State of the Art: Spinal Cord Injury Research

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1. Spinal Cord Injury (SCI)

Spinal cord injury (SCI) is injury to the spinal cord due to trauma, tumor, infection, degeneration, or other causes. In canine patients, it includes intervertebral disc disease (IVDD), herniated nucleus pulposus (HNP), acute non-compressive nucleus pulposus extrusion (ANNPE), and fibrocartilaginous embolism (FCE), among others.

Olby et al (2020) in the CANSORT-SCI project suggested a method by which to prognose recovery in animal patients with SCI. These criteria include: recovery of ambulation, return of urinary and fecal continence, resolution of pain, intact dep pain perception (DPP), and the absence of development of progressive myelomalacia. This is not considerate of post-injury intervention, including surgical, medical, or physical therapy and rehabilitation treatment.

SCI leads to sensory and motor impairment and maladaptive neuroplastic changes in the cerebral cortex, resulting in chronic functional limitation and disability. We can, however, implement physical therapy and rehabilitation medicine strategies in the early stages to further improving prognosis for recovery of function via activation of alternative pathways while the original pathways are healing, recovering, and regenerating, without a need for healing to be complete. Some of these strategies used in human patients with SCI which can and have been adapted to canine patients include: Activity Based Therapy, Electrical Stimulation, Physical Modalities, Molecular and Regenerative Medicine, and promotion of the expression of Brain Derived Neurotrophic Factor (BDNF) for neuroplasticity via various physical and medical interventions.

2. Activity Based Therapy (ABT)

Regardless of the species, physical therapy and rehabilitation goals following SCI are to:

- Maintain and promote quality of life,
- Reduce compensations/complications which could lead to injury or further functional decline,
- Enhance and promote functional recovery,
- Minimize potential for neuroplastic pain and maladaptive neuroplasticity,
- Promote adaptive neuroplasticity for and with adaptation, accommodation and functional recovery, and
- Develop a plan of care considerate of the patient and client/handler/owner.

Activity Based Therapy (ABT) or Task-Oriented Therapy (TOT) is a therapeutic approach promoting functional recovery through adaptive neuroplasticity and is inclusive of:

constraint induced movement therapy (CIMT), locomotor training (LT), functional electrical stimulation (FES), environmental enrichment (EE), cognitive training, and a sensory approach. Interventions are relevant, random, and repetitive to promote functional independence, neuroplasticity, and motor learning. ABT increases function, independence, and mobility and opportunities for neuroplasticity, and prevents secondary musculoskeletal impairments (Behrman and Harkema 2007).

CIMT is the forced use of an impaired limb or component through restriction or constraint of a stronger limb or component. The intensive use of the impaired limb leads to neuroplastic changes and, potentially, improved function of that limb. Traditionally utilized in patients with cerebrovascular accident (CVA), CIMT protocols can be adapted to the practice of physical therapy and rehabilitation with canine patients through modifications such as: task-specific patterned motor activity, resistance training targeting weakened muscles, and repetitive practice of physical movements. CIMT attempts to prevent learned non-use, in which movement is initially suppressed due to failure and adverse consequences encountered when a patient attempts to use the impaired limb. This results in persistent compensatory behaviours and subsequent suppression of use of the impaired limb, even when function may eventually be possible. CIMT potential can reduce a patient's reliability on compensatory strategies, enhance motor learning, and improve function.

Studies have demonstrated, through functional magnetic resonance imaging (fMRI) technology, that patients who engage in CIMT have been shown to have increased activity in their contralateral premotor and secondary somatosensory cortex in association with improved function (Johansen-Berg et al 2002). Sawaki et al (2008) showed that CIMT is associated with an enlarged motor cortex map for an "impaired" hand, while Gauthier et al (2008) showed an association of CIMT with increases in grey matter in the sensorimotor cortex of both hemispheres of the brain.

Livingston-Thomas and Tasker (2013) explored models of CIMT in pigs, rats and primates and found that with intensive, repetitive task practice (RTP) daily over two weeks in a rehabilitation clinic and with home practice and problem-solving sessions, there was increased transfer of skills using the impaired limb to daily activities.

3. Electrical Stimulation

Functional Electrical Stimulation (FES) is the application of neuromuscular electrical stimulation (NMES) in a static functional position or during a dynamic functional activity. It is a component of ABT and is widely used in physical therapy and rehabilitation for patients with SCI.

