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Enhancing plasticity in spinal sensorimotor circuits following injuries to facilitate recovery of motor control.

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Abstract

After spinal cord injury (SCI) considerable reorganization and plasticity is necessary for behavioural recovery. Plasticity enhancing interventions following SCI are varied and include but are not limited to: targeting the inhibitory environment, growth promoting transcription factors, stem cell therapy, neuromodulation via electrical stimulation and rehabilitation itself. These recent advances have led to extensive axonal growth and reorganization. However, this plasticity is not always accompanied by increased behavioural recovery. Here, we review the most recent literature demonstrating how combining these plasticity enhancing treatments with rehabilitation often leads to functional behavioural recovery. However, only few studies have attempted these combinatorial approaches and more work is needed to determine the type and timing of rehabilitation necessary for recovery.

Introduction

Recovery of sensorimotor and autonomic functions after severe spinal cord injuries (SCI) remains a formidable challenge for clinicians and scientists alike, despite promising progress in recent decades. The diminished or completely severed connections between areas rostral and caudal to a spinal lesion results in several cascades of events leading to an inability to voluntarily control movement. In severe lesions, this ability is never recovered spontaneously. Several of the mechanisms preventing such spontaneous recovery continue to be unravelled. Amongst those, there is reduced expression of growth factors combined with an up-regulation of inhibitory factors to axonal growth and lack of neurogenesis [1], resulting in insufficient compensatory plasticity and permanent loss of function.

Functional recovery following such severe lesions is associated with two major factors: changes in local spinal circuitry caudal to the lesion and/or sparing/reconnection of supra-lesion pathways. Plasticity within the spinal cord (caudal to the lesion) is a key mechanism associated with functional improvements with rehabilitation. Motor recovery following rehabilitation interventions have been associated with changes in neurotrophic factors [2-5], synaptic composition and neurotransmitter availability [6-9], ion channels and membrane receptors [10,11] and changes in motoneurone electrophysiological parameters [12,13]. These have been recently reviewed in Cowan & Ichiyama [14], however, many such mechanisms remain under-investigated.

Promising plasticity enhancing strategies have been developed and trialled pre-clinically in recent years demonstrating some degree of axonal regeneration/sprouting through a lesion and functional synaptogenesis. These have been recently reviewed[15,16]. Invariably, the major outcome measurement to test success of such interventions is recovery of sensorimotor function. Therefore, reorganization of sensorimotor spinal circuits in conditions of enhanced plasticity becomes a central topic of interest. Previously, some of those plasticity enhancing strategies have been combined with rehabilitative interventions such as locomotor training [17-20], cycling [21,22], swimming [23] or reaching and grasping with forelimbs [24]. In this review, we will focus on recent evidence investigating recovery of sensorimotor function and the crucial role rehabilitative interventions play, especially under conditions of enhanced plasticity. We have chosen to subdivide different interventions in broad sub-classes representing specific mechanisms addressed by each intervention.

Inhibitors of axonal growth

Axonal growth (regeneration or sprouting) is limited after SCI, therefore great focus has been given to growth inhibitory molecules such as Nogo-A and chondroitin sulfate proteoglycans (CSPGs). Nogo-A suppression enhances plasticity and results in functional recovery within 2-4 weeks of treatment commencement [25,26], and starting anti-Nogo-A antibody therapy immediately after SCI is more efficient than delaying treatment [27]. The reduced inhibition observed in Nogo-A knockout mice is enhanced by triple knockout of Nogo-A, myelin-associated glycoprotein (MAG) and oligodendrocyte myelin glycoprotein (OMGp) with greater axonal growth and improvements in open field locomotor score while MAG and OMGp deletion alone do not result in beneficial effects [28]. Interestingly, when anti-Nogo-A antibody was simultaneously combined with daily locomotor training a detrimental effect on functional recovery was observed[19]. However, sequential (not simultaneous) administration of anti-Nogo-A antibody followed by intensive treadmill training leads to significant corticospinal tract (CST) fibre sprouting and superior recovery of locomotor function [29]. This was also the case when anti-Nogo-A antibody was combined with intensive rehabilitation in a stroke model [30]. Clearly, the timing of delivery for each intervention is a critical parameter to be considered in combinatorial approaches.

