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Restoring Motor functions in Spinal cord injury, Hemiplegic Cerebral Palsy, and Stroke by Botulinum toxin-induced *Synaptic Competitive-Learning* Therapy

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Abstract

Botulinum toxin (BoTx) is well known as a popular drug of choice for spasticity relief. Recent research shows that the toxin has synaptic competitive-learning (SCL) restoring plasticity properties acting at peripheral and central nervous sensory-motor centers. In the intact brain, SCL is naturally-endowed, that controls-regulates all learn-register-recall-execute (motor) functions, and memory storage functions during development and throughout adult life. In spinal cord injury (SCI), hemiplegic cerebral palsy (HCP), and stroke, there is partial/complete cessation of all SCL mechanisms in those injured and denervated centers. The denervated synaptic fields soon become reinnervated by spontaneous growths of aberrant, maladaptive synaptic weights. The massive loss of neurons in the injured site/s and the resultant synaptic weights (=defined as learned motor experiences stored as memory weights) distortions in the denervated centers cause spasticity and sensory-motor paralysis. It is known that BoTx spasticity relieving effects in single, isolated muscle/s are short-lived. However, clinical studies indicate that when given to multiple spastic muscles in serial/ repeats, BoTx generates significant recovery. Basic science studies show that BoTx generates neosynaptogenesis at motor-endplates, on spinal motoneurons and motor cortex. It reinstalls the three cardinal courses of SCL viz. initial redundant connections, activity-dependent, competition-based pruning-selection refinement of connections at these sites. This paper presents i) a cognitive systems perspective of spasticity and motor paralysis, ii) a low-dose, multi-muscles BoTx treatment protocol designed to keep its paralyzing effects minimized, while prolong its SCL duration in order to initiate and consolidate long-lasting motor recovery in these disorders.

Keywords: Acetylcholine (Ach); Botulinum Toxin (BoTx); Hemiplegic Cerebral Palsy (HCP); Motor recovery; Spinal Cord Injury (SCI); Stroke; Synaptic Competitive-Learning (SCL); Neurorehabilitation; Traumatic Brain Injury (TBI)

Introduction

Botulinum toxin (BoTx) is well known as a popular drug of choice for spasticity relief [1-3]. Recent research shows that BoTx has *synaptic competitive-learning* (*SCL*) restoring properties that act at neuromuscular, spinal cord, and central nervous sensory-motor centers [4-6]. Contemporary research in sensory-motor cognitive systems indicate that in SCI, HCP,and stroke the motor paresis/paralysis, and spasticity is caused by partial/complete disruption of all SCL mechanisms in the injured and denervated target neuron centers synaptic fields [5-7]. In the intact brain-cord, SCL is naturally-endowed, that controls-regulates all sensory-motor learn-register-recall-(motor) execute functions, and memory storage functions during development and throughout adult life. SCL consists of an initial redundant numbers of synaptic connections, muscles activity-dependent, competition-based selection of appropriate connections and pruning of inappropriate ones. Basic science research shows that BoTx has SCL-restoring properties that act transiently (weeks) at neuromuscular synapses, spinal cord motoneuron pools and the motor cortex [4-7]. Until now BoTx use in motor paralytic disorders is limited to spasticity/overactivity relief in isolated limb muscles and in dyssynergic bladder-sphincters. BoTx administration into spastic/overactive muscle causes transient blockade of Ach release from the motor axon terminals, and extensive sprouting of the terminals; the paralyzing effect lasting 3-5 months [1-3,8,9]. This paper explains the SCL-restoring properties of BoTx acting at neuromuscular synapses, spinal motoneurons-interneurons and at the cerebral motor cortex [5,10,11] and presents a low-dose, multi-muscles, serial/repeat BoTx treatment protocol designed to prolong the SCL duration in the affected neural centers in the above disorders so as to initiate and promote motor recovery.

What is Synaptic Competitive-Learning (SCL)?

