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Research Paper

Corticospinal circuit neuroplasticity may involve silent synapses: Implications for functional recovery facilitated by neuromodulation after spinal cord injury

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ABSTRACT

Spinal cord injury (SCI) leads to devastating physical consequences, such as severe sensorimotor dysfunction even lifetime disability, by damaging the corticospinal system. The conventional opinion that SCI is intractable due to the poor regeneration of neurons in the adult central nervous system (CNS) needs to be revisited as the CNS is capable of considerable plasticity, which underlie recovery from neural injury. Substantial spontaneous neuroplasticity has been demonstrated in the corticospinal motor circuitry following SCI. Some of these plastic changes appear to be beneficial while others are detrimental toward locomotor function recovery after SCI. The beneficial corticospinal plasticity in the spared corticospinal circuits can be harnessed therapeutically by multiple contemporary neuromodulatory approaches, especially the electrical stimulation-based modalities, in an activity-dependent manner to improve functional outcomes in post-SCI rehabilitation. Silent synapse generation and unsilencing contribute to profound neuroplasticity that is implicated in a variety of neurological disorders, thus they may be involved in the corticospinal motor circuit neuroplasticity following SCI. Exploring the underlying mechanisms of silent synapse-mediated neuroplasticity in the corticospinal motor circuitry that may be exploited by neuromodulation will inform a novel direction for optimizing therapeutic repair strategies and rehabilitative interventions in SCI patients.

Abbreviations: SCI, spinal cord injury; CST, corticospinal tract; BMIs, brain-machine interfaces; NMDARs, N-methyl-D-aspartate receptors; AMPARs, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors; NHPs, non-human primates; TMS, transcranial magnetic stimulation; CPG, central pattern generator; PSNs, propriospinal neurons; ESS, epidural spinal stimulation; tcSCS, transcutaneous spinal cord stimulation; tDCS, transcranial direct current stimulation; DBS, deep brain stimulation; MEPs, motor-evoked potentials; rTMS, repetitive TMS; BDNF, brain-derived neurotrophic factor; TBS, theta burst stimulation; iTBS, intermittent TBS; cTBS, continuous TBS; TrkB, tropomyosin-related kinase B; mTOR, mammalian target of rapamycin; STDP, spike timing-dependent plasticity.

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1. Introduction

As summarized in previous reviews, spinal cord injury (SCI) leads to severe sensory, motor, and autonomic dysfunction (Boulenguez and Vinay, 2009; Brown and Martinez, 2019; Courtine and Sofroniew, 2019; Guerout, 2021; Kazim et al., 2021) by disrupting descending and ascending nerve fibers between the spinal cord and supraspinal cortical motor circuits that are essential for maintaining many normal physiological functions (Brown and Martinez, 2019; Courtine and Sofroniew, 2019; Prochazka, 2016; Urbin et al., 2019; Walker and Detloff, 2021). SCI can lead to partial or complete loss of functions of the legs (paraplegia) below the site of injury or of all four limbs (tetraplegia or quadriplegia), or even death, depending on the level and severity of the nerve damage (Guerout, 2021; Prochazka, 2016; Walker and Detloff, 2021). Thus, it is described as a "devastating" neurological syndrome, as it results in not only the acute and chronic sensorimotor dysfunction but also significant morbidity and lifetime disability (Brown and Martinez, 2019; Huie et al., 2017; Kazim et al., 2021; Khorasanizadeh et al., 2019). SCI compromises the quality of life in patients by a complex correlation between physical well-being and multiple psychosocial factors as well as environmental influences (Eisdorfer et al., 2020; Fehlings et al., 2017; Tramonti et al., 2014; Urbin et al., 2019). The past decades have witnessed increased prevalence of SCI globally, ranging from 236 to 1298 patients per million individuals (Khorasanizadeh et al., 2019). Statistics from the World Health Organization (WHO) estimate that there are between 250,000 and 500,000 new SCI cases annually (WHO, 2013), and a total of 7,000,000 people are afflicted by SCI worldwide (Prochazka, 2016). The estimated average healthcare expenses and lifetime costs related to SCI are enormous, and average life expectancies of SCI patients are significantly below those of non-SCI individuals (NSCISC, 2021). Therefore, it is imperative for researchers and clinicians to identify underlying mechanisms of SCI to further our understanding of its pathophysiology, which could eventually lead to improvement of therapeutic repair strategies and rehabilitative paradigms (Brown and Martinez, 2019).

Historically, SCI has been considered as "untreatable" as documented in the Edwin Smith papyrus written in the 16th century B.C., which first defined the nonregenerative neurological nature of spinal neurons (Guerout, 2021; van Middendorp et al., 2010). Due to the minimal regenerative capability of neurons in the adult central nervous system (CNS), long-distance axonal regeneration is rarely observed in the adult spinal cord following SCI (Brown and Martinez, 2019; Jack et al., 2020; Kazim et al., 2021). This has long convinced people that the loss of sensory and voluntary motor functions after SCI is permanent, but this assumption has been recently challenged (Behrman et al., 2006; Boulenguez and Vinay, 2009).

