

State of the Art: Neuroplasticity

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1. Injury

When an injury occurs, there are changes in vascular, neural, structural, contractile, and connective tissues, both grossly and at a cellular level. Initially, the inflammatory, neurochemical, and immune responses lead to degeneration of involved tissues. A secondary response to injury occurs via the immune system, with subsequent degeneration, demyelination, apoptosis (or cell death), and atrophy.

Injury, whether neurological or musculoskeletal, results in an alteration in sensory input to the cerebral cortex, a process called **cortical silencing**. This, in turn, causes an altered motor response, altered sensory feedback, and **cortical smudging**. This entire process might lead to further injury and/or chronic changes in the nervous system.

2. Functional Recovery

Functional recovery can occur via regeneration, compensation and/or neuroplasticity.

Regeneration or neurogenesis is the healing of nervous tissue through formation of new neurons and neural connections. Regeneration is a delicate process and requires:

- The right thing (eg., stimulus, stress, reason, goal),
- At the right time,
- In the right place, and
- In the right environment.

Neurochemicals released at the time of neurological injury result in changes in the cellular environment and promote regeneration by preventing cell death and inducing axonal growth. These include cytokines, growth factors, and neurotrophic factors. Cytokines are signaling peptides or proteins which mediate and regulate immunity, inflammation, and hematopoiesis. Growth factors include proteins and hormones which stimulate cell proliferation, wound healing and cellular differentiation. Neurotrophic factors are peptides or proteins which support growth, survival, and differentiation of developing and mature neurons. Examples of these include insulin, interleukins, and brain derived neurotrophic factor (BDNF)). All are integral to the process of regeneration following neurological injury.

Compensation or substitution is the completion of a functional task via alternative behavioral strategies and utilization of stronger or uninvolved limbs or body parts. These strategies do not utilize the original processes or connections. The goal of compensation is return to prior level of function (PLOF) as soon as possible, with less emphasis on quality of postures and control of movements. Undesirable results of compensation include weakness and atrophy, contracture, asymmetry and deformity, pain and dysfunction, neglect, and

secondary injury. This is because of the secondary stresses of the substitutive, inefficient, and abnormal movement strategies and postures.

Hubel and Wiesel demonstrated the challenges due to compensation for altered visual input in kittens and adult cats. In kittens, the investigators sutured one eyelid closed, which resulted in the neurons of the visual cortex responding only to the open eye and long term effects on vision (even when the sutured eyelid was opened later). This demonstrated evidence of a “critical period” in the development of vision. Alternatively, in an seeing adult cat who had an eyelid sutured closed, there were no changes in cortical distribution after visual input deprivation.

3. Neuroplasticity: When Things Go Right

Neuroplasticity is “the ability of the nervous system to respond to intrinsic or extrinsic stimuli (or experiences) by reorganizing its structure, function, and connections.” Neuroplasticity can be adaptive (or positive) or maladaptive (or negative).

The neuroplastic process results in the brain using latent capacities that have been present since birth, not creating new functions in previously unrelated areas but “increasing the volume” and “fine tuning” the area that was less involved prior to injury. This is similar to trimming branches of a tree in order to strengthen the remaining branches.

4. Neuroplasticity: When Things Go Wrong

The cortical map or homunculus is a sensory and motor map or representation of body parts “on” the brain. Neuroplasticity (and the alteration of the cortical map) is directed by multiple factors, including:

- Injury characteristics (eg., location, size, function, time since injury/chronicity, post-injury interventions)
- Microenvironment (eg., homeostasis in proteins, chemical signals, growth factors, neurotransmitters, hormones)
- Structure of the neurological system, including availability, concentration, and intensity of activation of sensory receptors, neural circuitry, and spared and redundant connections
- Stress
- Gene expression
- Modulation (inhibitory or facilitatory)
- Age, experience, development, maturation, and age at the time of injury
- Environment (whether sensory deprived or enriched)
- Temperament
- Activity and active use of a body part
- Species- and breed-specific
- Motor learning characteristics, including practice, repetition, reinforcement, prior experience, skill acquisition, and motivation

Though we may be oversimplifying the definition, maladaptive neuroplasticity occurs when a connection made in the brain produces aberrant or negative symptoms (Puderbaugh and Emmady 2023). Maladaptive neuroplasticity is a result of cortical silencing and cortical smudging.

