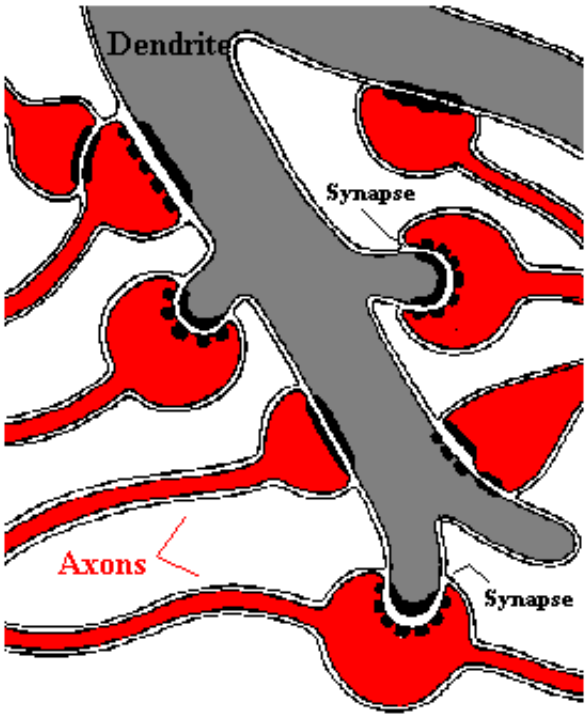
Structural dynamics underlying memory in aging brains

April 17 2013, by John Hewitt



Credit: Eric H. Chudler - "Neuroscience for kids"

(Medical Xpress)—When the brains of those who have succumbed to age-related neurodegeneration are analyzed post-mortem, they typically show significant atrophy on all scales. Not only is the cortex thinner and sparser, but the hollow ventricles inside the brain are grossly enlarged. In the absence of any specific disease, these general trends are still familiar. It has traditionally been assumed that the dynamic microfeatures of aged

brains—the growth of the fine neurites and the synapses they make—would similarly be degenerate. In other words, synaptic growth would have either entered some form of stasis, or alternatively, a state of permanent decay with replacement by matrix or scar tissue. Contrary to these expectations, recent research shows increased structural plasticity in the axonal component of synapses in the aged mouse cortex. Reporting in the current issues of *PNAS*, researchers provide evidence that the observed behavioral deficits in these animals may be due to an inability to maintain persistent synaptic structure, rather than because of a loss of plasticity.

Specifically, the researchers found dramatic increases in the rates of synapse formation and elimination. They used two-photon microscopy to image axonal arbors and boutons in aged brains over time. Compared to young adult brains, established synaptic boutons in aged brain showed 10-fold higher rates of destabilization, and 20-fold higher turnover. The researchers also demonstrated, that while the size and density of synapses was comparable, size fluctuations were significantly higher in the aged brains.

Changes in synaptic structure are believed to be the mechanism for encoding long-term memory in the brain. In the absence of the full molecular picture underlying the way they change and grow, macroscopic appearance (size) is a convenient stand-in used to gauge relative importance of a particular synapse. Among other things, a larger synapse has greater resource at its disposal to reliably match incoming spikes to transmitter release. Not only can a larger synapse generally do this matching faster, they can do it for a longer time. The new studies suggest, however, that decreased ability to form new memories, or learn new behaviors, results from synapses being too fickle, rather than from loss of flexibility.

Clearly the full behavior of synapses is far from understood, despite it

being one of the central preoccupations of experimental neuroscience. It is generally believed that the average synapse is at best able to match an incoming spike with fusion of a vesicle (and subsequent transmitter release) roughly half of the time. Many theoretical efforts have been made to account for this fact. One approach has been to do a strict accounting analysis of the energetic use of ATP by a neuron's entire signalling tree. In other words, estimate how a neuron partitions its ATP budget between transmitting information in the form of spikes down the axon, and that spent in completing the hand-off to the next neuron at the synapse.

Detailed and painstaking measurements of axonal structural dynamics, as done here by the authors, is critical ground-floor work towards understand neural circuits. Isolated molecular details, while important, will never be sufficient to completely understand how learning and memory emerge from architectural changes. The current efforts of the BRAIN Initiative to map the complete connectome of a brain, together with a full activity map, will also need to include efforts to create what might be called, a theory of neurons. The ways in which neurons budget their energy, is likely to a central component of such a theory.

As a start, one postulate of a theory of neurons, that is consistent with the one-half probability for synaptic information transfer, might be the following: neurons tend to match the energy spent in sending spikes through their entire axonal arbor, with the sum total of the energy spent at all terminal boutons of that axon. The temporal aspects of how synapses are generated and eliminated in a short-lived animal, like a mouse, may be far different than those in a human. Understanding how these processes change with age, and with the amount of energy available to synapses to effect that change, will help complete the larger picture.

More information: Increased axonal bouton dynamics in the aging

mouse cortex, *PNAS*, 2013. doi:10.1073/pnas.121873111 .
www.pnas.org/content/110/16/E1514.long

Abstract
Aging is a major risk factor for many neurological diseases and is associated with mild cognitive decline. Previous studies suggest that aging is accompanied by reduced synapse number and synaptic plasticity in specific brain regions. However, most studies, to date, used either postmortem or ex vivo preparations and lacked key in vivo evidence. Thus, whether neuronal arbors and synaptic structures remain dynamic in the intact aged brain and whether specific synaptic deficits arise during aging remains unknown. Here we used in vivo two-photon imaging and a unique analysis method to rigorously measure and track the size and location of axonal boutons in aged mice. Unexpectedly, the aged cortex shows circuit-specific increased rates of axonal bouton formation, elimination, and destabilization. Compared with the young adult brain, large (i.e., strong) boutons show 10-fold higher rates of destabilization and 20-fold higher turnover in the aged cortex. Size fluctuations of persistent boutons, believed to encode long-term memories, also are larger in the aged brain, whereas bouton size and density are not affected. Our data uncover a striking and unexpected increase in axonal bouton dynamics in the aged cortex. The increased turnover and destabilization rates of large boutons indicate that learning and memory deficits in the aged brain arise not through an inability to form new synapses but rather through decreased synaptic tenacity. Overall our study suggests that increased synaptic structural dynamics in specific cortical circuits may be a mechanism for age-related cognitive decline.