Neuromodulatory techniques and modalities, including peripheral electrical stimulation (with TENS, NMES, or FES), transcranial direct current stimulation, or repetitive transcranial magnetic stimulation, have been demonstrated to alter cortical sensitivity and enhance brain sensitivity in preparation for more traditional physical therapies, including manual therapy and therapeutic exercise, especially in the case of patients with movement disorders (Chipchase, L. S., Schabrun, S. M., and Hodges, P.W., 2011). The researchers also note that the successful use of TENS requires a variable intensity with long-duration stimulation above

the motor threshold while stimulation below a motor threshold (and above a sensory threshold) shows inconsistent results.

Meesen et al (2011) found evidence of neuroplasticity with a significant increase in cortical motor representation of all finger and forearm muscles of 24 human subjects treated with sensory-threshold TENS (constant, biphasic symmetrical rectangular, 100 Hz, 250 μs, 60 minutes/day, 21 days). Results were not significant for the control group.

Research is now focusing on the utilization of electrotherapy, in the form of epidural, deep brain (DBS), and non-invasive brain stimulation to promote neuroplasticity, especially in patients with neurological injuries and disorders. Neuroprostheses are also being utilized more frequently.

Epidural stimulation is a method of "electro-enabling motor control" in which the spinal cord below the level of injury is directly stimulated. The goal of this is to potentially restore motor and autonomic function using activation of proprioceptive pathways. This was demonstrated in a clinical trial of a patient with C7-T1 motor complete SCI who participated in locomotor training (LT) and epidural stimulation over 26 months. In follow-up, over 18 months later, the patient had recovered active control of weight bearing, was independently standing, had active postural control, and was able to rhythmically step with the stimulation.

Deep brain stimulation (DBS), more commonly used in patients with Parkinson disease, has been used to successfully restore walking ability in two cases with incomplete SCI (Cho et al 2024).

Neuroprotheses show promising results in both research and clinical applications with:

- Improved functional mobility,
- Improved walking speed,
- Improved spatiotemporal parameters, and
- Reduced physiological cost of walking.

Tabot et al (2015) was able to use a neuroprosthesis to restore touch, proprioception, and dexterity by electrical stimulation of the somatosensory cortex. This intracortical microstimulation (ICMS) provides artificial somatosensory feedback. Success in this intervention is believed to be due to adaptive neuroplasticity through biomimicry, in which neuronal activity due to novel sensory input results in neuronal activation patterns which resemble natural patterns. Another example of a neuroprosthesis is the use of a functional electrical stimulation (FES) device commonly used for foot drop or paralysis of the anterior tibialis muscle (https://www.shepherd.org/programs/services/shepherd-step).

Robotics has been utilized in rehabilitation through various means including: robotic assistance with haptics, robotic perturbation (providing sensory feedback and feedforward), virtual reality with robotic-mediated therapy (providing environmental enrichment), and brain-robotic interfaces, such as neuroprostheses or orthotics with electrical stimulation components. Though robotics continue to evolve, especially with the advent of artificial intelligence (AI) and machine learning, there is a need for "progressive, challenging motor skill learning, rather than merely providing repetitive motor tasks."

4. Physical Modalities

Physical modalities, including pulsed electromagnetic field therapy (PEMF), photobiomodulation (PBM) via near-infrared (NIR) or low-level LASER therapy (LLLT), and shockwave therapy have also been found to promote neuroplasticity.

PEMF is theorized to promote neuroplasticity by:

- Increasing levels of growth factors, neurotrophic factors, and BDNF,
- Providing protection against neurotoxic environments which are found with progressive neurological diseases and ischemic damage
- Inducing vasodilation, increasing microvascular blood flow velocity, and increasing brain tissue oxygenation
- Reducing pain and inflammation

Transcranial Near Infrared Light (NIR) is the application of a class III, low powered red or NIR LASER (600-2500nm, 1-500mW) in patients with brain injury, Alzheimers, Parkinsons, CVA, and depression. NIR has been demonstrated to: enhance ATP biosynthesis, regulate mitochondrial homeostasis, facilitate neurogenesis and/or neuroplasticity, reduce progression and/or improvement of neurodegenerative processes, manage brain energy metabolism, and regulate chronic brain inflammation.