1.1. Corticospinal motor circuit plasticity in rehabilitation after SCI

The corticospinal motor circuitry is composed of cortical motor map, corticospinal tract (CST) widely terminating within spinal gray matter, and spinal motor network (Fig. 1). It is primarily responsible for skilled movement control, motor sequences planning and coordination in rodents and mammals (Kazim et al., 2021; Lemon, 2008; Martin, 2016; Oudega and Perez, 2012; Serradj et al., 2017). Among all the components of the corticospinal motor circuitry, the CST function is especially critical for skilled voluntary motor and dexterous forelimb movements (Martin, 2016; Serradj et al., 2017). CST axons are often damaged and fail to regenerate and form functional network below the lesion level, thereby resulting in irreversible locomotor function deficits after SCI (Brown and Martinez, 2019; Eisdorfer et al., 2020; Serradj et al., 2017). Fortunately, as most SCIs in humans are incomplete anatomically (Guerout, 2021; Martin, 2016), significant neuronal reorganization and plasticity in the spared corticospinal motor circuits have been demonstrated in experimental SCI models associated with functional recovery (Brown and Martinez, 2019; Filli and Schwab, 2015; Fouad and Tse, 2008; Kazim et al., 2021; Moxon et al., 2014). This phenomenon, either spontaneous or activity-dependent, is mediated by sprouting of residual CST axons proximal to the injury site (Eisdorfer et al., 2020; Jack et al., 2020; Kazim et al., 2021; Martin, 2016) and serves as a compensatory or regenerative mechanism underlying partial sensorimotor recovery following SCI (Martin, 2016; Walker and Detloff, 2021). The spontaneous neuroplasticity is an intrinsic capacity of corticospinal circuits to adapt and reorganize after SCI, and reflects a compensation for the lost connections between corticospinal neurons and the spinal cord (Filli and Schwab, 2015; Walker and Detloff, 2021). It involves corticospinal axonal sprouting, molecular and morphological modifications at the synapses, and cortical motor map and CST reorganizations (Brown and Martinez, 2019; Kazim et al., 2021; Weidner et al., 2001). This provides a theoretical basis for harnessing the beneficial neuroplasticity of spared nerve fibers to repair the injured corticospinal motor system in order to promote functional recovery following SCI, which has become one of the most important agreements toward developing appropriate neuromodulatory therapeutic approaches (Brown and Martinez, 2019; Courtine and Sofroniew, 2019; Eisdorfer et al., 2020, Guerout, 2021; Kazim et al., 2021; Martin, 2016, Walker and Detloff, 2021).

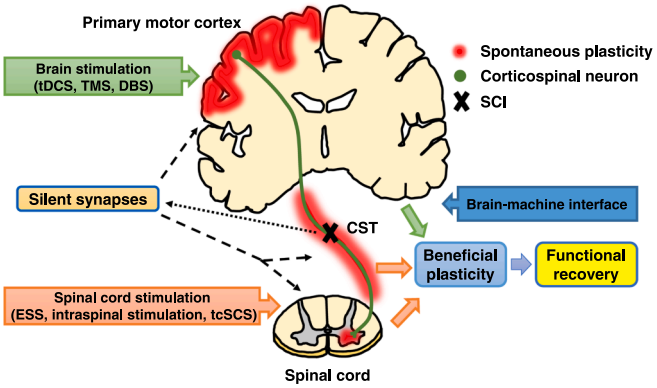

Fig. 1. Presumptive silent synapses in the corticospinal motor circuitry underlie neuroplasticity-mediated functional recovery after SCI. The black dotted line arrow indicates that SCI potentially generates silent synapses. The black dashed line arrows denote that the silent synapses may mediate spontaneous plasticity in different segments of the corticospinal circuitry. The colored arrow blocks represent that brain and spinal cord electrical stimulations can harness beneficial neuroplasticity, respectively. SCI, spinal cord injury; CST, corticospinal tract; tDCS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation; DBS, deep brain stimulation; ESS, epidural spinal stimulation; tcSCS, transcutaneous spinal cord stimulation.

1.2. Neuromodulation for functional recovery after SCI

Neuromodulation is a novel and fast-evolving technology that modifies or modulates neuronal activity by directly stimulating the central and peripheral nervous systems through electrical interfaces (Cajigas and Vedantam, 2021; James et al., 2018). Current neuromodulation strategies that can enhance corticospinal motor circuit plasticity include brain stimulation, spinal cord stimulation, and brain-machine interfaces (BMIs) (Kazim et al., 2021). These methods have been successfully employed clinically in the treatment of several neurological disorders based on the principle of altering neuronal and synaptic properties, which also enables them as promising therapeutic interventions to facilitate functional improvement post-SCI (James et al., 2018; Zheng et al., 2020). Repeated stimulation of spared descending nerve fibers, as well as local motoneuron and interneuron circuits by these modalities can produce functional reorganization leading to regeneration and new neuronal connection formation in spinal sensorimotor networks. The neuroplasticity induced by these techniques plays an essential role in spinal cord neuromodulation for post-SCI rehabilitation (Cajigas and Vedantam, 2021).

1.3. Silent synapses in neurological disorders

Silent synapse usually refers to a glutamatergic synaptic contact where N-methyl-D-aspartate receptors (NMDARs) are stably expressed postsynaptically whereas functional α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) are minimal, thus the regular excitatory synaptic transmission is inadequate (Atwood and Wojtowicz, 1999; Hanse et al., 2013; Kerchner and Nicoll, 2008). These AMPAR-silent synapses are ubiquitously enriched in multiple brain areas in early developmental stages but are progressively eliminated as the CNS matures (Atwood and Wojtowicz, 1999; Dong, 2016). This dynamic regulation of silent synapses occurs in parallel with loss of regenerative capability in developed brain. More importantly, unsilencing of the silent synapses is also activity-dependent (Dong and Nestler, 2014; Gasparini et al., 2000; Hanse et al., 2013), suggesting that it may act as a substrate for Hebbian neuroplasticity (Huang, 2019; Xu et al., 2020) to "rejuvenate" the associated neural circuitry (Dong, 2016; Dong and Nestler, 2014). Hitherto, silent synapses have been implicated in a wide range of neurological diseases, such as neurodevelopmental dysfunctions, addiction, emotional disorders, and traumatic brain injuries etc. (Callsen-Cencic and Mense, 1999; Jing et al., 2017; Lo and Erzurumlu, 2007; Wang et al., 2019, 2021a, 2021b; Xia et al., 2017), suggesting its universal existence under nonspecific pathological circumstances. Consequently, an intriguing question arises: can silent synapses be generated in the corticospinal motor circuitry by SCI and does their unsilencing contribute to the neuroplasticity potentially harnessed by neuromodulation to strengthen the spared corticospinal synaptic connections after SCI?

To address this question, this review focuses on the beneficial neuroplasticity induced by electrical stimulation-based neuromodulatory approaches in the corticospinal motor circuitry after SCI in experimental animals and humans, and discusses one of its potential mechanisms mediated by silent synapse regulation. We start with a brief introduction of the neuroplasticity concept, followed by a summary of neuroplasticity occurring either spontaneously or in an activity-dependent manner in the corticospinal motor circuitry after SCI. Then we offer an overview of the electrical stimulation-induced neuroplasticity in facilitating functional recovery after SCI. Lastly, we review the fundamental features of silent synapses and their roles in CNS development and under various pathological conditions, and propose their potential involvement in the neuroplasticity contributing to strengthening of neurotransmission in the intact corticospinal motor circuits in SCI. The ultimate goal of this article is to provide a prospective insight into one of the neuroplastic mechanisms at the synaptic level through which the corticospinal motor circuitry remodels itself, aiming at opening a novel avenue for future SCI therapeutic and rehabilitative research.