The common signalling pathway for the above inhibitory proteins is the Rho/ROCK pathway. RhoA is a regeneration inhibitor and blocking it with Cethrin increases tissue sparing around the lesion area leading to improvements in locomotor recovery [31]. Different Rho inhibitors are currently being tested in phase 1 clinical trials [32,33]. A recent study found an antibody against LPAR1 (known to activate RhoA) or overexpression of LPPR1 (a negative regulator of LPAR1) leads to enhanced sprouting of intact CST axons and fewer missed steps in the grid walk test following injury [34]. ORL1 signalling can also activate the Rho/ROCK pathway and it encodes the receptor for the opioid related peptide, nociceptin, and leads to increased surface expression of the Nogo receptor Ngr1. After SCI, ORL1 antagonists improved open field locomotor function and 5 hydroxytryptamine (5-HT) fibres sprouting; these effects were further enhanced when ORL1 inhibition was combined with NgR1 deletion [35]. Although statistically significant behavioural improvements were observed (grid-walk test or open field scores), the lesions were less clinically relevant (pyramidotomies or dorsal hemisections) and none of these studies combined a rehabilitation intervention. Nonetheless, they illustrate new directions in this line of promising approaches to enhance axonal sprouting after lesions.

It is well established that CSPG digestion by chondroitinase ABC (ChABC) treatment improves many forms of motor and sensory function after SCI [36-39]. Combining ChABC with intensive voluntary forepaw motor rehabilitation resulted in significant improvements in manual dexterity, while general enriched environment increased ladder walk recovery but had a negative effect on manual dexterity [24]. Only the animals in the combination group achieved significant behavioural improvements. These results were replicated when the combination therapy was initiated four weeks after the initial lesion [40]. Interestingly, unlike the combination with anti-Nogo-A antibody, simultaneous delivery of ChABC and rehabilitation did not result in detrimental effects on behaviour. Noteworthy, when both anti-Nogo-A antibody and ChABC were combined with delayed (4 weeks after injury) reaching training the triple combination showed the greatest recovery [41]. More recently, a peptide mimetic was generated which blocks the dystrophic cone forming action of CSPGs on the receptor protein tyrosine phosphatase σ; this resulted in increased 5-HT fibre sprouting and improved behavioural recovery following SCI [42]. The glial scar itself has long been described to have inhibitory effects on recovery [43]. However, recent studies have shown that eliminating reactive astrocytes resulted in tissue disruption and severe motor deficits [44], and astrocytes seem to be vital for axonal regeneration following SCI [45]. Although, these latest developments have yet to be tested in combination with rehabilitation interventions. In summary, restricting inhibitory factors allows the CNS to achieve some regeneration and behavioural recovery; understanding the type and timing of rehabilitation is vital for future combinatorial treatments.

Transcription factors and growth promotors

A variety of transcription factors (TFs) have been investigated in the context of axonal growth and their various mechanisms have been recently review by Venkatash and Blackmore [15]. Here we focus on those TFs used in recent years to promote axonal growth and/or recovery following SCI. First, it is important to remember that not all axonal growth leads to functional behavioural improvements. Viral overexpression of the TF Sox11 (a TF common in regenerating neurons) increased CST sprouting and reduced axonal dieback following pyramidotomy [46**]. However, Sox11 overexpression was found to actually decrease step accuracy in a horizontal ladder task. Combined deletion of the inhibitors phosphatase and tensin homolog (PTEN) and Nogo led to increased CST regeneration and sprouting but no locomotor or behavioural improvements following dorsal hemisection in a mouse[47*]. Numerous other studies also show increased axonal regeneration with various TFs or other treatments but fail to report relevant motor function data [48-53]. It is now common to observe anatomical axonal sprouting but lack of functional recovery, which suggests such interventions are insufficient. Disinhibiting or promoting growth is a first necessary step, but this needs to be further guided for functional and meaningful synapses to be (re)formed.