Cortical silencing occurs when the cortex is “silenced” in the areas previously activated by neural input from the injured area due to absence or alteration of sensory input or feedback, motor activation or output, or autonomic activity in or from the injured area. It is indicative of pathology and is not exclusive to musculoskeletal injury but occurs following injury to the central or peripheral nervous systems as well. The cortex is “silenced” in the areas previously activated by neural input from that area. Cortical silencing can result in:

- Sensory dysfunction or paresthesia,
- Altered pain, temperature, two-point discrimination, vibration, and proprioception sense,
- Cortical smudging,
- Alteration of the cortical map,
- Motor dysfunction,
- Weakness, immobility, and/or neglect, and/or
- Arthrogenic muscle inhibition (AMI).

Arthrogenic muscle inhibition (AMI) is the disruption of neurological function following a musculoskeletal injury. This “protective mechanism” limits the patient’s ability and capacity to contract a muscle or muscle group through full range of motion (ROM), interfering with recovery of strength, but protecting healing tissues. Unfortunately, AMI results in further changes to the sensory cortex via cortical silencing.

Cortical smudging is the reduced awareness of a body part with a faulty, fragmented, blurry, or less accurate representation of that body part on the homunculus. Intact areas (of the body) provide (abnormal) input to the area that SHOULD be activated by the target area (to fill in for absent sensory input). The brain fills in with “pain” for the absent sensory input. The abnormal primary sensory cortex changes in association with negative, stressful, or painful experiences or application of post-injury interventions in a suboptimal way. Cortical smudging can result in:

- Immobility
- Complex regional pain syndrome (CRPS)
- Sensory integration disorder or dysfunction (SID)
- Sensory defensiveness
- Spasticity
- Use-dependent dystonia (writer’s cramp)
- Paralysis
- Hypo- or paresthesia
- Hyperalgesia (increased pain/tenderness/sensitivity)
- Cold sensitivity
- Chronic neurogenic or neuropathic pain
- Phantom limb pain/sensation
- Drug addiction
- Obsessive-compulsive disorder
- Inflexibility/tightness
- Weakness
- Avoidance or neglect: a general inattention to the side of the body contralateral to the lesion of the brain
- Difficulty in functional use

To better describe cortical smudging, “if your pain is spreading from your lower back to your neck, it’s very unlikely that you have a back problem that’s spreading up. It is more likely that your brain is losing the precision in localising body parts.”
(<https://medicalrepublic.com.au/smudging-when-pain-moves-and-grows/51772>)

Kakavas et al (2020) suggested that cortical smudging might occur in ACL injury. When the ACL is ruptured, the CNS relies on alternative sensory inputs (for example, visual feedback) rather than proprioception. The study found brain activation differences between ACL-deficient subjects who did not return to previous levels of physical activity and a healthy control group. ACL-deficient subjects exhibited increased activation in:

- Posterior inferior temporal gyrus (visual processing)
- Pre-supplementary motor area (motor planning)
- Secondary somatosensory area (pain and sensory processing)

Some research regarding musculoskeletal injury has focused on the influence of neuroplasticity on recovery and pain management. Brumagne et al (2019) noted that in chronic low back pain there is a change in the processing of nociception and pain and a change in the structure and function of the sensorimotor regions of the cortex because of maladaptive neuroplasticity. Stanton et al (2013) found disruptions in the representation in primary sensory cortex related to knee pain or low back pain and contributing to the chronicity of such painful conditions. Wand et al (2010) reported that tactile acuity and voluntary lumbopelvic control was reduced in patients with low back pain. The researchers concluded that there is a cortical rather than peripheral sensory dysfunction associated with these conditions.

