Renee Lee
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Article Summary

Article: “A metaplasticity view of the interaction between homeostatic and hebbian plasticity”

In this article, the researchers investigated the relationship between homeostatic and Hebbian plasticity, and previous research showing how they interact with each other. Homeostatic plasticity is how a neural network maintains itself while Hebb’s rule of plasticity is the mantra of ‘neurons that fire together, wire together” (Yee et al., 2017). From previous research, Cooper, Liberman and Oja initially made the CLO model, which proposed Hebbian and anti-Hebbian rules of synaptic plasticity capable of synaptic weakening and strengthening. Due to flaws found from the model from testing, Bienenstock, Cooper and Munro modified the original model to make the BCM model, which proposed the addition of a sliding modification threshold to the CLO model. There are no hypotheses or predictions proposed in this paper, as it is based on past research on the metaplasticity of the influence of Hebbian plasticity and homeostatic plasticity.

Based on circuit mechanisms, the competition model of Hebbian plasticity was created to reflect how the strength of responses compete to be strengthened or weakened. Based on Hebbian plasticity, when there is a competition between two inputs, the stronger input is strengthened while the weaker input is further weakened. An example given was an experiment done by Hubel and Wiesel in which monocular deprivation (MD) was manipulated on a kitten eye to see if it affects ocular dominance plasticity (ODP) during their critical period. This is due to a synaptic depression of excitatory input from the thalamus, and as MD is prolonged it leads to a second Hebbian phase of the non-deprived eye’s potentiation of responsiveness.

Oppositely, the overall strengthening or weakening of inputs is influenced by homeostatic plasticity as shown in Fig. 1 (Wiesel & Hubel, 1963). The inputs from the deprived eye are shown to be strengthened by excitatory synapses (Yee et al., 2017). Homeostatic strengthening occurs during MD or dark rearing and is shown during and after the critical period. These deprivation studies showed that competing input strength activates Hebbian plasticity, while homeostatic plasticity is changed overall.

Another experiment in which the researchers trimmed off the whiskers of young rats during their critical period is done to test the activation of the somatosensory cortex (Yee et al., 2017). The cortex overall experiences deprivation from the whisker trimming (barrel cortex) or modification for lack of tactile input. The modification is followed by an increase then decrease in strength of feedback of homeostatic plasticity. The Hebbian plasticity shows weakening of the excitatory input and neuron response.

In the functional interaction of Hebbian and homeostatic plasticity, there was an *in vitro* study of hippocampal slides with tetrodotoxin (TTX) used for homeostatic scaling of 'silent synapses' (Yee et al., 2017). This reactivates the silent synapse for increased levels of long-term potentiation (LTP). Another study used hippocampal slices with TTX and APV (a NMDA receptor blocker) with similarly increased LTP. In vivo studies using sensory deprivation showed that during dark rearing, synaptic activity in the visual cortex decreased while LTP increased. These experiments show the lasting effects of the homeostatic response to sensory deprivation and how it affects Hebbian plasticity.

It is important to note that changes to either Hebbian or homeostatic plasticity does not necessarily have to affect the other. However, between them is shared molecular regulators, which is mediated by receptor trafficking pathways. One shared part is Arc/ Arg3.1 and is upregulated by increased synaptic activity and regulates AMPA receptors and is involved in hippocampal LTP and LTD and homeostatic plasticity of the hippocampus and cortex (Yee et al., 2017). There are differences between the two plasticity as their AMPA receptors are different as the pathways are engaged in different signaling components. The conclusion found in these studies is that some types of synaptic plasticity were said to be Hebbian but also showed they were regulated by homeostatic plasticity and altering the pathways could affect the other pathways even when not directly affecting one, however, to determine that there needs to be a dissection of one pathway without affecting the others.

There are distinct players in homeostasis plasticity that affect the pathways for homeostatic plasticity directly. TNFalpha, a glial-derived factor which is not involved in Hebbian LTP and LTD, participates in homeostatic plasticity along with retinoic acid (RA). This was shown within *in vivo* mice who had TNFalpha knockout that showed Hebbian weakening of visual cortical responses from short periods of MD, but did not show homeostatic recovery (Yee et al., 2017). TNF alpha is used for reducing excitatory synaptic transmission and for driving synaptic AMPA receptor trafficking reduces glutamatergic synaptic strength. This is shown in Fig. 2, as an experiment with cocaine and AMPA/NMDA ratio and growth, showing that TNFalpha knockout mice did have an increased ratio with cocaine exposure compared to WT. Also, RA is very important for homeostatic plasticity, as it is activated by redacted excitatory synaptic transmission and calcium levels of dendritic cells are decreased. Both of these components can be excitatory and inhibitory synapses for synaptic transmission strength, and both are not directly involved in Hebbian plasticity making them great candidates for investigating the influence of homeostatic plasticity on a Hebbian intact circuit.