2. CNS neuroplasticity

Neuroplasticity is defined as the ability of the CNS to continuously modify its functional connectivity or anatomical structures in response to external stimuli including experience and injury, thereby establishing new neural pathways and synapses associated with acquired new behavioral patterns (Dunlop, 2008; Walker and Detloff, 2021). These plastic properties have been suggested to underlie learning, memory, and recovery from neural injury (Dunlop, 2008; Kusiak and Selzer, 2013; Lynskey et al., 2008).

Neuroplasticity has also been assumed as an adaptation to the rearrangement of functional connections between neurons in both the brain and the spinal cord, which is a prominent feature recognized during development of the CNS (Dunlop, 2008; Walker and Detloff, 2021). One of the most important attributes of neuroplasticity is the strengthening or weakening of synaptic transmission strength in response to environmental inputs. Accordingly, depending on whether it is transient or long-lasting, neuroplasticity is categorized into short-term facilitation/depression and long-term potentiation (LTP)/depression (LTD), respectively. The well-known LTP and LTD are two mechanisms underlying long-term learning and memory, and they also contribute to motor control circuitry remodeling in the spinal cord under normal and pathological conditions (Walker and Detloff, 2021). The CNS has been reported to display substantial anatomical and functional plasticity following injury. Anatomical neuroplasticity is mediated by synaptogenesis in the sprouting of intact or damaged axons and the dendritic remodeling, whereas functional plasticity is mediated by changes in neuronal excitability, conduction velocity, and synaptic transmission efficacy (namely LTP and LTD). Furthermore, the anatomical neuroplasticity has been suggested to be the result of LTP and LTD. LTP can produce synaptic sprouting or synaptogenesis, whereas LTD induces synaptic pruning and subsequent elimination of the inactive synapses. Synaptogenesis and synaptic pruning both play a significant role in plasticity after injury. These two aspects of neuroplasticity comprises the basis for functional recovery and compensatory behaviors after SCI (Dunlop, 2008; Kusiak and Selzer, 2013; Walker and Detloff, 2021).

3. Spinal neuroplasticity after SCI

In the context of SCI, damage to the corticospinal motor system and peripheral nociceptive stimulation induce substantial neuroplasticity in the motor cortex, CST, spinal gray matter, and afferent fibers, respectively. These neuroplastic changes are typically shown as reorganization of associated neural circuits mediated by axonal outgrowth and sprouting in various animal models and humans (Brown and Martinez, 2019; Filipp et al., 2019; Kazim et al., 2021; Serradj et al., 2017; Urbin et al., 2019).

However, it must be recognized that although some of these neuroplastic forms are beneficial toward functional recovery following SCI, the axonal outgrowth and sprouting can also result in aberrant synaptogenesis and thus are maladaptive or even detrimental (Ferguson et al., 2012; Filipp et al., 2019; Huie et al., 2017; Kazim et al., 2021).

3.1. Detrimental neuroplasticity

Neuropathic pain, autonomic dysreflexia, and spasticity are deleterious consequences of maladaptive neuroplasticity following SCI, which are commonly observed in SCI patients (Ding et al., 2005; Ferguson et al., 2012; Finnerup, 2017; Kazim et al., 2021) and could be exacerbated by increased aberrant axonal sprouting as evidenced in animal models (Filipp et al., 2019; Kazim et al., 2021). Neuropathic pain is triggered by lesions to the somatosensory system, while spasticity results from damage to the upper motor neurons. Interestingly, the central neuropathic pain shares certain common features with spasticity, such as late onset and slow development after SCI, and thus is also named "sensory spasticity", although they may develop independently (Finnerup, 2017). Both neuropathic pain and spasticity involve complicated mechanisms yet in somewhat different neural circuits, including disinhibition from loss of descending pathways or interneurons, neuronal hyperexcitability, ectopic firing, sprouting, receptor upregulation, neuronal deafferentation, glia activation, and neuroinflammation (Finnerup, 2017).

Chronic central neuropathic pain and hyperreflexia/spasticity representing maladaptive sensory and motor plasticity occur spontaneously after SCI, and they can also be produced by peripheral injury or inflammation (Ferguson et al., 2012; Huie et al., 2017). These noxious afferent inputs contribute to induction of the maladaptive forms of neuroplasticity by increasing excitability of neurons in spinal gray matter, i.e. central sensitization of nociceptive pathways in spinal cord (Ferguson et al., 2012; Ikeda et al., 2006; Sandkuhler and Liu, 1998). Accumulating evidence has unraveled mechanistic similarities between the spinal central sensitization and hippocampal LTP (Dougherty et al., 1992; Ji et al., 2003; Ruscheweyh et al., 2011; Tan and Waxman, 2012), a canonical synaptic plasticity model that is believed to be the cellular substrate of learning and memory. Hence, central nociceptive

sensitization has been proposed as a "pain memory" accounting for persistence of the intractable neuropathic pain (Drdla-Schutting et al., 2012; Tan and Waxman, 2012), which is mediated by expression of LTP in spinal nociceptive pathways (Edgerton et al., 2004; Ferguson et al., 2012; Huie et al., 2017). This maladaptive nociceptive plasticity has been suggested to impede adaptive spinal learning by engaging a generalized hyperexcitability and is detrimental to locomotor function recovery after SCI (Ferguson et al., 2012; Huie et al., 2017; Walker and Detloff, 2021).

Findings from research in rodents, non-human primates (NHPs) and humans suggest that subcortical and cortical, especially motor and sensory cortical reorganizations occurring after SCI, are associated with development of phantom limb sensations and neuropathic pain in addition to functional recovery (Filipp et al., 2019; Gustin et al., 2012, 2010; Navarro et al., 2007; Wrigley et al., 2009). A variety of synaptic mechanisms contribute to induction and maintenance of the reorganizational alterations at cortical and subcortical levels after SCI, in which activation of pre-existing functionally silent synapses may play a crucial role (Navarro et al., 2007) that will be discussed in detail in later parts of this review. The unmasking of these latent synapses involves enhanced excitatory neurotransmission both pre- and post-synaptically at the weak connections, and disinhibition of excitatory inputs due to elimination or withdrawal of inhibitory projections after nerve lesion (Filipp et al., 2019; Navarro et al., 2007). Because a considerable portion of cortical neurons are GABAergic interneurons which project widely within the intracortical area, the reduced inhibitory innervation can contribute to a sustained elevated excitation state that could reshape the somatosensory cortex (Chen et al., 2002; Navarro et al., 2007). This finding may explain why hyperexcitability of neurons in the sensory pathways induced by injuries to peripheral and central nervous systems can induce the plasticity in somatosensory cortex associated with neuropathic pain (Filipp et al., 2019; Navarro et al., 2007).