In the intact brain and spinal cord SCL is a naturally-endowed developmental event during motor/locomotor learning and maturation in the neuromuscular junctions, spinal motoneurons, Renshaw neurons, cerebellar cortex Purkinje neurons, and cerebral motor cortex. SCL is not unique to the motor system alone. SCL is the natural developmental process in the visual cortex, lateral geniculate ganglion, and in the autonomic ganglia [10]. SCL consists of generation of an initial redundant numbers of synaptic connections, activity-dependent, competition-based, selection of connections, and redundancy pruning [5,12-15]. A striking example from human perinatal life is that, both sides motor cortexes project nearly equal numbers of corticospinal tract (CST) axons to each side of the spinal cord ventral horn neurons. Later, by around twelve years, by motor/locomotor learning activity-dependent, competition-based, selection-pruning process over 85 percent of axons from the contralateral motor cortex are selected and retained, while only around 15 percent CST axons retained from the ipsilateral motor cortex, and locomotor maturity reached [14,15]. Cognitive systems studies have come out with further interesting, complementary findings. In the intact adult brain-spinal cord centers too SCL is the principal form of sensory-motor skills learning and

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acquisition throughout adult life [5]. A principal difference, however, between the *developmental SCL,* and *adult SCL* is that in the former, there is actual growth of redundant synaptic connections and their competitive selection-elimination. Where as in the latter, there is no actual large scale growth, but redundant sets of connections are allocated from existing ones in the synaptic fields for competitive-interplay (SCL) and selection [5,7,16,17]. Both basic science and cognitive systems studies taken together convincingly show that in SCI, HCP, and stroke there is partial/complete cessation of all SCL mechanisms in the injured and denervated synaptic fields which cause spasticity, paresis/paralysis.

Sensory-Motor Paralysis: Clinical and Cognitive Systems Perspective

Clinical perspective

In these disorders, i) there is large scale degeneration/death of neurons at the injured site/s, ii) the target center/s these neurons project into (e.g. spinal cord ventral horn neurons, cerebellar cortex, thalamus) become denervated at varying degrees of severity. In the next several weeks, the remaining intact inputs to those target center/s *spontaneously* sprout-out and reinnervate the denervated synaptic sites [5]. In SCI paralytics there is extensive local sprouting and compensatory reinnervation at spinal cord, thalamus, cerebellar and cortical levels [18-20]. In cortical/sub-cortical stroke and in CP paralytics there is extensive local sprouting, and compensatory reinnervation of the denervated areas at ipsi-lesional, contra-lesional cerebral cortex. Following unilateral motor cortical damage there is compensatory sprouting of ipsi-lesional side corticospinal tract in the spinal cord [21-26]. The usefulness or otherwise of such local compensatory connections in these paralytics towards motor recovery is a subject of ongoing debate. Clinicians are currently speculating how this compensatory plasticity could be exploited to promote motor relearning and recovery [23,26]. Depending on the severity and extent of injury the clinical picture presents as i) spasticity/overactivity/paresis/paralysis across limb muscles, ii) excitation-inhibition imbalance between synergists-antagonists [5,7,27], iii) the motoneuron's firing properties are in severe disarray, iv) orderly recruitment-derecruitment of motor units within and across muscles are severely impaired/lost, v) failure of adequate numbers of motor units activation presents as muscle weakness, vi) abnormal co-contractions of synergists-antagonists muscles [27]. Also see below, what current clinical investigations, cognitive systems, and brain-modeling studies have to say.

Cognitive systems perspective

In the intact brain sensory-motor centers' synaptic fields all learn-register-recall-execute functions and memory storage functions are controlled-regulated by two core fundamental brain properties, namely *self-organizing,* and *stability-plasticity balancing* [5,7]. In SCI, HCP, and stroke these two vital functions become severely disrupted/ease altogether in the injured and denervated centers. *Self-organizing* is defined as the brain's inherent property to continually evolve in time and space that begin as simple networks in fetal life and progress into increasingly complex network systems that exhibit a hierarchy of emergent (e.g. motor) properties [16,17]. The learned-experiences (e.g. spontaneous movements in fetal life; hands-eyes-head coordination, reaching and grasping in the baby; crawling, sitting, standing, stepping, and walking in the infant; swimming, bicycling, playing piano in the adult) are stored at specific sites in the synaptic fields as *memory weights* in a *self-organizing* manner on the basis of previously learned, and closer to functionally associated weights [*associative memory* 16,17]. *Stability-plasticity balancing* is a fundamental brain property that controls and regulates all learn-register-recall-execute functions, and memory storage functions in the sensory-motor synaptic fields throughout life. While plasticity enables continual learning, stability ensures the storage of the learned experiences into memory weights [5,7]. In SCI, HCP, and stroke the spontaneously added compensatory, aberrant weights are not competition-based, nor activity-dependent. They distort partially/completely all memory traces and SCL mechanisms. New learning and recalls of previously learned skills into motor tasks execution are severely disrupted/lost altogether--known as *stability-plasticity dilemma* [5,7]. In brief, cognitive systems studies point out that restoration of self-organizing and stability-plasticity balancing properties are essential pre-requisites for motor recovery to occur. This also sends a clear message to other therapies e.g. stem cells that they should, first address these issues.

