

## Stroke of Genius: Provoking Plasticity

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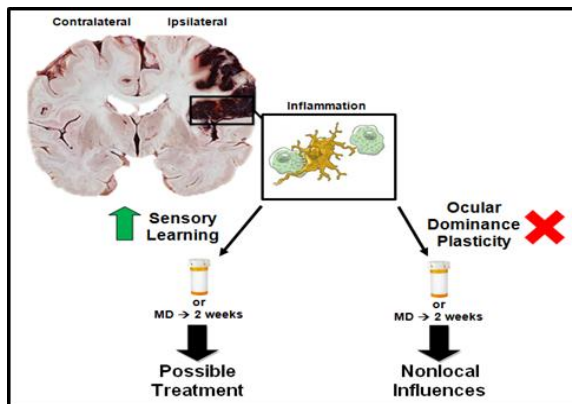
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**Optimizing cortical plasticity after a stroke leads to improved recovery. Two forms of plasticity have shown to have different cellular mechanisms that suggest different treatments to be examined for each.**

A stroke is like a rock dropped into the water; ripples reverberate causing widespread changes that affect different people in different ways. Aside from the millions going into research and treatment, and the hardship put on caregivers, stroke is the leading cause of long-term disability in the United States.<sup>1</sup> There are few treatments currently available to patients, leaving them with grim prognoses or hope for recovery. Any optimism of recovery comes from changes happening in the brain – new connections, new spines, and new maps. To better understand how to optimize stroke recovery, Greifzu et al. (2011) studied the efficacy of anti-inflammatory treatments in different types of plasticity by examining the cellular mechanisms<sup>2</sup>.

Following damage, learning and plasticity work to rewire connections in the brain that lead to recovery. Specific cellular changes occur in multiple areas of the brain, including areas with or without damage. Some of these changes include GABA activity which decreases, while overall neuronal activity increases.<sup>3</sup> Understanding why and how these and other changes happen in the intact areas of the brain poses a large mystery left to be uncovered.

Strokes evoke an inflammatory response in the cortex (Fig. 1); previous research showed a possible relationship between this response and the outcome of the lesion size.<sup>4</sup> Greifzu et al. (2011) also believed that a link existed between this inflammatory response and the modification of plasticity, which no one had previously studied.



**Figure 1. Two types of plasticity paradigms have different outcomes when treated with ibuprofen.** Following stroke, an inflammatory response occurs. Sensory learning restored when treated with ibuprofen and with delayed monocular dominance. However, ocular dominance plasticity did not return with either, suggesting different cellular mechanisms underlying the two paradigms. More specifically, nonlocal influences must play a role in OD-plasticity.

One connection between plasticity and inflammation is glial cells. These cells surround inflamed, damaged neurons

and also assist glutamatergic neurons in the re-uptake of glutamate when released into the synapse. NMDA receptors, which are present in glutamatergic synapses, play crucial roles in plasticity. Although no one has studied this connection, it explains one link between plasticity and inflammation.

Two paradigms that exist to study plasticity in mouse models are the enhancement of visual acuity and ocular dominance plasticity.<sup>5</sup> To provoke plasticity they used a well-known model called monocular deprivation (MD), which covers one eye of the mouse forcing use of the other.<sup>6</sup> The MD started either immediately or one or two weeks after the researchers lesion the brain, lasting seven days. They had this variance because patient studies have conflicting results regarding when treatment should be started.<sup>7</sup> Understanding how timing, type of treatment, and plasticity interconnect increases the chances that stroke victims have positive outcomes. Greifzu et al. (2011) first show that anti-inflammatory treatment, via ibuprofen, reestablish both visual acuity and contrast sensitivity after MD back to the levels of control mice. They also show that when MD is delayed two weeks, it also restores sensory learning without the aid of ibuprofen. Contrary to these findings, the other paradigm of ocular dominance plasticity did not restore with ibuprofen treatment nor did it delay MD. The different reactions each of the plasticity paradigms had to the treatments suggest that different cellular mechanisms underlie them.

Greifzu et al. (2011) did not expect to find these conflicting results between the two paradigms, so they decided to extend the research in hopes of better understanding these findings. First they examined the contra- and ipsi-lateral hemispheres. Sensory learning plasticity reduced regardless of which side MD occurred, suggesting a brain-wide disturbance. However, ocular dominance plasticity remained in the non-lesioned hemisphere. The reduction in the lesioned hemisphere must be caused from a specific process, not an overall "brain-sickness" that some have suggested follows stroke. Although these findings between the two paradigms conflict again, it does support the idea of distinct cellular mechanisms.

These results show that plasticity in general is a complex process in the adult brain. The sensory learning plasticity paradigm showed damage throughout both hemispheres and recovered after both anti-inflammatory treatment and a delay of two weeks for the onset of MD. The researchers suggested that anti-inflammatory treatment may be a possible treatment for patients; however, that notion is a long way off because the late onset MD alone showed the same recovery of plasticity. The researchers even stated that the inflammation may be a transient problem. The ocular dominance plasticity decreased in the lesioned hemisphere, suggesting the opposite of a "whole brain sickness." However, neither treatment restored the plasticity; these results led Greifzu et al. (2011) to infer that nonlocal influences play a role in the lack of recovery.

Future studies need to examine how these possible treatments may work in patients. Diving deeper into the role of the molecular mechanisms of the relationship between the immune response to inflammation and plasticity would offer more information to whether or not anti-inflammatories would provide successful treatments. Additionally, the cellular mechanisms behind the plasticity paradigms would reveal more information regarding the role of nonlocal influences. Although there are many holes in this large mystery

concerning plasticity and inflammation, it is important to keep studying this possible connection to improve stroke victims' outcomes.

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