As such, disinhibited excitatory synaptic transmission by reducing GABAergic inhibition post-SCI is of great importance in short-term plasticity induction (Navarro et al., 2007), whereas long-term plastic changes involve more stable functional or structural mechanisms. These mechanisms include intracortical and cortico-subcortical LTP and *de novo* neural circuits formed by axon collateral sprouting, dendritic elongation and branching, and synaptogenesis (Chen et al., 2002; Navarro et al., 2007). Indeed, axonal sprouting in the brainstem and between borders of hand and face representations in somatosensory cortex has been shown to produce phantom limb sensations instead of functional recovery (Filipp et al., 2019; Kaas et al., 2008).

In the case of incomplete CST injury, compensatory axonal outgrowth, arborization, and synaptogenesis of the uninjured CST axons are associated with elevation of relevant growth factors in the denervated spinal gray matter (Maier et al., 2008; Raineteau and Schwab, 2001). In most cases, these factors can promote local sprouting of the interneurons adjacent to the motor neurons deprived of regular corticospinal innervation, thereby developing aberrant synaptic contacts between the interneurons and the somatic membrane of the deprived motor neurons, resulting in formation of abnormal reflex pathways that are necessary for spasticity occurrence (Kazim et al., 2021; Raineteau and Schwab, 2001; Trompetto et al., 2014; Weidner et al., 2001). In addition, brainstem descending motor pathways (reticulospinal, vestibulospinal, tectospinal, and rubrospinal tracts) could be recruited to take over some motor functions impaired by the disrupted CST as well (Kazim et al., 2021; Trompetto et al., 2014). Unlike CST axonal terminals synapsing with the interneurons, which modulate sensorimotor and autonomic functions thereby maintaining a normal muscle tone (Zholudeva et al., 2021), the excitatory synaptic inputs between axonal terminals in these pathways and spinal motoneurons may lead to the exaggeration of the stretch reflex due to loss of inhibitory supraspinal control, thus causing muscle hyperactivity and spasticity (Kazim et al., 2021; Trompetto et al., 2014).

Having explored the negative consequences of spinal neuroplasticity following SCI, its beneficial aspects are actually the basis on which rehabilitation develops and remain the focus of this article. Studies across a variety of different animal models and humans have shown that the beneficial neuroplasticity after SCI is exhibited in a spontaneous or an activity/use-dependent (or so called "treatment-induced") manner (Brown and Martinez, 2019; Filipp et al., 2019; Kazim et al., 2021).

3.2. *Spontaneous beneficial neuroplasticity*

Extensive reorganization of the CNS following SCI, including synaptic plasticity, axonal sprouting, and cellular proliferation, has been found to spontaneously occur along the entire corticospinal neuraxis (Lynskey et al., 2008). In some cases, the neural circuit reorganization may mediate the spontaneous corticospinal function recovery after SCI and thus appears to be adaptive (Dunlop, 2008; Kazim et al., 2021; Lynskey et al., 2008).

Cortical motor map is a topographic map at the primary motor cortex representing movements of distinct body parts that can be typically revealed by transcranial magnetic stimulation (TMS) in humans (Hallett, 2007) and by intracortical microstimulation in animal models (Gioanni and Lamarche, 1985). Mammalian cortical motor maps constantly change their spatial organization in response to external stimuli during development and after motor learning as well as injury (Filipp et al., 2019; Kazim et al., 2021). Cortical motor map plasticity during motor learning has been shown as an increase in the cortical area dedicated to learned tasks among species, which can be induced by acquisition of a skilled behavior (Brown and Martinez, 2019; Kazim et al., 2021). Multiple factors collectively contribute to the motor map remodeling upon motor skill learning, including remodeling of dendritic spine of pyramidal neurons, synaptogenesis, structural and functional modifications of synaptic transmission in cortical neurons, and long-lasting protein synthesis (Brown and Martinez, 2019; Kazim et al., 2021; Kleim et al., 2002, 2003; Monfils and Teskey, 2004; Wang et al., 2011; Xu et al., 2009).

Spontaneous cortical motor map reorganization is found at both cervical and thoracic levels after complete or incomplete SCI, where cortical representations of less-impaired or unaffected movements expand and shift while the representations of more-impaired movements shrink or vanish (Brown and Martinez, 2019; Kazim et al., 2021). Recent findings regarding the cortical motor map plasticity in experimental SCI animal models can be summarized as follows: 1) cortical motor map reorganization after a complete SCI is shown as expanded cortical movement representations for limbs innervated by spinal segments rostral to the injury site, which are less impaired and can replace the cortical territory of representation of deafferented limbs caudal to the injury; 2) spontaneous motor map reorganization of movements caudal to the injury after an incomplete SCI, demonstrated as shrunken cortical motor representations of the injured limbs, can be enlarged by rehabilitative training and is associated with spontaneous locomotor function recovery; and 3) spontaneous cortical motor map plasticity in the uninjured side following a unilateral corticospinal injury can acquire a movement representation of the injured limb (Brown and Martinez, 2019; Kazim et al., 2021). Potential cellular and molecular mechanisms underlying the cortical motor representation plasticity have already been reviewed in this and other articles (Serradj et al., 2017).