Can SCL be Re-installed in the Injured Brain-spinal Cord Synaptic Fields?

When a motor nerve is sectioned and allowed to regenerate into its muscle, or the nerve is crushed (neurapraxia), or the muscle partially denervated, or BoTx injected into muscle [5,10,11] the motoneurons transiently display for some weeks, a number of SCL-restoring plasticity properties. In each of the above procedures, the motor axons sprout and hyper-innervate (polyneuronal) the denervated muscle fibers. The motoneuron *soma size* enlarges, dendrites hyper-expand; new dendro-dendritic electrotonic couplings become established between motoneurons. Transient neosynaptogenesis develops on the motoneuron soma-dendrites, and on pre-motoneuronal interneurons. This is followed by activity-dependent, competition-based (SCL) selection, and pruning of redundant connections at these two sites. The principal difference between the naturally-endowed developmental SCL and the induced SCL (by nerve section, neurapraxia, partial denervation, BoTx etc) in the adult is that the former lasts for several weeks/months. In the latter procedures, the induced SCL is rather localized and short-lived, lasts for few weeks. The pressing question is that how to prolong the SCL duration in the injured brain-cord as comparable to developmental SCL processes?

BoTx Peripheral and Central Mechanisms of Action in Spasticity Relief

The beneficial effect of BoTx in spasticity relief is generally attributed to its Ach release blocking action at the motor terminals, the altered afferent signals from the injected muscle on to its synergists-antagonists, and the sensory plasticity at spinal and supra-spinal levels [1-3]. It should be stated however, that the far-reaching actions of BoTx at the motor system have been overlooked for far too long [4-6]. BoTx causes extensive sprouting of intramuscular motor axons, resulting in transient hyper-innervation (polyneuronal) of the injected muscle [4,6,8-10]. The motor units in that muscle start sharing each other's territories and thus the average size of motor unit becomes larger. This retrogradely acts on the motoneuron's soma-dendritic membrane. The *soma size* transiently increases together with hyper-expansion of the dendrites, and neosynaptogenesis occurs on the motoneuron-interneurons [4-6] (Figure 1). In spinal motoneuron, its *soma size* is one of the most important determinants of its firing properties. In the intact adult spinal motoneuron its soma size is directly proportional to its motor unit size. Excitability of the motoneuron is inversely related to its soma size. Large motoneurons are less readily excitable than smaller ones (Henneman's *size principle* of the motoneuron) [28,29]. To sum up, the motoneuron's firing properties are determined

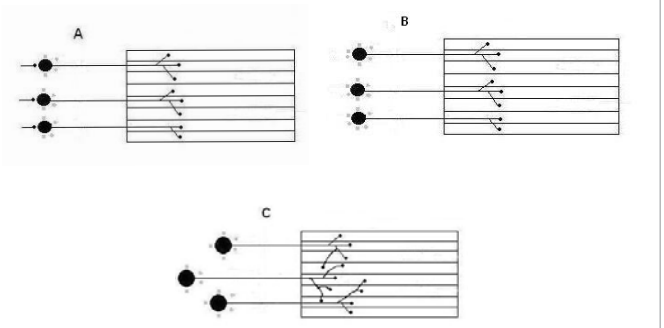

Figure 1: BoTx-induced SCL in the injured spinal cord: A) Intact sensory-motor-neuromuscular system. The three large black spheres are alpha-motoneurons that innervate the muscle (rectangle with eight muscle fibers). Each muscle fiber receives a single motor axon terminal at its endplate (mononeuronal innervation). Grey dots are spindle and tendon organ afferents synapses. Black dots are synapses from descending motor tracts. Grey squares are spinal interneuronal synapses. These synapses on the motoneuron represent the *learned motor experiences* stored as motor memory weights [7]. **B) Spinal cord complete injury (SCIc):** Note all descending motor tracts weights inputs are lost. The vacated synaptic sites have been taken over by *spontaneous, compensatory sprouts* of muscular afferents and interneuronal synaptic weights [5,18]. The weights distortions in the motoneuron pool results in sensory-motor paralysis and spasticity [7]. **C)** BoTx injection into the spastic muscle causes blockade of Ach release at the motor axon terminals, and extensive sprouting of the terminals that form additional endplate synapses (polyneuronal innervation). Also note the enlarged motoneuron *soma sizes* and concurrent neosynaptogenesis. When Ach release resumes, *competition* (SCL) ensues at the neuromuscular synapses and at the motoneuronal synapses. In the following weeks, the redundant neuromuscular synapses are pruned, motoneuron somas become *resized*; the weights on the soma-dendrites repositioned and rebalanced. In BoTx into single, isolated muscle/s the above transient beneficial SCL effects are confined to that single muscle and its motoneuron pool [4-6,10].