Many other studies have found varying (limited) degrees of behavioural improvement along with considerable axonal growth. For example, co-deletion of PTEN and cortical suppressor of cytokine signalling 3 (SOCS3) showed increased CST sprouting and reduced forelimb errors on a horizontal ladder with no open field locomotor differences following unilateral pyramidotomy [54]. Similarly, combined treatment with insulin like growth factor 1 (IGF-1), osteopontin (OPN) and another compound 4-aminopyridine-3-methanol (4-APmeOH) significantly increased CST and 5-HT fibre sprouting and reduced error rate on a horizontal ladder, but had no effect on weight supported stepping or toe dragging following a lateral hemisection [55]. Docosahexaenoic acid (DHA), a well-known neurite growth enhancer[56], led to increased axonal sprouting of the CST and 5-HT pathways and was accompanied by improvement in a pellet reach task following a cervical hemisection [57]. However, no significant lasting improvement in locomotor function was observed. Lastly, epothilone B, a neuron targeting microtubule stabilizing drug, increased axonal regeneration and led to improved gait regularity and stride length and reduced footfall errors following a mild contusion injury in rats [58*]. The inclusion of a contusion injury in the latter study is of notice as none of the other studies above used the more clinically relevant contusion injury model. All of these studies reported extensive axonal sprouting with their manipulations but limited sensorimotor recovery. Importantly, none of those studies introduced a rehabilitative strategy.

Combining rehabilitation with plasticity enhancing treatments is vital if meaningful behavioural recovery is to be achieved. Unfortunately, relatively few groups have done so previously, but such studies have been increasing in numbers more recently (Table 1). Recovery in a reaching task was only significant following a C4 lesion when a CST specific protein kinase A inhibitor was combined with reaching training [59]. Similarly, either an antibody against or a motor cortex specific knockout of the repulsive Wnt receptor RyK increased CST sprouting following a cervical dorsal column lesion in a mouse [60]**. However, cortical reorganization and motor improvements in a reaching task were only seen if animals were given weekly reaching testing, which repeatedly exposed the animals to the task producing a training effect in the long term. Rehabilitative reaching training was also found to be vital with increased reaching accuracy and increased CST sprouting observed when reaching training was combined with a mild inflammatory lipopolysaccharide following a dorsal column lesion [61]**. Lastly, DHA and reaching training were found to have a synergistic effect on CST and 5-HT fibres sprouting, as well as on reaching task, but not grid walk recovery following a C5 lateral hemisection in a rat [62]**. Similar to the anti-Nogo-A antibody and ChABC studies combined with rehabilitation, these studies clearly demonstrate the synergistic effect of rehabilitation with axonal sprouting interventions. It is also clear that further investigation on task specificity of training is necessary as there is not always a positive transfer of the practiced task onto other behavioural outcomes, and in some cases there is even negative transfer [24,63]. At present rehabilitation is routinely delivered as part of treatment for SCI, therefore further research into combining plasticity enhancing treatments with rehabilitative therapy is vital for positive translational results.

Stem cells

Research into stem cell treatments for SCI is a fast evolving field which has expanded greatly in the past 10 years, recently reviewed by Assinck, et al. [64] . Work by Tuszynski and others have demonstrated significant axonal sprouting and synaptic plasticity and in some cases leading to behavioural recovery. Lu et al [65] demonstrated that combinatorial therapies using fibrin matrices and cocktails of growth factors along with neural stem cell (NSC) transplantation have been shown to increase axonal growth and lead to recovery of hindlimb movement following a complete thoracic transection. Using a similar protocol, multipotent NSCs have also been shown to cause CST regeneration following a complete transection. In the same study improvements in a reaching task following a cervical CST lesion were observed[66]. Other types of stem cells have also demonstrated efficacy. Intravenous injection of mesenchymal stem cells has led to open field locomotor recovery and sprouting of the CST and 5-HT fibres following a moderate contusion injury [67]. Similarly, combinatorial NSC therapies have also shown behavioural improvements including combining: a tumor necrosis factor alpha antagonist [68], chondroitinase ABC with various growth factors [69], and histone deacetylase inhibitor [70]. However, a common observation from most of these and previous studies is the significant but modest changes in functional recovery, such as 2-3 more pellets reached or ability to move three joints in the hindlimb extensively in open field but not weight support, etc. Nonetheless, these observations strongly suggest that a window of opportunity is opened by such interventions to modify sensorimotor circuits.