Based on how homeostatic plasticity impacts the function of Hebbian plasticity it is questionable whether homeostatic plasticity is a form of metaplasticity. The research done to uncover this question serves around altering only homeostatic plasticity and see the effects on

Hebbian plasticity. Visual deprivation facilitates LTP and restricts LTD in rodents for MD as ODP is recoverable in dark environments. More were asked about dark exposure to animals without homeostatic plasticity and if they react differently when deprived of it. Homeostatic plasticity has very generalized inputs compared to Hebbian plasticity which is very specific. More research shows that it also changes in local areas, so more questions were asked. RA has both local and global effects on neurons and shows the possibility for local use of homeostatic plasticity.

The conclusion says that we know a lot more about Hebbian plasticity than homeostatic plasticity and observing them in *in vivo* studies. The molecular mechanisms involved more in just homeostatic plasticity and that in helps with learning more about Hebbian functions. RA shows how homeostatic plasticity is a type of metaplasticity by the similar function it has to Hebbian plasticity.

What I found interesting from this article is that homeostatic and Hebbian plasticity interact in a variety of ways, from globally to local scales. This sort of interaction reminded me of how there's so many different influences for plasticity that students are not initially aware of in early biology and bio psych classes. Since this is a research article on past experiments, I would say that there could be more research about homeostatic plasticity as there is not much known about it, and more experiments with RA could be done.

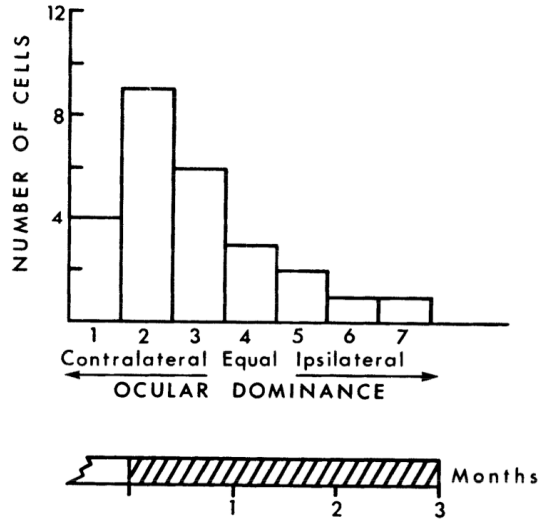

FIG. 12. Ocular-dominance distribution of 26 cells recorded in the left visual cortex of an adult cat whose right eye had been covered by lid suture for a period of 3 months. As in the normal cat, the contralateral eye—in this case the deprived eye—dominated.

Fig 1. This graph from Wiesel and Hubel (1963) represents the decrease in the number of cells for ocular dominance on the contralateral and ipsilateral sides of the visual cortex from the right eye during the MD Hubel and Wiesel experiment. The right eye of a kitten was sutured shut, and the left visual cortex was recorded to see the difference between the left and right eye on the ipsilateral side to find if they have been interrupted by the MD. Findings show that the

number of cells in the contralateral cortex to the right eye does have a decrease in the total number of cells. The bottom bar of this graph is supposed to represent the total amount of time from when the manipulation started, but it is difficult to see how it is used in this graph.

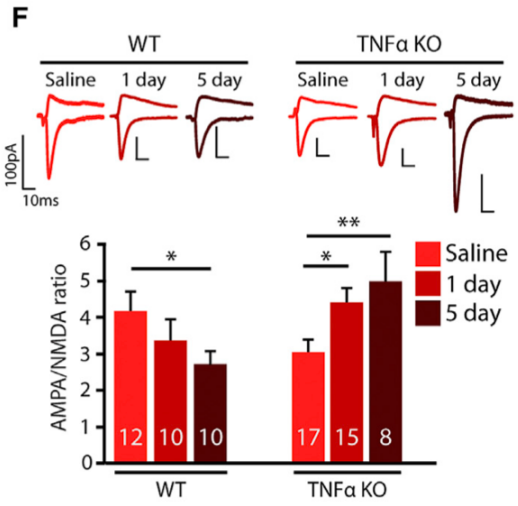

Fig 2. This graph from Lewitus et. al. (2016) shows the TNFalpha knockout experiment to see if the AMPA/NMDA ratio changed over time as TNFalpha is said to reduce excitatory transmission for the increase of AMPA receptor growth. The days represent the amount of time with exposure to cocaine and the bar graph shows AMPA/NMDA ratio. With cocaine the wild type (WT) has a decrease in ratio, while the TNFalpha has an increased ratio instead. The line graphs above seem to show the overall change in the direction of growth during the time of cocaine exposure. Unsure what the numbers on the bars mean.

Lewitus, G. M., Konefal, S. C., Greenhalgh, A. D., Pribiag, H., Augereau, K., & Stellwagen, D. (2016). *Microglial TNF-α Suppresses Cocaine-Induced Plasticity and Behavioral Sensitization. Neuron, 90(3), 483–491.* doi:10.1016/j.neuron.2016.03.030

Wiesel, T. N., & Hubel, D. H. (1963). Single-cell responses in striate cortex of kittens deprived of vision in one eye. *Journal of Neurophysiology, 26(6), 1003–1017.* doi:10.1152/jn.1963.26.6.1003

Yee, A. X., Hsu, Y. T., & Chen, L. (2017). A metaplasticity view of the interaction between homeostatic and Hebbian plasticity. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *372*(1715), doi: https://doi.org/10.1098/rstb.2016.0155.