by- i) its *soma size*, ii) the precise locations of the learned weights (excitatory, inhibitory, and disinhibitory) on the dendrites, soma and axon hillock, iii) the relative distances between the weights. These three regulatory mechanisms finely balance each other during development and throughout adult life. In SCI, HCP, and stroke all the above three regulatory mechanisms are thrown into disarray and hence the normal firing pattern of the motoneuron is severely disrupted.

Following BoTx injection into single, isolated spastic muscle/s the initial increase in motoneurons *soma sizes* and the resultant decrease in their excitability ameliorate the overactivity-spasticity [4,6]. The neosynaptogenesis at the spinal motoneurons-interneurons and the motor cortex repulses growth of aberrant synaptic weights. In the ensuing weeks, Ach release gradually resumes and muscle contractions begin. Competitive-selection-pruning of connections occurs at motor endplates and in spinal motoneuron circuits. The motoneurons soma sizes become reduced and *resized* and thus the synaptic weights become repositioned in a self-organizing process [4-7]. But then, all the above beneficial SCL peripheral and central plasticity lasts only for some weeks. Then spasticity returns to the muscle, warranting repeat BoTx injections. Thus we see that BoTx has two distinct, but closely inter-related function facets. First is its acetylcholine release-blocking property that relieves spasticity by paralyzing that overactive muscle. However, as the effect of the toxin vanes off the spasticity returns [1-3]. The second is its SCL-restoring property at motor endplates, spinal motoneuron soma-dendrites, spinal interneurons, and cerebral sensory-motor cortex. This includes motoneuron soma size, formation of new dendro-dendritic coupling, new synapses formation, modification of excitation-inhibition balance, motoneuron firing frequency, reflex response, long-latency polysynaptic pathways, motor cortex maps reorganization [4-6]. Now the question is how to sustain this transient SCL effects to long periods? Basic science and clinical studies indicate that instead of injecting single, isolated muscle/s, if given in smaller doses to multiple, opposing muscles, in serial-repeats BoTx will reinstall-replay the SCL processes in several motoneuron pools as happens during infant motor-locomotor learning [4-6,11]. As until now, BoTx treatments have not taken these points into consideration.

Clinical Outcomes in BoTx Spasticity Therapy

The older clinical studies used BoTx in isolated muscle/s in a single session injection protocol with the sole objective of spasticity relief [1-3]. Thus the benefits were transient and spasticity returned later. But then, clinical neurologists had suspected that besides relieving spasticity, BoTx brought improvement in function. It was concluded then, that the existing study designs, injection protocols, the choice of outcome measures, and an incomplete understanding of the pathophysiology of motor paralysis were all the reasons for not detecting precisely the function improvement [30-33]. Later studies that used BoTx in repeat/serial sessions, and long-term for spasticity relief in SCI [6,34-38] in CP [39-43] and, in stroke [44-47] had reported improvement in function besides spasticity relief. Note that in all the above studies the dosing, the number of muscles, and spacing between injections were, in principle, designed for spasticity relief. Non-spastic, synergists-antagonists muscles were not treated. Even so, significant, and lasting improvements in function appeared. A number of clinical studies have vouched support on motor recovery brought by BoTx treatment. In CP in younger children each additional injection of BoTx had shown further gain in function improvement [40]. Studies further show that low-dose, and repeat injections are as effective [41-44] compared to high-dose single session procedures. In stroke, and brain injured spastics, serial injections of BoTx was found to be a useful strategy to avoid drug toxicity and resistance formation [38]. In stroke, SCI, CP, and traumatic brain injury (TBI), repeated treatment with BoTx showed sustained or enhanced improvement in efficacy/and or duration over a follow-up period of up to ten years. In stroke hemiparetics BoTx, besides reducing spasticity in the paretic arm, also significantly reduces *associated reactions*, thus reducing the adverse impact of associated reactions on daily activities [46]. In all the above studies, despite the rather limited objective, namely spasticity relief, the improvement in function reported is strongly suggestive of the SCL effects of this drug. This clearly shows that if SCL-restoring objectives were also included in the treatment procedure, then far significant improvements in function would emerge. It should be mentioned here that few, if any, of the above studies explained the neurobiology-plasticity mechanisms as to how the function improvement occurred in their patients.

