



# Rise and Fall of the Empire: Conquering Alzheimer's Disease by Targeting Adult Neurogenesis

Epilepsy Currents  
2019, Vol. 19(6) 411-413

© The Author(s) 2019

Article reuse guidelines:

sagepub.com/journals-permissions

DOI: 10.1177/1535759719874813

journals.sagepub.com/home/epi



## Early Seizure Activity Accelerates Depletion of Hippocampal Neural Stem Cells and Impairs Spatial Discrimination in an Alzheimer's Disease Model

Fu CH, Iacone DM, Petrof I, Hazra A, Zhang X, Pyfer MS, Tosi U, Corbett BF, Cai J, Lee J, Park J, Iacovitti L, Scharfman HE, Enikolopov G, Chin J. *Cell Rep.* 2019;27(13):3741-3751.e4. doi:10.1016/j.celrep.2019.05.101. PMID:31242408.

Adult hippocampal neurogenesis has been reported to be decreased, increased, or not changed in patients with Alzheimer disease (AD) and related transgenic mouse models. These disparate findings may relate to differences in disease stage, or the presence of seizures, which are associated with AD and can stimulate neurogenesis. In this study, we investigate a transgenic mouse model of AD that exhibits seizures similarly to patients with AD and find that neurogenesis is increased in early stages of disease, as spontaneous seizures became evident, but is decreased below control levels as seizures recur. Treatment with the antiseizure drug levetiracetam restores neurogenesis and improves performance in a neurogenesis-associated spatial discrimination task. Our results suggest that seizures stimulate, and later accelerate the depletion of, the hippocampal neural stem cell pool. These results have implications for AD as well as any disorder accompanied by recurrent seizures, such as epilepsy.

## Commentary

Alzheimer's disease (AD) is a neurodegenerative disorder and contributes to more than two-thirds of dementia cases all over the world. Ever since its first description in a lecture delivered by Alois Alzheimer (a psychiatrist) in 1906, a century has been spent investigating the pathology, etiology, mechanisms, and treatment strategies for AD. At the histopathological level, AD is characterized by deposition of plaques and tangles in brain and extensive neuronal loss. While plaques are a result of accumulation of abnormally folded A $\beta$  (amyloid-beta) peptides (a cleavage product of amyloid precursor proteins [APP]), neuronal tangles are formed by intracellular connections of hyperphosphorylated cytoskeletal tau proteins.<sup>1</sup> Moreover, a review of clinical literature shows that epileptiform activity is also often associated with AD and the appearance of seizures has been reported to happen as early as in the age-group of 50 to 60 years.<sup>2-4</sup> The association between AD and epilepsy has also been shown in mouse models of AD.<sup>5,6</sup> This early association of seizures in AD raises the possibility of their crucial role in the progression of the disease.

Characteristic pathological symptoms of AD include memory loss, mood impairments, and cognitive decline. Noticeably, the hippocampus has been extensively studied and reported to be critical for above mentioned pathological abnormalities. The hippocampus is also considered to be the most vulnerable brain structure in AD.<sup>7</sup> Adult neurogenesis, a

process defined as the generation of new neurons from a pool of neural stem cells (NSCs), occurs in the dentate gyrus (DG) of the hippocampus.<sup>8</sup> While decades of work have established that new neurons are continuously generated in rodent hippocampus and play a crucial role in memory and cognition under physiological conditions, the very existence and relevance of adult hippocampal neurogenesis in humans is still an open question.<sup>9,10</sup> A study published last year demonstrated robust presence of adult neurogenesis in humans, consistent with other work,<sup>11-14</sup> and also showed that neurogenesis decreased consistently in patients with AD,<sup>15</sup> although this is still a matter of debate.<sup>16,17</sup> Lineage tracing studies in rodents have shown that NSCs go through different developmental stages over a period of 4 to 6 weeks to become a fully mature granule neuron and integrate into the existing dentate circuitry. While this process is tightly regulated under physiological conditions, the scenario becomes different in a pathological condition such as epilepsy and AD.<sup>18</sup> Seizures have been shown to modulate the levels of hippocampal neurogenesis.<sup>18-20</sup> Alterations in levels of hippocampal neurogenesis have also been reported in mice that express high levels of A $\beta$  peptides.<sup>21,22</sup> Although these studies provide clues that seizure activity and hippocampal neurogenesis could together modulate the pathology of AD, it is still unknown whether there is a convergent mechanism in regulation of seizures, adult hippocampal neurogenesis, and AD.



Creative Commons Non Commercial No Derivs CC BY-NC-ND: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 License (<http://www.creativecommons.org/licenses/by-nc-nd/4.0/>) which permits non-commercial use, reproduction and distribution of the work as published without adaptation or alteration, without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).