Prominent spontaneous reorganization also occurs in the CST after SCI and may contribute to locomotor function restoration as well (Kazim et al., 2021; Oudega and Perez, 2012) (Fig. 1). In rodent SCI models, compensatory sprouting of the CST projecting from the hindlimb sensorimotor cortex into the cervical spinal cord after thoracic spinal cord lesions has been observed. Interestingly, the sprouting is accompanied by shifts of the hindlimb motor map and expansion of the forelimb sensory map overlapping the sprouting hindlimb motor representation, along with formation of a new forelimb corticospinal projection from the rearranged hindlimb cortex into the cervical spinal cord rostral to the lesion (Fouad et al., 2001; Ghosh et al., 2010). The

hindlimb CST axon sprouting into the cervical gray matter has been shown to synapse with long propriospinal neurons (PSNs), which arborize on lumbar motor neurons, thus indirectly relaying supraspinal input to its intraspinal targets (Bareyre et al., 2004; Oudega and Perez, 2012). These results suggest that axotomized hindlimb corticospinal neurons can be integrated into sensorimotor circuits of the intact forelimbs. Furthermore, dorsal CST lesions can cause spontaneous sprouting in its ventral counterpart, while disruption of both prevents the sprouting and consequent functional recovery (Weidner et al., 2001). The spontaneous sprouting of CST axons after experimental SCI has also been identified in NHPs (Mc et al., 1958; Rosenzweig et al., 2010), but has seldom been observed in human studies (Kazim et al., 2021; Oudega and Perez, 2012).

Local spinal circuits exhibit remarkable functional automaticity, i.e. the capacity to perform posture and locomotion control such as standing and stepping, and spontaneous plasticity following a partial or total disruption of supraspinal motor input due to SCI (Edgerton et al., 2004; Kazim et al., 2021) (Fig. 1). Descending supraspinal control, central pattern generator (CPG) activity, and peripheral inputs together are implied in the automaticity generation. Following SCI, the CPG circuitry below the lesion site still maintains functional capability for generating oscillating coordinated motor patterns, which can combine with peripheral sensory input to produce the automaticity (Edgerton et al., 2004). On the other hand, both complete and incomplete SCIs can produce dendritic structure alterations in motor neurons within the local spinal circuitry (Bose et al., 2005; Gazula et al., 2004). These morphological plastic changes dramatically influence synaptic integration and intrinsic electrophysiological properties of spinal neurons, thereby modifying functions of the spinal cord circuitry (Lynskey et al., 2008; van Ooyen et al., 2002). As a result, these spontaneous structural and functional neuroplasticity recruit novel neural pathways that bridge the lesion gap between supraspinal CST axons and their target spinal neurons and potentially underpin spontaneous functional recovery after SCI (Kazim et al., 2021; Lynskey et al., 2008).

The aforementioned spontaneous neuroplasticity can mediate restoration of locomotor functions after SCI by compensating for the lost neural connections, which is nevertheless limited in the absence of therapeutic interventions (Boulenguez and Vinay, 2009). It will be of great clinical importance to understand that this adaptive plasticity of spinal circuitry can be harnessed therapeutically in an activity-dependent manner that is deemed beneficial toward improving functional outcomes post-SCI (Kazim et al., 2021) (Fig. 1).

3.3. *Activity-dependent adaptive neuroplasticity*

Activity-dependent plasticity is one of intrinsic plastic properties of the CNS that is critical to development of the corticospinal circuitry, in which connectional specificity through axonal pruning and outgrowth and synaptic competition among CST terminals is established (Martin, 2005, Martin, 2016). Moreover, substantial evidence has indicated that spinal plasticity shares certain identical cellular and molecular mechanisms with learning and memory in other brain areas (Ferguson et al., 2012). In the case of neurorehabilitation after SCI, plasticity has been defined as the consequence of interaction between physical and neural activities, while the term “activity” is synonymous with rehabilitative physical exercise no matter whether it is voluntary, forced, or task-specific. The activity has been proposed to greatly affect spinal cellular and molecular plasticity (Dunlop, 2008). Physical activity in animal models has been shown to have positive neurorehabilitative and neuroregenerative attributes (Filipp et al., 2019).

Results from plasticity studies indicate that cellular biochemical changes in the spinal cord can be induced activity-dependently and are associated with sensorimotor recovery post-SCI (Edgerton et al., 2004). Plasticity within residual spinal circuits after SCI that can be modified by physical activity tremendously contributes to functional recovery and is under intensive investigation, which will advance our understanding of mechanisms driving activity-dependent plasticity and assist in developing proper rehabilitative strategies (Dunlop, 2008).

The spontaneous plasticity occurring in experimental SCI animals can be directed toward regenerative in an activity-dependent manner by a variety of rehabilitative strategies, including locomotor training, regenerative stem cell replacement therapy, pharmacological manipulation, and/or electrical stimulation etc., even in the absence of supraspinal innervation (Boulenguez and Vinay, 2009; Huie et al., 2017). The plasticity induced by these therapeutic approaches is capable of better facilitating functional recovery after SCI (Brown and Martinez, 2019; Edgerton et al., 2004; Ferguson et al., 2012; Kazim et al., 2021), by guiding either existing or nascent neural connections to reinstate their normal functions (Walker and Detloff, 2021). However, it must be careful to modulate afferent inputs to obtain optimal adaptive structural and functional plasticity while mitigating maladaptive neuroplasticity at multiple levels of the neuraxis (Ferguson et al., 2012; Huie et al., 2017; Lynskey et al., 2008). A combination of these interventions is thought to be more effective than their individual application (Cajigas and Vedantam, 2021; Edgerton et al., 2004).

Locomotor training, as a commonly used rehabilitation therapy, takes advantage of the activity-dependent intrinsic plastic capacity of the CNS to promote functional recovery after SCI. As shown in a few animal models, successful implementation of locomotor training appears largely task-specific, indicating that the training-induced plasticity depends on the repetition of a specific pattern of movement (Boulenguez and Vinay, 2009; Filipp et al., 2019; Huie et al., 2017). It has been assumed that the ability of the spinal cord to learn and perform a specified motor behavior can be altered by related locomotor training regimens, thereby shaping the functional state of the spinal cord. As a result, activity-dependent locomotor training has been demonstrated to facilitate recovery of posture and locomotion after a complete SCI in mammals (Edgerton et al., 2004). Application of this method in the clinic is based on the idea of activating the neuromuscular system below the injury level by motivating the residual neural networks via sensory input, thus inducing adaptive neural output and promoting modifications within the network.

Besides locomotor training, some other therapeutic efforts have been attempted to induce and/or potentiate locomotion by directly modulating the excitability of corticospinal neurons (Huie et al., 2017). Since the main focus of this review is on the role of neuromodulation-induced neuroplasticity in SCI recovery, the electrical stimulation approach will be highlighted and discussed in detail below. Activity-dependent neuroplasticity, as an important basis for functional recovery with physical rehabilitation after an injury to the CNS, can be combined with electrical neuromodulation to further enhance motor function gains after SCI (Cajigas and Vedantam, 2021; Hofer and Schwab, 2019).

