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Origin of synaptic pruning process linked to learning, autism and schizophrenia identified

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Research led by SUNY Downstate Medical Center has identified a brain receptor that appears to initiate adolescent synaptic pruning, a process believed necessary for learning, but one that appears to go awry in both autism and schizophrenia.

Sheryl Smith, PhD, professor of physiology and pharmacology at SUNY Downstate, explained, "Memories are formed at structures in the brain known as dendritic spines that communicate with other brain cells through synapses. The number of brain connections decreases by half after puberty, a finding shown in many brain areas and for many species, including humans and rodents."

This process is referred to as adolescent "synaptic pruning" and is thought to be important for normal learning in adulthood. Synaptic pruning is believed to remove unnecessary synaptic connections to make room for relevant new memories, but because it is disrupted in diseases such as autism and schizophrenia, there has recently been widespread interest in the subject.

Dr. Smith continued, "Our report is the first to identify the process which initiates synaptic pruning at puberty. Previous studies have shown that scavenging by the immune system cleans up the debris from these pruned connections, likely the final step in the pruning process.

"Working with a mouse model we have shown that, at puberty, there is an increase in inhibitory GABA receptors, which are targets for brain

chemicals that quiet down nerve cells. We now report that these GABA receptors trigger synaptic pruning at puberty in the mouse hippocampus, a brain area involved in learning and memory." The report, published by *eLife*, "Synaptic pruning in the female hippocampus is triggered at puberty by extrasynaptic GABAA receptors on dendritic spines," (Afroz, S., Parato, J., Shen, H. and Smith, S.S.), is online at: http://elifesciences.org/content/5/e15106v1 .

Dr. Smith adds that by reducing brain activity, these GABA receptors also reduce levels of a protein in the dendritic spine, kalirin-7, which stabilizes the scaffolding in the spine to maintain its structure. Mice that do not have these receptors maintain the same high level of brain connections throughout adolescence.

Dr. Smith points out that the mice with too many brain connections, which do not undergo synaptic pruning, are able to learn spatial locations, but are unable to re-learn new locations after the initial learning, suggesting that too many brain connections may limit learning potential.

These findings may suggest new treatments targeting GABA receptors for "normalizing" synaptic pruning in diseases such as autism and schizophrenia, where synaptic pruning is abnormal. Research has suggested that children with autism may have an over-abundance of synapses in some parts of the brain. Other research suggests that prefrontal brain areas in persons with schizophrenia have fewer neural connections than the brains of those who do not have the condition.

More information: Sonia Afroz et al, Synaptic pruning in the female hippocampus is triggered at puberty by extrasynaptic GABAreceptors on dendritic spines, *eLife* (2016). DOI: 10.7554/eLife.15106