Principles of Neuroscience example essay 2

Jia et al. offered evidence that hotspots of calcium transients in the dendrites of a postsynaptic neuron originate from excitatory synaptic inputs on active dendritic spines. If true, this brings up a host of interesting questions. First of all, the notion that these calcium transients spread from individual spines warrants further investigation. In Figure 2, it appears that spines are also found in areas without hotspots. Do spines located in a hotspot differ morphologically from non-hotspot spines? This could be addressed with fluorescent imaging techniques such as those presented in the article, comparing enlarged views of dendritic hotspots versus areas where no hotspot activity can be seen. I predict that readily discernable morphological differences between these two groups will not be found, as these particular hotspots were measured in response to a particular visual orientation. Since each neuron receives inputs from many differently-tuned neurons, it is possible that different orientations of visual stimuli will result in different hotspot locations.

Bloodgood et al.'s 2009 PLoS Biology's paper argues that dendritic spine morphology and, in particular, that of the spine neck, serve to filter synaptic activity and regulate calcium influx. Taking this into account, can a correlation be found between the relative "hotness" of the hotspot and the resistance of the spine neck? It could be that the strength of the postsynaptic response is mediated more by spine neck morphology rather than presynaptic factors, such as increased rate or quantity of neurotransmitter release. This could be tested in part by plotting the relative fluorescence of hotspots against the composite spine neck volume of all spines that can be visualized within the hotspot. However, due to the inherent difficulty in measuring distances at such a small scale, spine neck measurements will probably be rough and have a high degree of error. It would also be impossible to control for the quanta of presynaptic neurotransmitter release *in vivo*. Thus, it may be useful to use 2-photon laser photoactivation *in vitro* by uncaging

a specific amount of glutamate on spines that have either long and skinny (high resistance) or short and fat (low resistance) necks. This way, the effect of spine neck resistance on calcium influx can be measured with greater accuracy. Still, an important point to remember is that the imaging rate for these "high speed" scans is 30 frames/second, and each hotspot is the result of averaging 100 frames. Consequently, trying to base analyses on the rapid temporal dynamics of calcium flux may not be particularly fruitful in this situation.

The biggest question raised by Jia et al. is how neurons can output a single orientation preference while receiving many individual differently-tuned inputs with no apparent spatial organization. What is the nature of the computational process in "deciding" which orientations to enhance or ignore? The simplest answer would be that of brute force, where the orientation preference with the most inputs or hotspots wins. If this is the case, it may be possible to change the orientation preference of a neuron by selectively ablating hotspots or even whole dendritic branches that display the same tuning preference as the output. I am not aware of any technique with the precision to prune a dendritic arbor, but perhaps the 2-photon laser can be modified to deliver a focused beam so high-energy that it can disrupt portions of plasma membrane. Theoretically, in a structure as small and thin as a dendritic process, it may be possible for the remaining membrane to pinch off and "heal" without the ablated portion. However, even if it were technically possible, the probability of this damaging or killing the cell would be very high; among other issues, trauma to the plasma membrane may cause uncontrollable cation influx, signaling to the cell that it is injured and causing it initiate apoptosis. Because of these confounds, it may be more realistic to functionally disable selective areas of the dendrite by using 2-photon laser activation to uncage a molecule such as APV that inhibits NMDA receptors. This would keep the structural integrity of the neuron intact as well as afford the experimenter spatial control over his or her manipulations at the level of individual dendritic spines.