4. Neuromodulation-induced neuroplasticity

Given that spontaneous neuroplasticity is extensively expressed in the corticospinal motor circuitry and can be harnessed beneficially to facilitate functional recovery following SCI, multiple neuromodulatory approaches have been applied to take this advantage to promote axonal regeneration, sprouting, and establishment of new functional connections to repair the damaged corticospinal system (Kazim et al., 2021; Martin, 2016). Electrical stimulation, the most prevalent neuromodulatory tool, is currently used clinically to directly activate distinct motoneuron pools or to increase excitability of neuronal networks below the level of injury, thereby facilitating functional recovery in individuals with SCI. However, by virtue of its ability to upregulate axon growth-promoting factors and regeneration-associated genes in injured and spared neurons, electrical stimulation can also be employed at the spinal injury site to promote neuronal outgrowth of the lesioned tissue, at the motor cortex to promote CST axonal outgrowth, and to produce the Hebbian or associative plasticity (Jack et al., 2020). In particular, the Hebbian plasticity mediated by concurrent pre- and post-synaptic

activation can be induced by repetitive, paired, and closed-loop stimulation paradigms (Jack et al., 2020; Jackson and Zimmermann, 2012).

The major electrical stimulation approaches that have been adopted to promote neuroplasticity for functional improvement after SCI contain epidural spinal stimulation (ESS), intraspinal microstimulation, transcutaneous spinal cord stimulation (tcSCS), transcranial direct current stimulation (tDCS), TMS, deep brain stimulation (DBS), and BMIs (James et al., 2018; Kazim et al., 2021) (Fig. 1). These modalities, except for BMIs and closed-loop spinal stimulation, can be classified into open-loop systems, while BMIs are regarded as closed-loop.

Generally, a typical electrical stimulation protocol is applied in open-loop mode to deliver consistent pre-programmed stimulation to the target organs or physiological systems irrespective of their dynamic states. In contrast, closed-loop systems continuously monitor brain or physiological activity, decode relevant neural signals in real time, and modulate such activities by stimulation when certain physiological states or conditions are met (Haeusermann et al., 2021). The stimulation parameters can also be adjusted dynamically in real time to acquire desired state-specific effects while minimizing the undesired side effects, therefore the closed-loop mode is thought to be more dynamic and efficient than the open-loop systems (Haeusermann et al., 2021; Zanos, 2019). The closed-loop neuromodulation systems have been used experimentally to facilitate the activity-dependent adaptive neuroplasticity leading to sensorimotor function restoration after SCI, and might have sustained therapeutic benefits in chronic applications (Jackson and Zimmermann, 2012; Zanos, 2019).

4.1. Spinal cord stimulation

ESS and intraspinal microstimulation are two invasive neuromodulatory approaches commonly used for investigating pattern-generating networks in the spinal cord. In the ESS studies, trains of electrical pulses delivered through electrodes surgically implanted on the dorsal surface of spinal cord dura mater improved both voluntary and involuntary movement in SCI patients (James et al., 2018; Prochazka, 2016). Intraspinal microstimulation is a more specific stimulation mode precisely targeting interneuron and motoneuron pools, which involves direct implantation of electrodes into the spinal cord to stimulate the targeted neuronal populations (Jack et al., 2020). Both epidural and intraspinal stimulation have been suggested to produce beneficial neuroplasticity in the corticospinal motor circuitry, by activating local spinal circuits and/or the CPGs to elicit or facilitate functional movement patterns and morphological reorganization after SCI in human and animals (Jack et al., 2020; Kazim et al., 2021; McPherson et al., 2015; Sharpe and Jackson, 2014). However the underlying mechanisms are not fully determined.

It is generally held that ESS contributes to sensorimotor improvement following SCI by activating large- and medium-diameter afferent nerve fibers within the spinal dorsal roots, especially group Ia/Ib/II proprioceptive and low-threshold cutaneous afferents (Choi et al., 2021; Eisdorfer et al., 2020). Several hypotheses regarding sensorimotor plasticity induced by ESS have been proposed, including strengthening of monosynaptic transmission between proprioceptive afferents and motor neurons, dynamic reorganization of propriospinal circuitry around the lesion site and within the CPGs to promote rhythmic activity and hindlimb coordination, and spatiotemporal integration of the internal model with peripheral afferent inputs to aid error correction and learning of proper motor output (Eisdorfer et al., 2020).

tcSCS is a noninvasive method of passing high frequency current pulses or direct current stimulation through paired electrodes attached on the skin surface over the vertebral column, which activates spinal cord circuitry by modulating functional status of spinal network below injury. Accordingly, it has been shown to enhance voluntary motor drive by increased spinal excitability following sensory afferent stimulation (James et al., 2018; Kazim et al., 2021; Megia Garcia et al., 2020), thereby improving upper limb strength and prehension (Inanici et al., 2018) and volitional stepping-like movements after chronic SCI (Gerasimenko et al., 2015). More recently, it has been shown to attenuate spasticity in SCI patients by enhancing pre- and post-synaptic spinal inhibitory mechanisms (Hofstoetter et al., 2020), which is indicative of its therapeutic potential for antagonizing maladaptive neuroplasticity.

4.2. Brain stimulation

Considering that most SCI cases observed clinically are incomplete, with some descending CST connecting supraspinal and spared spinal motor circuits, an important strategy for promoting recovery of impaired motor functions is to augment and strengthen the connections in the CST. Informed by this knowledge, diverse brain stimulation techniques, either invasive or noninvasive, have been introduced to induce beneficial neuroplasticity in the corticospinal circuitry for functional recovery post-SCI (Gunduz et al., 2017; James et al., 2018; Kazim et al., 2021; Martin, 2016).

tDCS is a noninvasive cortical stimulation approach for modulating cortical excitability by delivering low-intensity direct current through paired electrodes placed over the scalp, and has been widely used in treatment of several neuropsychiatric diseases (James et al., 2018; Kazim et al., 2021; Medeiros et al., 2012). It has been reported to improve functional outcomes in subjects with chronic motor-incomplete SCI by enhancing neural transmission in the corticospinal circuitry (Gomes-Osman and Field-Fote, 2015a, 2015b; Kazim et al., 2021; Raithatha et al., 2016). This tDCS-induced neuroplasticity is associated with modulation of glutamatergic, GABAergic, dopaminergic, serotonergic, and cholinergic activity (Kazim et al., 2021; Medeiros et al., 2012). tDCS is typically applied in combination with locomotor training to promote activity-dependent plasticity (James et al., 2018; Kazim et al., 2021).