Extracorporeal shock wave therapy (ESWT) effects neuroplasticity through mechanotransduction and cavitation. The process of mechanotransduction, in which the cell membrane is polarized, radicals form, cells proliferate, and growth factors are produced, results in transmission of mechanical stimuli into biochemical signals, modulating the functions of cells, including migration, proliferation, differentiation, structure, and homeostasis. Cavitation, which is the formation, expansion, and implosion of air bubbles due to negative pressure. Cavitation causes excitation of nerves, stimulation of axons, and reduction of pain, influencing stem cells, cytokines, Schwann cells, endothelial cells, and sodium channels. Cavitation via shockwave therapy can result in tissue regeneration and repair, angiogenesis, pain relief, metabolic activation, and reduction in inflammation.

Though research regarding shockwave therapy in neurological rehabilitation is limited, Afzal et al (2023) found improved lower limb motor function and reduced spasticity in patients with CVA treated with shockwave therapy. There was no change in walking performance in these patients. Onin et al (2022), however, documented reduced hemineglect symptoms in patients with CVA after shockwave therapy treatment.

5. Molecular and Regenerative Medicine Approaches

Enviromimetics are “brain boosters” or medications that mimic or enhance the beneficial effect of cognitive stimulation and physical exercise. Some of these medications include: selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, serotonin, noradrenergic reuptake inhibitors (SNRIs), such as duloxetine, cholinergic agonists, such as donepezil, and glutaminergic partial antagonists, such as amantadine. Research suggests improved recovery, cognitive functioning, and left prefrontal cortex activation in patients treated with enviromimetics after traumatic brain injury (TBI)

Scientists are able to identify cells and receptors which are integral for neuroplasticity. Manipulation of these could potentially allow for better influence and control over the processes of neuroplasticity. N-methyl-D-aspartate (NMDA) receptors are formed by a

glutamate receptor and ion channel protein found in a nerve cell. They are activated when glutamate and glycine bind to the receptor to allow positively charged ions to flow through the cell membrane. This is important for controlling synaptic plasticity and memory.

Glial cells are non-neuronal cells in the nervous system that do not produce electrical impulses. They serve to maintain homeostasis, form myelin, and provide support and protection for neurons

Scientists are also investigating the molecular mechanisms responsible for regeneration in the nervous system. SCI pathology results in intraneuronal and regenerative microenvironment imbalance. Regeneration can be promoted by altering this imbalance with medications, cell transplantation, exosomes, tissue engineering, cell reprogramming, and rehabilitation (Yang, Zhang, Cheng, 2020).

Scientists at Stanford are using measurement of the width of spared spinal cord tissue at the injury site by MRI to accurately predict a patient's potential for functional recovery. Based on this, UCSF scientists have attempted to modulate scar tissue with medications after SCI. Cerebrospinal fluid (CSF)-contacting neurons and k-opiods lead to scarring after SCI. Some scarring is protective, though excessive scarring is inhibitory to recovery

Stem cell therapies can potentially improve sensory and motor function and significantly improve the quality of life for patients with SCI. A study by Zeng (2023) demonstrated improvements in bladder compliance and axonal regeneration, with no adverse findings over a 30-month follow-up.

6. BDNF and Neuroplasticity

Brain-derived neurotrophic factor (BDNF) promotes neuroplasticity and neurologic recovery by supporting survival of existing neurons, encouraging growth and differentiation of new neurons, dendrites, and synapses, and preventing GABAergic signaling activities (which results in maintenance of elevated levels of neuronal excitation). BDNF is present in the hippocampus, cortex, forebrain (important for learning, memory, and thinking), retina, kidneys, motor neurons, skeletal muscle, saliva, and prostate. Reduced levels of BDNF are associated with depression, schizophrenia, Alzheimers, pain sensitivity (short-term promotion, long-term inhibition), obesity, and itching with eczema. Exercise, sleep, adequate nutrition (reduced fat and sugar intake; niacin supplementation), and reduced stress causes increased release, upregulation, synthesis, and expression of BDNF. Physical exercise, including high intensity cycling and aerobic exercise, triples the rate of synthesis of BDNF in the brain. This results in exercise-induced neurogenesis and improvements in cognitive function.

Interestingly, many of the recent medical innovations and modern physical therapy and rehabilitation interventions benefit people and animals with SCI through promotion of neuroplasticity and functional recovery. The future may hold more hope for those with these injuries and disorders.

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