. Hence, the results can be easily interpreted. On the other hand, brain-spinal cord associative stimulation may be able to help control of the muscles in the trunk, for example, sphincter urethrae muscle which participate in urinary function. Thus, these two treatments should have different targets.

TMS is commonly used in diagnosis of neurological disorders that effect on corticomotor conduction of impulses (Groppa and others 2012) and adverse side-effects rarely occur (Rossi and others 2009). Once the treatment effect is recognized by the field, the work can be easily translated into clinical practice. Current technology does not allow TMS to be used in home rehabilitation. If in the future, TMS designs could be more operator-friendly and more affordable, chances are that care-takers can operate PAS at home daily. More frequent treatment may lead to better recovery.

Conclusions

PAS is a non-invasive treatment with rare cases of adverse side effects for SCI patients. ~~Statistically significant improvement in motor functions has been shown by several groups.~~

Although PAS has widely been studied and shown statistical significant improvement in motor functions through brain-peripheral nerve stimulation, its benefit over brain-spinal cord PAS is unknown. More study has to be done on brain-spinal cord paired stimulation to find its benefits on SCI rehabilitation. With further standardization of the technique, PAS could be a promising treatment for functional rehabilitation of SCI patients.

Conflict of Interests

The authors declare that they have no affiliations with or involvement in any organization or entity with any interest, financial or non-financial, in the subject matter or materials discussed in this manuscript.

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Figure Captions

Figure 1 (Top) Spinal cord injury classification with examples of common incomplete injuries. (Bottom) Primary and secondary injuries in the spinal cord injury cascade, which involves a range of mechanical injury, disruptions, ischemia, inflammation and reactive oxygen species (ROS)-based excitotoxicity. Figure modified from (Doulames and Plant 2016).

Figure 2 (a) The schematic of biological neurons and (b) the spike-timing dependent plasticity (STDP) showing long-term potentiation (LTP) and long-term depression (LTD) according to the time-interval between the pre- and post-spike. Neuron A repeatedly gives spikes which arrive at the synapse after the firing of neuron B, generating a lasting increase in synaptic strength known as LTP. On the contrary, neuron C fires spikes which arrive at the synapse before neuron B, synaptic strength is therefore reduced known as LTD. Reprinted with permission from (Kang and others 2015).

Figure 3 Calculation of interspike interval from motor evoked potential and F latency where uCT stands for upper motoneuron conduction time, and lCT stands for lower motoneuron conduction time. Reprinted with permission from (Shulga and others 2015).

Figure 4 (a) Repetitive pairing of motor cortex and spinal cord stimulation produces lasting (b) increases in motor evoked potential (MEP) and (c) decreases in spinal threshold (ST). (d-e) Percentage increase in amplitude of motor evoked potential (MEP) with paired stimulation on different medio-lateral position of spinal stimulating electrodes. Reprinted with permission from (Mishra and others 2017).

Figure 5 Illustration of (A) the spike time-dependent plasticity (STDP) protocol and (B) the control protocol in brain-peripheral nerve stimulation study. Motor evoked potential (MEP) elicited by transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (TES)

was recorded every ten minutes after the stimulation in spinal cord injury patients and healthy controls (C-F). Error bars indicate the SE. *$p < 0.05$. Reprinted with permission from (Bunday and Perez 2012)

Figure 6 Research directions in brain-peripheral or brain-spinal cord paired stimulation for spinal cord injury rehabilitation. 1) The characteristics of the group of patients who will benefit most from the treatment, e.g. the level and type of injury; 2) the target muscle(s) which can be benefited from the treatment and how they can be targeted; 3) the effective time for intervention after the injury; 4) the duration and frequency of intervention to achieve the best treatment outcome.