Similar to tDCS, TMS is another noninvasive technique that relies on a rapidly changing magnetic field penetrating through the scalp and skull to induce transient electric current pulses in the brain to excite cortical neurons, especially in the superficial cerebral cortex (Gunduz et al., 2017; Kazim et al., 2021; Rossini et al., 2015). A recent study in a rat contusion SCI model, using motor-evoked potentials (MEPs) as a quantification method to assess recovery, suggested that applying TMS to sensorimotor cortex facilitated reorganization and resultant neuroplasticity of the CST leading to behavioral recovery after SCI (Krishnan et al., 2019). So far, most rehabilitative therapies adopt a repetitive form of TMS (rTMS), in which TMS pulses at different intensities, frequencies, and numbers are delivered sequentially to induce LTP/LTD at the corticospinal connections (Gunduz et al., 2017). Application of rTMS on human subjects has yielded some promising results by improving hand functions in tetraplegic individuals, and further research is warranted in larger patient populations to optimize this technology (Alexeeva and Calancie, 2016; Gomes-Osman and Field-Fote, 2015a, 2015b; James et al., 2018; Kazim et al., 2021). Two potential mechanisms conducive to the beneficial reorganization of corticospinal motor circuitry by rTMS have been identified: rTMS-induced gene expression favoring neurite outgrowth (Grehl et al., 2015) and rTMS-induced upregulation of brain-derived neurotrophic factor (BDNF) (Makowiecki et al., 2014).

Theta burst stimulation (TBS) is a patterned form of rTMS that consists of 3-pulse 50-Hz bursts delivered at 5 Hz. Derived from TBS, intermittent TBS (iTBS) involves a total of 600 pulses delivered as 2-s trains of TBS followed by an 8-s interval repeated every 10 s. iTBS was initially demonstrated to most effectively and reliably produce LTP; whereas continuous TBS (cTBS) lasting for 40 s generates LTD-like plasticity in motor cortex (Gunduz et al., 2017; Huang et al., 2005; Rossini et al., 2015). Martin laboratory has uncovered that prolonged motor cortex iTBS, with and without simultaneous trans-spinal direct current stimulation, led to a marked outgrowth of spared CST axons in the lesioned rat spinal cord associated with restoration of skilled locomotor movements (Martin, 2016; Song et al., 2016). Most recently, in an ensuing mechanistic research, Amer et al. in the Martin group have combined motor cortex iTBS with spinal cord multichannel recording to

report that iTBS of the rat motor cortex produced a monosynaptic LTP at the CST-spinal interneuron synapses, as well as an oligosynaptic LTP localized to the corresponding motoneuron pool within spinal gray matter in an activity-dependent manner (Amer et al., 2021).

In contrast, DBS is an invasive approach involving implanting electrodes within targeted areas of cortical and deeper brain structures to stimulate specific nuclei in the regions; this approach is well acknowledged for its capability of ameliorating symptoms in movement disorders such as Parkinson's disease, dystonia, and essential tremor (James et al., 2018; Kazim et al., 2021). Several lines of research have shed light on its application for improving motor function after targeted stimulation of subcortical locomotor regions in rat SCI models (Bachmann et al., 2013; Hentall and Gonzalez, 2012). This effect appears to involve increased synaptic plasticity via enhancing BDNF synthesis and activation of tropomyosin-related kinase B (TrkB)–protein kinase B (PKB/Akt)–mammalian target of rapamycin (mTOR) pathway, which plays pivotal roles in neuronal survival as well as axonal growth and regeneration (Kazim et al., 2021; Wang et al., 2020).

4.3. Brain-machine interfaces

Aside from the open-loop neuromodulatory approaches mentioned above, BMIs are a cutting-edge and most sophisticated closed-loop neuromodulatory modality employed to improve functional outcomes post-SCI, which emerged during the last decades with remarkable progress achieved only until recent years (Jackson and Zimmermann, 2012; James et al., 2018). They utilize electrodes implanted in the motor cortex or surface electrodes attached to the scalp to record the motor intention-related neural signals, which are then decoded by a computer algorithm into commands to drive external prosthetic devices such as a robotic arm (Hochberg et al., 2012) or to reanimate paralyzed limbs using electrical stimulation to resume motor function (Bouton et al., 2016). The observations that BMIs, when combined with rehabilitative training, can enable functional recovery synergistically after SCI suggest that they may harness brain and spinal cord neuroplasticity through activity-dependent and spike timing-dependent plasticity (STDP) mechanisms (James et al., 2018; Kazim et al., 2021; Zanos, 2019). The STDP can be induced by electrical or sensory stimulation that elicits postsynaptic depolarization immediately after the detection of a spontaneous presynaptic action potential (Zanos, 2019), and it reflects change of synaptic strength as a function of the relative timing of pre-and post-synaptic excitations.

5. Silent synapses and post-SCI neuroplasticity

Silent synapses were first proposed as "ineffective synapses" existing between primary afferent sensory fibers and spinal dorsal horn sensory neurons (Kerchner and Nicoll, 2008; Malenka and Nicoll, 1997; Merrill and Wall, 1972; Zhuo, 2000), and they were later reported to distribute in multiple brain regions including hippocampus, neocortex, and, of particular interest in this article, the spinal ventral horn motor neurons (Atwood and Wojtowicz, 1999; Malenka and Nicoll, 1997; Redman, 1990; Zhuo, 2000). As depicted in the previous section, the AMPAR-silent, NMDAR-only synapses are mostly silent due to Mg^{2+} blockade of NMDARs at resting membrane potential, but can be revealed by the NMDAR-mediated current when cells are depolarized to remove the Mg^{2+} blockade. Silent synapses can be generated by insertion of NMDARs into nascent synaptic contacts via synaptogenesis, and they may be unsilenced/activated by coincident pre- and post-synaptic activity to stabilize the synapses (Dong, 2016; Isaac et al., 1995; Kullmann, 2003; Liao et al., 1995). Unsilencing of the AMPAR-silent synapses by this pairing protocol may account for induction of canonical NMDAR-dependent associative LTP, in that requirements for LTP induction such as the correlated pre- and postsynaptic activity, NMDAR activation, postsynaptic calcium concentration elevation, and resultant exocytosis and lateral diffusion of postsynaptic AMPARs are also necessary for the unsilencing (Dong, 2016; Hanse et al., 2013; Lo and Erzurumlu, 2007). Therefore, these evidence suggests that the LTP induction is mediated by NMDAR-dependent AMPAR trafficking mechanisms by recruiting AMPARs into the postsynaptic density (Kullmann, 2003; Malenka and Nicoll, 1999), and highlights the importance of LTP for the activity-dependent generation of functional glutamatergic synapses in synaptic plasticity and neuronal development (Dong, 2016; Durand et al., 1996).