Combination of NSCs and rehabilitative therapies have rarely been used in SCI studies so far. One recent study found open field locomotor improvements only in those mice receiving both treadmill training and NSC transplantation following a thoracic SCI [71]**. While this study shows some promising results, the behavioural improvements seen although significant, were still modest, and more work is needed to achieve fuller recovery. Treadmill training in rats receiving acute NSC transplantation has also been found to increase NSC survival, 5-HT fibres sprouting, and significant locomotor recovery compared to NSC treatment alone [72]*. There is a wide field of research using NSCs for SCI treatment, however much more work is needed to understand their mechanisms of action, how to combine them with rehabilitation, and whether the secretion of growth factors, increased direct or indirect connections, increased myelination or some other mechanisms is leading to the results seen. Underlining our lack of knowledge regarding cell transplantation is a study using olfactory ensheathing glia (OEG) following SCI. When OEG implantation was combined with training, axonal reorganization and initial improvements in plantar stepping were seen; however, retransection of the OEG implanted spinal cord after training resulted in increased locomotor performance [20]. The stem cell and SCI field is growing exponentially, however confounds including animals self-training in cages, and the unknown mechanisms for many of the treatments has led to a paucity of combinatorial treatments which include rehabilitation.

Other treatments

There is some spontaneous axonal regeneration and recovery following SCI. In rodent models after incomplete injury, habitual cage movements (self-training) are critical for functional recovery [73] . Recently some of these changes have been studied using previously unavailable chemogenetic silencing techniques. Spared dorsolateral CST sprouting [74], reticulospinal sprouting onto propriospinal neurons [75,76], and a new rubro-raphe pathway [77] have all been implicated in motor recovery following incomplete SCI. Some of the studies below attempt to tap into existing or spared circuitry in order to overcome behavioural deficits, either via changes in local spinal or in supraspinal connectivity.

An example of changing excitability of local spinal circuitry is spinal stimulation (direct or indirect) which is often combined with training to increase plasticity and result in step kinematics improvements [78,79]. A recent study combining epidural stimulation and 5-HT agonist treatment along with locomotor training was shown to increase locomotor recovery and movement following a severe contusion injury [80]. This recovery was shown to be mediated by a cortico-reticulo-spinal pathway which only appeared following combinatorial treatment. Similarly, electromagnetic spinal stimulation and/or NT-3 treatment were only found to improve grid and beam walking accuracy when combined with exercise training following a thoracic contusion [23]. These neuromodulation interventions have received considerable interest and recent results from human experiments have demonstrated their vast potential to recover standing, stepping and voluntary control of movement even after clinically complete lesions [81-85].

5-HT agonists have also been demonstrated to engage spinal circuitry following severe lesions. A recent study combined 5-HT treatment along with passive cycling, and treadmill training demonstrating increased cortical reorganization leading to an increase in open field locomotor function and increased weight supported steps following a complete thoracic transection in a rat [86]. Increased cortical reorganization was seen in the above combinatorial therapy and loss of this reorganization led to elimination of the locomotor recovery previously observed. These results certainly demonstrate positive changes in circuitry, but the fact that behavioural tests were only completed after administration of 5-HT agonists confounds clear interpretations of these findings. Nonetheless, the key role played by rehabilitation in such combinatorial interventions is clearly demonstrated. Another very clear example of the need for rehabilitative therapies was observed using acute intermittent hypoxia (AIH) in a unilateral cervical CST lesion in a rat [87]. AIH only improved horizontal ladder performance if combined with task specific ladder training.

One interesting study used a chloride potassium symporter (KCC2) agonist to inhibit inhibitory interneurons and therefore allow new relay pathways to be active; these new pathways led to an increase in open field locomotor scores and some plantar stepping following a staggered lesion [88]. Other research on KCC2 has implicated a reduction in this membrane transporter as driving maladaptive nociceptive plasticity [89] and development of spasticity [10] following SCI.

Other treatments to induce axonal growth after SCI with accompanying motor recovery include epigenetic modulation using histone deacetylase inhibitors [90] demonstrating modest (1 point in BMS scale or beam walk) behavioural recovery [91], axonal growth [92], or anti-inflammatory actions [93]. Further anti-inflammatory targets include IL-4 and IL-10 as increasing these cytokines leads to some behavioural improvements following SCI [94,95]. Self-training or 'spontaneous recovery' induce some compensatory sprouting and rerouting of connections. It remains to be determined whether targeted rehabilitation and electrical, chemical, or physiological stimulation could further enhance this compensation leading to fuller recovery.