The new study in *Cell Reports* by Fu et al suggests that early seizure activity first increases adult hippocampal neurogenesis and then later accelerates the depletion of NSC pool in a transgenic mouse model of AD. This biphasic increase and decrease in the level of neurogenesis could have implications in the progression of AD. Using transgenic APP mice, the authors perform time-course analysis to delineate the role of seizures and neurogenesis in AD pathology. Consistent with other studies, they find that hippocampal neurogenesis increases after spontaneous seizure starts (around 2 months) and decreases with age.<sup>20,23</sup> However, they find that around 3 months, the level of neurogenesis is lower in APP mice as compared to nontransgenic (NTG) controls and this trend continues up to 14 months. This is a significant finding that after an initial burst of neurogenesis due to spontaneous seizures, the NSC pool might become exhausted, and therefore, normal levels of neurogenesis cannot be restored. This loss in restoration of normal levels of neurogenesis could ultimately lead to cognitive decline and memory impairments in AD animals.


Using cell labeling techniques, the authors demonstrate that at 2 months of age the rate of division of NSCs is higher in APP mice as compared to NTG controls. This provides evidence that an increased rate of cell division in APP mice leads to accelerated loss of NSC pool. The authors also show that this accelerated loss of NSC pool is not due to fundamental differences in neurogenesis but is a consequence of a higher number of NSCs engaged in cell division as compared to NTG controls. However, a limitation of the study is that authors did not evaluate AD mice at earlier stages (before 1 month) at a time when NSCs already show an increase in cell division but mice lack epileptiform activity. An additional cohort of animals with AD and no seizures (until and unless the majority of AD mice exhibit early seizure activity) could help disentangle the causal relationship between early epileptiform activity, recurrent seizures, and neurogenesis in the context of AD pathology.

The current study by Fu et al shows that early seizures in APP mice increase NSC division and depletion of the NSC pool. However, one question that remains unanswered is how does early NSC division and later depletion lead to changes in seizures and AD pathology? It has been shown that chronic temporal lobe epilepsy in rats is associated with severe decline in neurogenesis.<sup>23</sup> Similarly, do older APP mice (6 months and 14 months) with diminished neurogenesis exhibit more seizures? Is this a consequence of depleted NSC pool and/or increased deposition of A $\beta$  peptides? Another limitation of the study is that authors do not show causality of neurogenesis and seizures in APP mice. Is there aberrant neurogenesis in APP mice that can play a causal role in seizures/AD pathology? The authors did not find any obvious morphological differences in immature neurons in APP mice, but they did find ectopic granule cells in the hilus of DG. In future studies, ablation of neurogenesis in APP mice at various time points should be able to provide evidence of the causal role of neurogenesis in AD pathology.<sup>24</sup>


Another interesting finding by Fu et al is that chronic treatment of APP mice with levetiracetam (LEV), a known

antiseizure drug, normalizes neurogenesis and improves spatial discrimination. This is an exciting result as it provides evidence that controlling seizures early on in AD could help in cognitive abilities. However, the authors started the treatment either at the age of 1.5 months or 2 months, a time point where seizures are spontaneous and recurrent. Clinical studies suggest that early seizures in AD can sometimes remain undiagnosed due to several reasons.<sup>2</sup> Therefore, it would be interesting to see if the drug treatment at earlier stages (eg, at 3 weeks where there is an increase in the percentage of dividing NSCs, but not the presence of spontaneous seizures) helps in normalization of neurogenesis and restoration of spatial discrimination abilities. The authors do clarify that the restoration of spatial discrimination does not necessarily mean that it is the consequence of normalized neurogenesis by LEV. Therefore, the question remains that if the AD animals exhibit seizure activity at later stages of life, will the administration of antiseizure drugs still be effective in controlling cognitive disabilities? Or is there a therapeutic window for antiseizure drug treatment to mitigate cognitive decline? Additionally, using neurosphere cultures, the authors provide evidence that alterations in neurogenesis and rate of NSCs division are not cell autonomous and more likely a result of the network-level factors such as epileptiform activity. This also suggests that other cell types including glial cells could also be involved in the process, and therefore, a comprehensive targeting of multiple factors would be most effective in long-term restoration of cognitive abilities.

In summary, this is an exciting study providing evidence that seizures in AD cannot be ignored even if there is a diagnostic uncertainty. Early epileptiform activity does modulate neurogenesis and can play a significant role in AD pathophysiology. Importantly, control of seizures early in AD can prevent or delay cognitive impairment. Moreover, this study suggests that common mechanisms of altered neurogenesis and depletion of NSC pool could broadly impact other diseases such as Down syndrome, Parkinson disease, Rett syndrome, schizophrenia, and others where mood and cognitive impairments occur, and comorbid seizures have also been reported. Future studies using circuit and molecular tools such as rabies virus labeling and single-cell RNA sequencing can help elucidate the circuits and cell types involved in seizure generation and AD pathology. This could eventually lead to better diagnostic and therapeutic interventions.

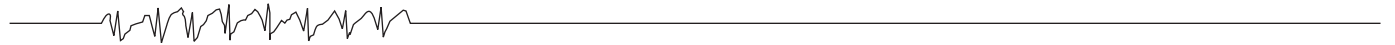
By Parul Varma and Jenny Hsieh 

#### ORCID iD

Jenny Hsieh  <https://orcid.org/0000-0003-0214-0771>

#### References

1. Bloom GS. Amyloid-beta and tau: the trigger and bullet in Alzheimer disease pathogenesis. *JAMA Neurol.* 2014;71:505-508. doi:10.1001/jamaneurol.2013.5847.
2. Noebels J. A perfect storm: converging paths of epilepsy and Alzheimer's dementia intersect in the hippocampal formation.