The generation of silent synapses and their subsequent maturation or elimination may act as underlying cellular substrates to redefine anatomical features of relevant neural circuits, leading to profound circuitry remodeling implicated in a variety of neurological disorders. The increased AMPAR-silent synapses due to trauma might result from *de novo* generation, as well as silencing of functional glutamatergic synapses. *De novo* generation of AMPAR-silent synapses in response to injuries may contribute to the aberrant synaptic reorganization, while silencing of functional synapses may be related to the elimination of synapses through AMPAR endocytosis and/or lateral diffusion to extrasynaptic membrane (Dong, 2016; Hanse et al., 2013). For example, unsilencing of the AMPAR-silent synapses converted from functional ones mediates synaptic reorganization in the dorsal horn following transection of peripheral nerves, and this has also been proposed to participate in chronic pain and central sensitization (Lo and Erzurumlu, 2007; Navarro et al., 2007; Zhuo, 2000). The transection can also lead to reactive synaptogenesis with increased number of NMDAR-mediated synaptic inputs and AMPAR-silent synapses in spinal cord (Lo et al., 2011). Recruitment of the AMPAR-silent synapses could dramatically enhance spinal nociceptive transmission underlying development of hyperalgesia and allodynia in chronic pain after the peripheral nerve injury (Navarro et al., 2007; Wall, 1977, 1988; Zhuo, 2000).

As has been discussed elsewhere in this review, mechanisms underlying spinal neuroplasticity resemble those of learning and memory in many aspects, as evidenced by the LTP/LTD induced in spinal sensorimotor circuits (Amer et al., 2021; Garraway and Hochman, 2001; Ji et al., 2003; Ruscheweyh et al., 2011; Rygh et al., 2002). The convergence on the common molecular and cellular pathways for both the spinal plasticity and the LTP/LTD, in particular the activity-dependent mechanisms, implies a potential involvement of silent synapses. *De novo* generation of AMPAR-silent synapses has been suggested to reshape the critical developmental period that is important for activity-dependent synaptic reorganization (Hanse et al., 2013). For this reason, it is compelling to associate the neuroplastic changes in the corticospinal motor circuitry following SCI with the AMPAR-silent synapses generation and recruitment processes. However, evidence supporting SCI-induced silent synapse regulation in the corticospinal motor circuitry has never been discovered as yet.

It is reasonable to hypothesize that SCI generates a considerable number of AMPAR-silent synapses in the corticospinal motor circuitry, either converted from functional synapses that may weaken corticospinal synaptic strength thereby aggravating the impaired motor function, or formed *de novo* for activity-dependent synaptic reorganization. They can be recruited to constitute the spontaneous reorganization and plasticity that can thereafter be harnessed beneficially by, if any, of the electrical stimulation-based neuromodulatory approaches to promote functional recovery post-SCI (Fig. 1). By adopting appropriate electrical stimulation protocols mimicking sensory inputs, peripheral nerve injury-induced maladaptive neuroplasticity in the CNS may be alleviated, while normal synaptic function lost after the injury may be restored by enhanced AMPAR exocytosis, indicating that normal sensory-driven activity can promote AMPAR unsilencing (Hanse et al., 2013; Lo and Erzurumlu, 2007). Moreover, the high-frequency stimulation paradigms inducing LTP applied during the critical period may represent as persistent sensory afferent inputs to promote AMPAR exocytosis, stabilization, and lateral diffusion into postsynaptic membrane leading to functional synaptic refinement and sprouting or synaptogenesis morphologically (Lo and Erzurumlu, 2007).

This hypothesis, although speculative, can be tested by using combined electrophysiological and ultrastructural optical imaging methods *in vitro*, which may deepen our understanding of pathogenesis of SCI and lead to improved therapeutic regimens.

6. Conclusions and perspectives

SCI adversely impacts human health in terms of its devastating neuro-traumatic nature, which leads to the traditional belief that it is incurable, based on the poor regenerative capability that the mature CNS thought to possess. This concept nevertheless needs to be revisited now with the advent of the contemporary neuromodulatory approaches. These approaches have been successfully translated from benchtop studies into clinical applications for sensorimotor function rehabilitation following SCI based on their unique biophysical properties, and they tend to displace the conventional use of medications under certain circumstances. Electrical stimulation-based modalities are robust neuromodulatory tools that have shown impressive therapeutic potential in promoting locomotor function recovery after SCI, supported by abundant evidence from experimental animal and human research.

Corticospinal motor circuitry as an integral part of mammalian CNS primarily dominating skilled voluntary motor functions exhibits opposite forms of neuroplasticity in different manners after SCI, in which the activity-dependent neuroplasticity can be utilized beneficially by electrical neuromodulation to improve functional outcomes. The key point is how to delicately manipulate the balance between detrimental and beneficial neuroplasticity, so as to achieve optimal therapeutic efficacy for locomotor function recovery. The idea of diminishing the undesired maladaptive neuroplasticity while boosting the adaptive neuroplasticity has been well accepted in SCI research community.

It is worth noting that although silent synapse regulation has been extensively accessed in other neurological disorders including pain originating in spinal cord, its role in the corticospinal motor circuit neuroplasticity following SCI has never been examined. Elucidating temporal and spatial characteristics of spinal silent synapse generation and recruitment after SCI will update our current knowledge regarding cellular and circuitry processes underlying the post-SCI neuroplasticity from a new perspective, and will inform a novel direction for optimizing neuromodulatory therapeutic protocols.

Ethics approval

This article does not contain any studies involving animals performed by any of the authors. This article does not contain any studies involving human participants performed by any of the authors.

Informed consent was obtained from all individual participants included in the study.

Conflicts of Interest

The authors have no competing interests to declare.

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