Final Remarks

There has been a great expansion in the amount of plasticity enhancing interventions used to treat SCI. The Nogo-A and CSPG fields have both been studied extensively with still new downstream and related pathways being found. These have been combined with rehabilitation in many different ways with variable results depending on type and timing of rehabilitation [96]. A substantial variety of TFs, growth factors, and other plasticity enhancing treatments have been found and tested in SCI in recent years; however, relatively few of these have been combined with rehabilitation and of those even fewer use the more clinically relevant contusion injury model. Stem cell treatments along with growth factor cocktails and fibrin based hydrogels are an increasingly studied field. Again, rehabilitative therapy is rarely used alongside stem cell treatments, but there is great potential for combinatorial treatments in this field. Other extensively studied plasticity enhancing interventions include spinal and cortical stimulation, acute intermittent hypoxia, HDAC inhibitors, mild inflammation, and exercise by itself. Many of these have been combined with task specific rehabilitation for synergistic effects on plasticity and behavioural recovery.

The evidence so far strongly suggests that in conditions of enhanced plasticity following lesions to the spinal cord, rehabilitative interventions should be introduced to promote recovery of function and avoid development of maladaptations (Figure 1). Unfortunately, there is very little evidence as to the specific mechanisms associated with such processes. We have recently demonstrated that anti-Nogo-A antibody significantly increases muscle spindle Ia afferents in the spinal cord, but locomotor training significantly reduces those levels [29]. Modulation of Ia afferent activity seems to be a critical component for recovery of locomotor function [97,98] and spasticity [99]. Clearly, further understanding of such mechanisms are vital targets of future studies.

It is important to remember that enhanced plasticity does not necessarily translate into functional recovery. Maladaptations such as development of spasticity, neurogenic pain, allodynia, detrusor dissynergia, autonomic dysreflexia, etc., have also been reported. Unfortunately, such effects are rarely reported although some studies have addressed a few of these issues directly. Recovery of sensorimotor function after SCI will depend greatly on further understanding circuitry within the spinal cord controlling movement. Locomotor training and exercise alone have previously been shown to facilitate functional recovery repeatedly. A recent study showed that voluntary wheel running increased

CST and 5-HT fibres sprouting and led to improvements on the horizontal ladder and in rotarod tests following a thoracic dorsal hemisection in a mouse [100]*. Investigations enhancing axonal sprouting/regeneration fail to determine which connections, if any, are reestablished. At this stage indiscriminate sprouting of CST or 5HT fibres are correlated with functional motor recovery. However, it remains to be determined how exactly the interplay between afferent, descending and spinal interneuronal networks are best manipulated to achieve functional recovery.

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Annotated

*of special interest

**of outstanding interest

** Tashiro et al 2018
The combination of training and NSC transplantation caused increased below lesion levels of pGAP43, which is specifically found in regenerating, but not intact, axons. Combinatorial treatment also increased Synapsin-1 and Vglut-1 boutons and increased the number of Gad65+ cells which provide some of the inhibitory control needed for central pattern generator function. Motor evoked potential (MEP) amplitude and duration were increased and MEP latency was decreased most in the combinatorial treatments.

** Wang et al 2015
Sox11 is a TF found in many regenerating neurons but not the CST. Overexpression of sox11 in the CST via an AAV increased sprouting and axonal growth but reduced behavioural outcomes following a pyramidotomy or a dorsal transection.

*Geoffroy et al., 2015
Combined PTEN and NOGO deletion in a T8 dorsal hemisection. No synergistic effects on axonal sprouting with some increased axonal regeneration, however no behavioural improvements were observed.

*Ruschel et al., 2015
Epothilone B, a neuron targeting microtubule stabilizing drug increased axonal regeneration and specifically serotonergic sprouting. Fibrotic scarring was reduced as Epothilone B cause fibrotic growth cones to collapse while stabilizing neuronal growth cones, there was a reduction in both CSPGs and dystrophic growth cones following injury and treatment. Some behavioural improvements such as reduced footfalls in the ladder test, increased stride length and gait regularity were seen following the mild (150kdyn) thoracic contusion injury. The inclusion of a contusion injury marks it out as very few studies see behavioural improvements using the more clinically relevant contusion.