Persistent and permanent functional deficits can result from inadequate regeneration. For example, CNS neurons might lack the capacity for axonal regeneration due to injury intensity or location. Direct trauma to the spinal cord might result in glial scar formation. As well, an inhibitory or toxic microenvironment can prevent regeneration from occurring. Alzheimers, Huntingtons, and Parkinsons diseases, and dementia are neurological disorders that are likely affected by the microenvironment in which toxicity inhibits the brain’s ability for regeneration or compensation.

Research suggests, however, that environmental enrichment with intense physical activity and cognitive stimulation can delay the onset of and slow the progression of Huntingtons. Another study (Palasz et al 2019) used a mouse model of Parkinsons and demonstrated the ability for physical training, especially early onset, to protect and prevent degeneration of dopaminergic neurons and increase the release of BDNF and GDNF which are neuroprotective and promote neuroplasticity.

At times, even without treatment or with a toxic environment, compensation and neuroplasticity can be successful in functional recovery, for example, in 40% of SCI patients and in SCI animal models.

“People keep chasing that pain (with medications, injections, etc.) As if it was an ongoing injury... It’s the brain amplification, not the injury that’s causing the problem.”
(<https://medicalrepublic.com.au/smudging-when-pain-moves-and-grows/51772>)

Jones et al (2007) suggested that laminitis in horses resembles neuropathic pain as it results in an altered EMG (afferent changes) and behavioral changes.

Complex regional pain syndrome (CRPS) is the presence of chronic pain, out of proportion to the severity of injury or illness. There are two types: Type 1: reflex sympathetic dystrophy (RSD) and Type 2: causalgia, which is uncommon with a poorly understood cause. In all CRPS conditions, treatment is most effective when initiated early, potentially with improvement, and possibly with remission. Symptoms of CRPS include:

- Continuous burning or throbbing pain (usually in arm, leg, hand or foot)
- Sensitivity to touch or cold
- Swelling of the painful area
- Changes in skin temperature, color, and texture
- Changes in hair and nail growth
- Joint stiffness, swelling and damage
- Muscle spasms, tremors and weakness (atrophy)
- Decreased ability to move the affected body part

Peripheral nerve injuries (PNI), for example, to the brachial or sacral plexus or more distal peripheral nerves, due to trauma, fracture, and surgery, result in sensory and motor dysfunction. The sensory impact of these injuries can be quite challenging to manage, with anesthesia, paresthesia, or dysesthesia and resulting in pain behaviors, obsessive grooming, licking, and/or self-mutilation. Patients with PNI are likely to have neuromuscular impairments and gait deviations with weakness, flaccidity, neurogenic atrophy, and/or resulting secondary trauma to the distal limb.

Phantom limb pain/sensation (PLP) is the perception of pain or discomfort “in” an absent or lost body part after traumatic injury. It is not “residual limb pain” (or “stump pain”), which is pain that originates from the actual amputation site and which tends to resolve with wound healing. The theory is that PLP results when cortical neurons are abnormally activated by input from intact parts of the body (to fill in for the absent sensory input from the absent limb. The brain “creates” pain as a substitute for this absent sensory input.

Kaas et al (2008) suggested that the sensory cortex associated with a deafferented hand can be reactivation by inputs from the face. Unfortunately, this is more likely to result in phantom limb sensations than functional recovery.

5. Neuroplasticity and Rehabilitation

Rehabilitation is the action, process, or result of restoring, recovering, or returning to as close as possible to the patient’s prior level of function (PLOF) from impairment, functional limitation (dysfunction), or disability due to onset of injury, illness, or disorder, whether acute, chronic, or progressive, via physical therapy and rehabilitation.

Therapeutic and adaptive neuroplasticity is more likely when rehabilitation includes cognitive exercise (learning), physical exercise, and aggressive/intensive rehabilitation. “Exercising the brain” has been demonstrated to delay onset, slow progression and/or reverse symptoms of a disease. “Post-juvenile neuroplastic changes (are) associated both with learning and with drastic changes in sensory and motor experience.” (Lillard and Erisir 2011)

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