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Can New Neurons Replace Memories Lost?

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Over 10 years ago, it was “rediscovered” that the adult brain continues to produce new neurons throughout the life span (1-3). There had been some reports of neurogenesis previous to these, especially in avian species (4), but the demonstration in primates and, in particular, human primates initiated a revolution of sorts in the neurosciences--certainly, a paradigmatic shift (5). Since then, it has been demonstrated that adult-generated neurons are functional to the extent that they have electrical properties consistent with established neurons in the adult brain, and they project axons to afferent brain regions (6, 7) (see “[Newborn Neurons Search for Meaning](#)”). Nearly every week, a surprising, or at least unexpected, finding about adult neurogenesis is reported (see [Wise Perspective](#)); last week was no exception.

In the most recent issue of the *Proceedings of the National Academy of Sciences U.S.A.*, Jin *et al.* (8) report that neuronal markers for proteins that are associated with the production of new neurons are expressed in the hippocampus--a part of the brain critical for some types of learning and memory--of brains obtained from patients with [Alzheimer's disease](#) (AD). The most serious consequence of AD is the inability to form and use memories, especially those that are dependent on the hippocampal formation. In the study, patients with severe dementia at the time of their death had increased expression of neuronal markers, especially those associated with immature neurons such as doublecortin, polysialylated nerve adhesion molecule, NeuroD, and TUC4. The increase in expression of immature neuronal markers was observed in the dentate gyrus of the hippocampus, a brain region in which the vast majority of new neurons appear to proliferate and reside. They also reported increased expression in area CA1 in the hippocampus, which has not been shown to produce new neurons under normal disease- or injury-free conditions. It is important to note that the authors of this publication have not demonstrated that neurogenesis itself is increased; that is, they have not shown increased cell proliferation along with the expression of neuron-specific markers. It is possible that existing neurons may increase the expression of immature proteins when they are being taxed during a neuropathological process. Nonetheless, these new findings are thought-provoking.

AD is characterized by neuron loss and the presence of intracellular neurofibrillary tangles (which consist of the tau protein) and extracellular amyloid plaques in olfactory and limbic brain regions (see [Detangling Alzheimer's Disease](#)). These regions include the hippocampal formation and olfactory bulb, which are, as it happens, the brain sectors in which neurogenesis is most prevalent. If one were to predict the degree of neurogenesis that occurs during AD, one might expect to observe a decrease in proliferation, especially in the hippocampal regions, where the most devastating effects of the disease are observed. However, there have been a variety of reports in recent years predicting what was actually observed: an increase. In the 1990s, Gould and colleagues reported that injury induced in

rats by lesions to the entorhinal cortex greatly enhanced the proliferation of new neurons in the hippocampus (9). The entorhinal cortex, which is the origin of the neural fibers that carry sensory information to the hippocampus, is not known for its regenerative potential, but it provides the primary input into the dentate gyrus, where the vast majority of new neurons do proliferate and reside; the entorhinal cortex is a much, if not the most, affected brain region during the early progression of AD. It has also been shown that neurogenesis in the dentate gyrus of the hippocampus is increased by the death of granule neurons in this region of the brain (9). Thus, increases in neuronal production in AD patients might result from the destruction of afferents from cortical regions or from cell death in the dentate gyrus itself. So although at first it may seem counterintuitive that new neurons would be produced during the progression of a disease such as AD, it is not so unexpected if one considers the evidence that these cells proliferate in response to injury, specifically injury to those regions affected in AD.

Perhaps the most surprising finding in the Jin *et al.* study is the reported increase in the expression of immature neuronal markers in area CA1 of the hippocampus. Although area CA1 is also affected by AD, there is little evidence of substantial neurogenesis in this region under normal conditions. However, a relatively recent report illustrated that neuronal loss after ischemia is followed by the proliferation of new neurons in area CA1 of the hippocampus in mice (10). Treatment with growth factors further enhanced the restoration of neurons. Moreover, the learning deficits that emerged after ischemia were lessened after treatment with growth factors and the regeneration of neurons.

Whether the presence of new neurons in the AD brain represents a compensatory response to neuron loss or is occurring before the major devastation that accompanies the disease remains to be determined. Aside from their neurons, AD patients lose their memories and the ability to form new ones. It is thus relevant that adult-generated neurons appear to be involved in the formation of certain types of new memories, the types regarding which AD patients are most vulnerable. By treating rats with an antimitotic agent, we were able to show that a substantial reduction in neurogenesis in the dentate gyrus of the hippocampus results in learning impairments consistent with those observed in AD patients (11, 12). Others have shown that brain radiation, which eliminates nearly all of the new neurons in the hippocampus, is accompanied by learning deficits (13). Under normal conditions, most of the adult-generated neurons die within weeks. However, exposure to associative learning enhances the survival and longevity of the new neurons (Fig. 1) (14). The types of learning that rescue neurons from death include a task known as trace conditioning, in which an animal learns to associate stimulus events that are separated in time. This type of learning does not occur when the hippocampus is damaged (15). In humans, these types of learning tasks distinguish between the cognitive deficits associated with normal aging and those associated with AD (16). In summary, then, there appears to be a connection between neurogenesis and learning on one hand and putative neurogenesis and memory loss in AD on the other. However, Jin *et al.* (8) also reported that the expression of NeuN, a marker for more mature neurons, was not enhanced in the AD brain. These data suggest that, if new neurons are indeed being created in AD brains, they do not survive for very long after their generation. It may be that without connections to other more established neurons or without significant input from the entorhinal cortex, the new cells don't survive or become functionally incorporated.

My mother has a friend with AD and severe memory loss. A few weeks ago, he went off on his bike and was found nearly a week later sleeping in a pool of mud in the woods not too far away from his home. He had no memory of where he had been or what had happened, and because he was the only one there, no one will ever know. Without anecdotes such as these, it is difficult to fathom the degree of devastation and grief that this disease brings to

patients and their families. So is the suggestion of neurogenesis during the progression of AD good news or bad? Probably good, at least to the extent that the potential for new neuron growth remains even in the late stages of such a debilitating neurological disease. For decades, it had been believed that neurons were only produced during gestation and the early postnatal period, and not thereafter. According to this dogma, there was little hope of replacing neurons lost with aging or in response to neurodegenerative diseases such as AD. Of course, we now appreciate the potential, including the therapeutic implications, that the “rediscovery” of neurogenesis presents. In addition to the role that newly generated neurons may play in memory formation, there are nearly daily reports that experiences of many sorts can alter their production—everything from exercise to antidepressants to mental stimulation can enhance the generation of neurons in the adult hippocampus (17–19). It may be worth prescribing these activities as ways to boost the potential that is already there, before the serious loss of neurons and memories occurs. It couldn't hurt.

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Fig. 1.

Learning and memory. The graph shows the number of new neurons in the dentate gyrus of the rat hippocampus. Cells of the dentate gyrus of the rat hippocampus were labeled with BrdU, a marker of cell division, 1 week before training, and animals were either kept in their home cage (Naïve) or trained with 800 trials of trace conditioning (Learning), a learning task that is dependent on the hippocampal formation (15). The formation of trace memories enhanced the survival of newly generated cells, the vast majority of which coexpressed neuron-specific markers (14).