**Hollis et al., 2016
WNT receptor Ryk knockout or an antibody against Ryk using C5 dorsal column lesion increased CST sprouting in the knockout, but no functional recovery was observed unless the animals were given task

specific training. Cortical changes occurred where hindlimb areas took over controlling forelimbs, but this reorganization only happened if trained, otherwise antibody or knockout did not improve outcomes.

**Liu et al., 2017b
DHA and reach training were found to have synergistic effects on CST and serotonergic sprouting following a C5 lateral hemisection in a rat model. The combinatorial effects of DHA with training were significantly greater than either treatment alone, with increased CST and serotonergic sprouting along with improvements in a reaching task.

**Torres-Espin et al., 2018
Mild inflammation induced by lipopolysaccharide combined with training following a C4 dorsolateral quadrant lesion caused increased CST sprouting and improved reaching task ability following rehabilitation. Training increased recovery in a dose dependent manner with more training increasing behavioural results.

*Hwang et al., 2014
Treadmill training in rats receiving acute NSC transplantation one week after a moderate to severe thoracic contusion injury. An increase in NSC survival, serotonergic sprouting, and behavioural outcomes were observed when treadmill training was combined with NSC implantation compared to either training or NSC treatment alone.

*Loy et al., 2018
Voluntary wheel running alone led to increased CST and serotonergic sprouting and enhanced behavioural recovery on the ladder rung and rotarod tests following a thoracic dorsal hemisection in a mouse.

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Figure Legend

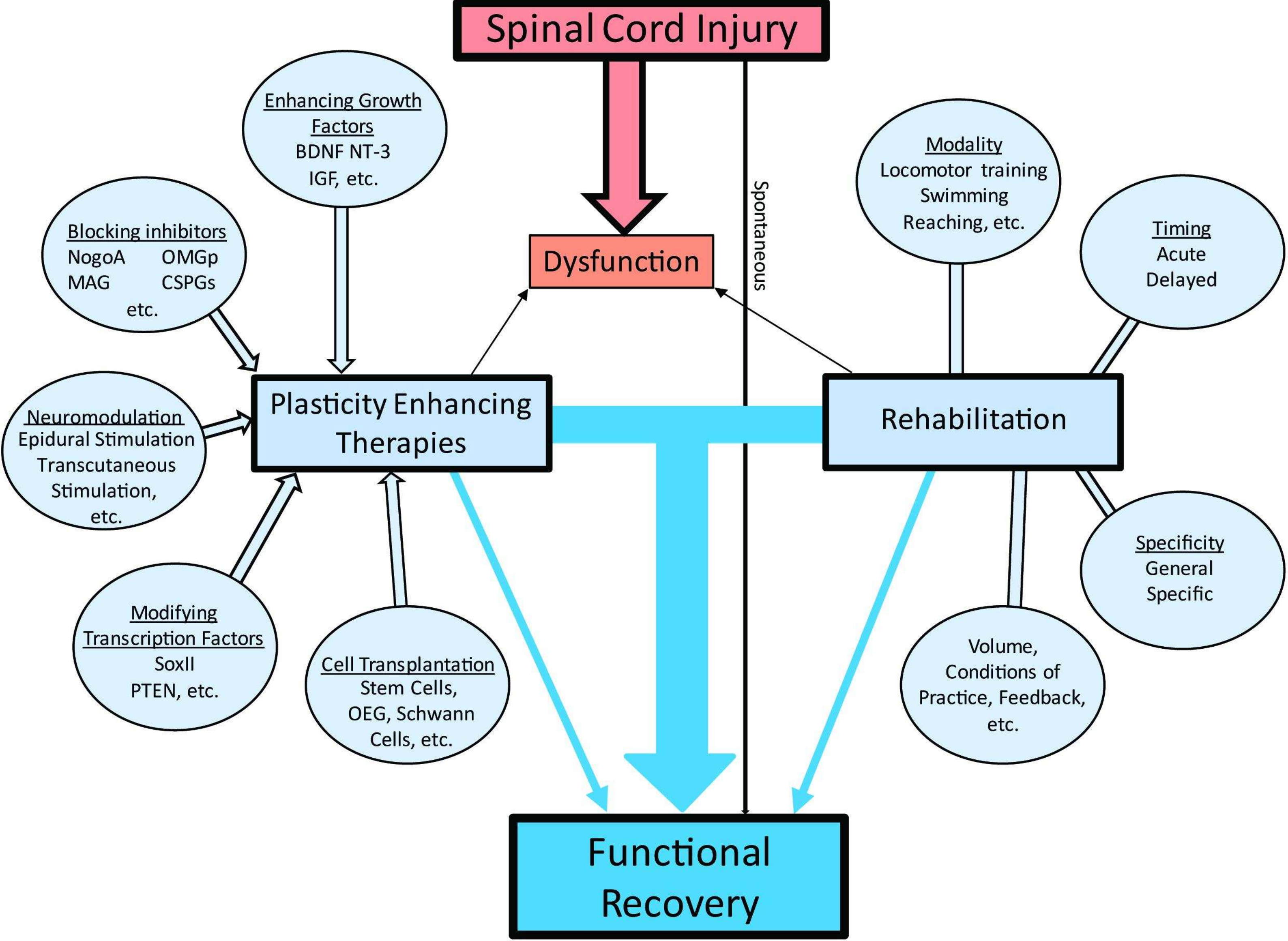
Figure 1. Severe spinal cord injuries result in chronic dysfunction and only minor spontaneous recovery. Both plasticity enhancing therapies and rehabilitation have been shown to facilitate recovery. The combination of the two factors have the greatest potential for functional recovery.

