Controlling Plasticity in the Adult Brain

The Role of Perineuronal Nets in Regulating Network Dynamics and the Potential for Plasticity-Based Therapies

Clare A. Gollnick, Seth D. Koenig, Daniel C. Millard, Garrett B. Stanley, Ravi V. Bellamkonda

Wallace H. Coulter Department of Biomedical Engineering, Georgia Institute of Technology & Emory University

Introduction

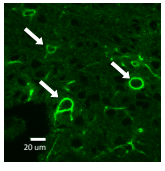
The human brain is plastic – it can change the way it responds to the same input over time.

Neuroplasticity is a central mechanism by which our brains develop, learn new things, and recover from injury. Plasticity requires specific timing of inputs in order to change the strength and locations of synapses.

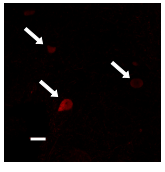
However, plasticity in the *adult* brain is largely limited in favor of stability. In certain situations (i.e. when interfacing with a neural prosthetic, or after an injury or stroke) it would be useful to be able to control the level of plasticity in an adult brain. The long-term goal of this project is to understand the regulation of plasticity in the brain well enough that it can be actively controlled (for review see Spolidoro 2009).

By studying the transition between high levels of plasticity during developmental 'critical periods' to low levels of plasticity in the adult, we can begin to understand how plasticity is regulated. Perineuronal net formation is an important event that causes the close of these critical periods.

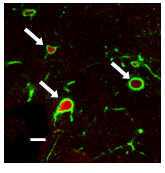
Perineuronal Nets



Perineuronal Nets (PNNs) are sugar-protein complexes that surround neurons in the adult cortex. Degradation of PNNs has previously been shown to reactivate certain types of plasticity. (Pizzorusso 2002)



Parvalbumin (PV) neurons are a specific type of inhibitory neuron that have been implicated in learning and development. The role of PV neurons in plasticity is not understood. (Morellini 2010)



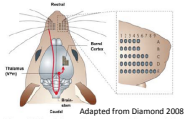
Perineuronal nets often surround cortical parvalbumin neurons, especially in sensory systems. However, the functional effects PNNs play on PV neurons (and the link to plasticity) has never been studied.

Hypothesis

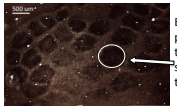
Perineuronal Nets reduce neural plasticity by **functionally s**tabilizing parvalbumin-expressing inhibitory neurons. When PNNs are degraded, the inhibitory influence is reduced -- resulting in greater neuroplasticity.

Model System: Rodent Somatosensory Cortex

The part of the cerebral cortex that processes information related to the whiskers is known as the barrel cortex.



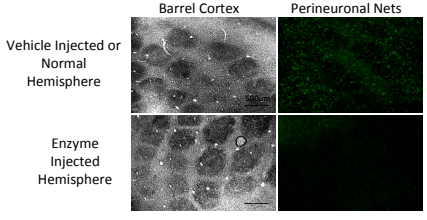
Adapted from Diamond 2008



Each 'barrel' is the part of the brain that responds to a specific whisker on the face.

The whisker map is preserved along all points in the anatomical pathway. Specifically a single whisker on the face maps to a single 'barrel' in the cortex of the brain. This discretization allows us to provide precise inputs (moving a single whisker at a known velocity).

Enzymatic Degradation of PNNs

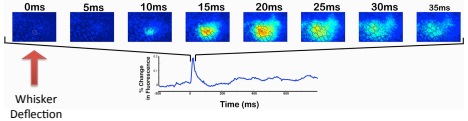


A bacterial enzyme, chondroitinase ABC (chABC), is injected in the barrel cortex. chABC breaks down the bonds between the sugars and proteins that comprise PNNs. Five days after injection PNN staining disappears, showing that PNNs no longer exist.

Measuring Activity with Functional Imaging

Because the brain encodes information in neuron membrane voltages, we use a voltage sensitive fluorescent dye (applied to the brain) to image brain activity.

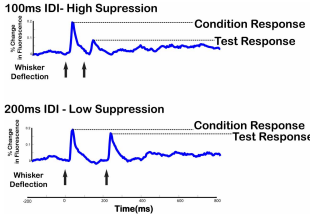
Example Response to Single Whisker Deflection



Quantifying the Inhibitory Input

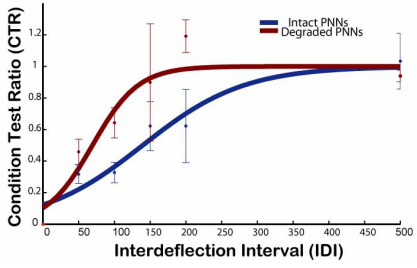
In normal animals, if two stimuli occur close together the response to the second is less than the first due to local inhibitory input (i.e. parvalbumin neurons). (Simons 1985)

By quantifying how long it takes for the neural network to return to baseline we can quantify the relative effect of the inhibitory input.



$$\text{Condition Test Ratio} = \frac{\text{Test Response}}{\text{Condition Response}}$$

PNN Degradation Results in a More Excitable Network



Animals that do not have PNNs in the barrel cortex return to a baseline faster than those with intact PNNs. This is interesting because more "excitable" neural networks are generally considered to be more plastic.

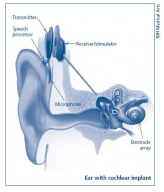
Significance

This is the first study to show a functional effect of PNN degradation prior to sensory deprivation. It is a first step to understanding how PNNs restrict plasticity. The results of this study have given rise to two significant hypotheses that will help guide further clinical studies.

1) The extracellular matrix plays a *functional* role for neural circuitry, not just a structural one.
2) Parvalbumin neurons may play a more important role in regulation of neuroplasticity than previously thought.

These both suggest novel pharmacological methods of regulating plasticity.

Clinical Need for Plasticity-Based Therapies



Credit: NIH Medical Arts

Children who are implanted with neuroengineered devices, like the cochlear implant, prior to the end of critical periods have greater success with them (Sharma 2002). If we can turn an adult's brain into a "highly-plastic" state, we could increase success with these and other neural prosthetics.

Additionally, since plasticity is the mechanism for central nervous system regeneration, by controlling plasticity we could increase success with:

- Rehabilitation after stroke or traumatic brain injury
- Minimizing deficits from developmental disorders
- Preventing seizures
- …and possibly many other central nervous system disorders.

(Wittenberg 2010)

Future Directions

While these results show that PNN degradation has an overall effect on the balance between excitation and inhibition, we have not conclusively shown that this is caused by parvalbumin neurons.

Future studies will be designed to understand the function of PNNs on these neurons directly and to try to establish a causal link between excitability and plasticity. Longer term studies will focus on testing the clinical implications of this discovery.

References

Diamond, M. E. et al. Nature Reviews Neuroscience 9, 601-12(2008).
Morellini, F. et al. Cerebral cortex 1-16(2010).
Pizzorusso, T. et al. Science 298, 1248-51(2002).
Sharma, A., Dorman, M.F. & Spahr, A.J. Ear and Hearing 23, 532-9(2002).
Simons, D.J. Journal of Neurophysiology 54, 615-35(1985).
Spolidoro, M. et al. Experimental Brain Research. 192, 335-41(2009).
Wittenberg, G.F. Neurobiology of Disease 37, 252-8(2010).

Acknowledgments

Clare Gollnick is supported by an NSF IGERT Fellowship.

Research supported by NIH Grant R01NS48285 (G.B.S.), Coulter Foundation (RVB), and R0143486 (RVB).