The BoTx-SCL Treatment Protocol: Keep the Paralyzing Effect Minimized--prolong the SCL Duration

The primary objective of BoTx-SCL treatment protocol presented is to keep the paralyzing effects minimized while prolong its beneficial SCL effects. To achieve this, besides spastic muscles other paretic/paralyzed muscles should be selected for low-dose BoTx treatment. Muscles should be selected after careful neurological examination and investigations (e.g. EMG). Spastic muscles should be given clinically effective doses of BoTx. Indeed they would need far smaller doses as several other muscles are being treated that have closely related motoneuron pools. If in the first session a prime mover muscle is injected, then in the subsequent sessions one of its synergists should be targeted for injection. Selected muscles should be given one third

or less the dose as indicated for spasticity. The optimum low-dose for various limb muscles will have to be investigated by clinical trials. In the lower limb the segmental innervation of tensor fascia lata=L4, 5; biceps femoris=L5, S1, 2; gastrocnemius-soleus=S1, 2; extensor digitorum brevis= L4, 5, S1. These muscles are anatomically far distant from each other, but their motoneuron pools are close together, indeed segmentally overlap each other. Thus injecting BoTx into one muscle will trigger SCL effects in the other three motoneuron pools (Figure 2) [5,6,11]. Such pools overlapping exist also in upper-limb muscles. Thus only few key important synergists-antagonists will need injections in a given time frame. The optimum dosage and intervals between injections for best SCL effects will need be worked out on an individualized basis. The low-dose, multi- muscles concept is based on findings in clinical studies. A clinical trial pilot study showed that one half or one quarter standard dose of BoTx given to elbow, wrist, and finger flexors within three weeks of stroke onset not only averted spasticity formation in the paretic arm, but also brought improvement in arm function [48]. Injections should be timed in such a manner that while in a first set of muscles competition comes to end there is beginning of competition in the second set of injected muscles. Hence while the paralyzing effects are confined to few muscles, the SCL duration is stretched to long periods, acting at several motoneuron pools. Injections may be repeated, if need be, as assessed by motor recovery outcome measures until satisfactory recovery is reached. How is the long-term safety and prolonged efficacy of this proposed treatment protocol envisaged? Available clinical evidence as of now suggests that repeated/serial BoTx administrations are safe; negligible or no adverse effects noted. Function improvements were sustained or enhanced for a follow-up period of few years and up to ten years [38,40,41,43,44].

BoTx-SCL Neurorehabilitation

As discussed earlier [4-7] BoTx recreates SCL environment in the denervated brain-cord centers; and that lasts only for few weeks. Secondly, the synapses thus generated are rather functionally *un-weighted*, dummy synapses. The new connections should now be *loaded with weights* (remember, weights are learned-experiences) which have to be acquired by concurrent activity-dependent retraining programs [5,7]. What is activity-dependent relearning? Infant motor development studies [49], and humanoid robot motor-learning [50] reveal that sensory-motor skills are learned-acquired by initial *random, exploratory, trial*-and-*error* movements executed in a number of different (*variability*) ways on which more complex movement skills are learned and added upon [7]. They show that systems that employ competitive-learning (SCL) principles learn 44 percent faster than other learning systems [50]. Clinical studies have confirmed these observations. In stroke patients, on whom variable training schedules and random functional movements were practiced have shown superior retention of the learned practices that *generalize* into activities of daily living [51].