Table Title

Table 1. Studies combining plasticity enhancing interventions with rehabilitation

Table 1 Studies combining plasticity enhancing interventions with rehabilitation

Study	Animal	Injury	Treatment	Training	Results
Chen et al., 2017	Rat	T9 T-lesion	Anti-Nogo-A antibody 11C7	Treadmill training with body weight support (BWS)	Increased locomotor recovery, improved stepping kinematics
Wei et al., 2016	Rat	C4 dorso-lateral quadrant lesion	PKA inhibitor	Reach training	Increased single pellet reaching scores
Hollis et al., 2016	Mouse	Cervical dorsal column lesion	RyK knockout	Weekly reach testing	Increased single pellet reaching scores
Torres-Espín et al., 2018	Rat	C4 dorso-lateral quadrant lesion	Lipopolysaccharide	Reach training	Increased single pellet reach and grasp scores
Liu et al., 2017	Rat	C5 lateral hemisection	DHA	Reach training	Increased reaching success, no change in grid walk recovery
Tashiro et al., 2016	Mouse	Chronic T9 70 kilodyne contusion	Neural stem cell (NSC) implant	Treadmill training with BWS	Increased open field locomotor recovery
Hwang et al., 2014	Rat	T9 200 kilodyne contusion	NSC implant	Treadmill training	Increased locomotor recovery. Reduced grid walk errors. Improved stepping kinematics
Asboth et al., 2018	Rat	T8/9 250 kilodyne contusion	5-HT agonist and epidural stimulation	Treadmill training with BWS	Increased locomotor recovery and stair-climb performance
Petrosyan et al., 2015	Rat	T10 150 kilodyne contusion	NT3 and spino-electro-magnetic stimulation	Swimming and walking in exercise ball	Improved performance on horizontal ladder and narrowing beam
Manohar et al., 2017	Rat	T9/10 full transection	5-HT agonists	Passive cycling and active treadmill training	Increase in weight supported steps
Prosser-Loose et al., 2015	Rat	C2 unilateral CST lesion	Acute intermittent hypoxia	Ladder training	Fewer errors on horizontal ladder
Loy et al., 2018	Mouse	T8 dorsal hemisection	Nothing	Voluntary wheel running	Increased rotarod scores, fewer errors on horizontal ladder


Spinal Cord Injury
Dysfunction
Spontaneous
Enhancing Growth Factors
BDNF NT-3
IGF, etc.
Blocking inhibitors
NogoA OMGp
MAG CSPGs
etc.
Neuromodulation
Epidural Stimulation
Transcutaneous Stimulation,
etc.
Modifying Transcription Factors
SoxII
PTEN, etc.
Cell Transplantation
Stem Cells,
OEG, Schwann Cells, etc.
Plasticity Enhancing Therapies
Rehabilitation
Modality
Locomotor training
Swimming
Reaching, etc.
Timing
Acute
Delayed
Specificity
General
Specific
Volume,
Conditions of Practice, Feedback,
etc.
Functional Recovery