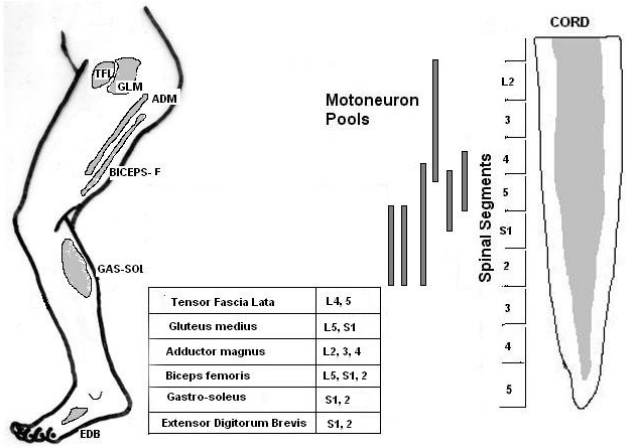

Figure 2: BoTx-induced SCL in the paretic/paralyzed lower limb
Low-dose BoTx is injected into a few, selected muscles in serial/repeat sessions. Muscles selected are from among flexors and extensors of the hip, thigh, leg, and foot. Contracting muscles are not injected. In the next few weeks, intramuscular motor axonal sprouting, polyneuronal innervation control of the muscles fibers, and synapse competition (SCL) will take place. In the mean time, plastic increase in motoneuron soma size, neosynaptogenesis, and synapse competition (SCL) will eventuate in the spinal cord and motor cortical circuits. Note the close proximity, and segmental overlapping of motoneuron pools, though the respective muscles are anatomically far distant apart. Remote, un-injected muscles will also participate in the SCL processes and develop signs of recovery due to the pools' segmental proximity. Thus only few key important prime mover-synergist muscles would need be injected in a given time-frame [5,6,11].

Computational modeling [52,53] and fMRI clinical study [54] of motor cortex hand map reveal that the maps are highly dynamic, malleable representations. Shifts in the map borders are resulted from continually ongoing *competitive* organizing process between neuron groups that control the map borders. Alterations in the hand map can be readily brought up by manipulations of the periphery, e.g. immobilization, amputation, BoTx treatment etc. For example, even a trivial procedure such as immobilizing two fingers together by a plaster-splint for a few weeks can blur the finger borders in the motor map which become reversed and borders become clearly defined once the splint is removed [54]. In hand muscles dystonia (Writer's cramp), the hand motor map is displaced from its normal site. BoTx injection into affected hand-forearm muscles brings relief of spasticity; restores the map to its original site. However, as the BoTx effect wears off, spasticity returns and the map is again displaced [55,56]. Why is the beneficial effect short-lived? This might be due to that only one or two affected hand, forearm muscles were injected in a single session and not repeated. Thus the SCL duration was *inadequate* for map's corrective processes to complete and establish. The inference is that in BoTx treatment, lasting functional gain can be achieved only by *sustaining* SCL processes to long periods for loading of weights to occur and establish [5,7]. Another example is from present-day rehabilitation programs for SCI paralytics. In these paralytics, even after intensive, long-term training (body-weight support treadmill) motor recovery appears long-delayed (five years), in small increments, and is rather marginal [57,58]. Why such long delay? As stated earlier the principal reason is that the affected neural circuits have lost their self-organizing capabilities, are in a state of stability-plasticity dilemma and thus re)learning-resistant. It should be pointed out that as until now rehabilitation programs have not addressed these concerns.

Most motor tasks e.g. arm reaching-grasping, are multi-joint, multi-muscles complex movement synergies. This means, hand motor map will receive from and project to shoulder, upper-arm, and forearm map regions. The human musculo-skeletal-motor system is endowed with redundant muscles, motor units, joints and degrees of movements [5,7]. Thus a specific movement can be performed in a number of different, *variable* ways. The maps complexity and the continually ongoing synapse competitive (SCL) processes will explain why multiple muscles, repeat BoTx injections, and relearning-time are needed for long lasting recovery to establish.

In stroke and CP hemiplegics, the possibility of using the undamaged hemisphere, e.g. the ipsilaterally descending cortico-spinal tract (CST) axons, the bilateral hemispheric pre-motor centers,

and bilaterally operating neuronal networks at brainstem and spinal cord levels etc have been proposed recently [22-26] for inducing compensatory recovery of motor function. In HCP children fMRI studies have shown that the normal competitive process between the crossed and uncrossed CST axons to gain connections with the spinal ventral horn neurons is severely perturbed [14,15,21]. In these paralytics the interruption-disruption of a fair competition and the occupation by aberrant, maladaptive weights has been recognized as factors that hinder motor recovery. This [14,15] is an important finding in the sense that it recognizes SCL as a fundamental neuronal process that controls and regulates motor development and maturation and that its disruption can affect normal motor maturation, and restoration. The present paper addresses these fundamental issues and the proposed BoTx-SCL treatment protocol is aimed to avert aberrant connections, reinstall SCL mechanisms and promote function restoration.

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