- 
- Epilepsia*. 2011;52(suppl 1):39-46. doi:10.1111/j.1528-1167.2010.02909.x.
3. Vossel KA, Beagle AJ, Rabinovici GD, et al. Seizures and epileptiform activity in the early stages of Alzheimer disease. *JAMA Neurol*. 2013;70(9):1158-1166. doi:10.1001/jamaneurol.2013.136.
  4. Vossel KA, Tartaglia MC, Nygaard HB, Zeman AZ, Miller BL. Epileptic activity in Alzheimer's disease: causes and clinical relevance. *Lancet Neurol*. 2017;16(4):311-322. doi:10.1016/S1474-4422(17)30044-3.
  5. Chin J, Scharfman HE. Shared cognitive and behavioral impairments in epilepsy and Alzheimer's disease and potential underlying mechanisms. *Epilepsy Behav*. 2013;26(3):343-351. doi:10.1016/j.yebeh.2012.11.040.
  6. Kam K, Duffy ÁM, Moretto J, LaFrancois JJ, Scharfman HE. Interictal spikes during sleep are an early defect in the Tg2576 mouse model of beta-amyloid neuropathology. *Sci Rep*. 2016;6:20119. doi:10.1038/srep20119.
  7. Halliday G. Pathology and hippocampal atrophy in Alzheimer's disease. *Lancet Neurol*. 2017;16(11):862-864. doi:10.1016/S1474-4422(17)30343-5.
  8. Ming GL, Song H. Adult neurogenesis in the mammalian central nervous system. *Annu Rev Neurosci*. 2005;28:223-250. doi:10.1146/annurev.neuro.28.051804.101459.
  9. Kempermann G, Gage FH, Aigner L, et al. Human adult neurogenesis: evidence and remaining questions. *Cell Stem Cell*. 2018;23(1):25-30. doi:10.1016/j.stem.2018.04.004.
  10. Kempermann G, Wiskott L, Gage FH. Functional significance of adult neurogenesis. *Curr Opin Neurobiol*. 2004;14(2):186-191. doi:10.1016/j.conb.2004.03.001.
  11. Boldrini M, Fulmore CA, Tartt AN, et al. Human hippocampal neurogenesis persists throughout aging. *Cell Stem Cell*. 2018;22(4):589-599 e585. doi:10.1016/j.stem.2018.03.015.
  12. Eriksson PS, Perfilieva E, Björk-Eriksson T, et al. Neurogenesis in the adult human hippocampus. *Nat Med*. 1998;4(11):1313-1317. doi:10.1038/3305.
  13. Spalding KL, Bergmann O, Alkass K, et al. Dynamics of hippocampal neurogenesis in adult humans. *Cell*. 2013;153(5):1219-1227. doi:10.1016/j.cell.2013.05.002.
  14. Tobin MK, Musaraca K, Disouky A, et al. Human hippocampal neurogenesis persists in aged adults and Alzheimer's disease patients. *Cell Stem Cell*. 2019;24(6):974-982 e973. doi:10.1016/j.stem.2019.05.003.
  15. Moreno-Jimenez EP, Flor-García M, Terreros-Roncal J, et al. Adult hippocampal neurogenesis is abundant in neurologically healthy subjects and drops sharply in patients with Alzheimer's disease. *Nat Med*. 2019;25(4):554-560. doi:10.1038/s41591-019-0375-9.
  16. Sorrells SF, Paredes MF, Cebrian-Silla A, et al. Human hippocampal neurogenesis drops sharply in children to undetectable levels in adults. *Nature*. 2018;555(7696):377-381. doi:10.1038/nature25975.
  17. Cipriani S, Ferrer I, Aronica E, et al. Hippocampal radial glial subtypes and their neurogenic potential in human fetuses and healthy and Alzheimer's disease adults. *Cereb Cortex*. 2018;28(7):2458-2478. doi:10.1093/cercor/bhy096.
  18. Overstreet-Wadiche LS, Bromberg DA, Bensen AL, Westbrook GL. Seizures accelerate functional integration of adult-generated granule cells. *J Neurosci*. 2006;26(15):4095-4103. doi:10.1523/JNEUROSCI.5508-05.
  19. Parent JM. The role of seizure-induced neurogenesis in epileptogenesis and brain repair. *Epilepsy Res*. 2002;50(1-2):179-189.
  20. Parent JM, et al. Dentate granule cell neurogenesis is increased by seizures and contributes to aberrant network reorganization in the adult rat hippocampus. *J Neurosci*. 1997;17(10):3727-3738.
  21. Chevallier NL, Soriano S, Kang DE, Masliah E, Hu G, Koo EH. Perturbed neurogenesis in the adult hippocampus associated with presenilin-1 A246E mutation. *Am J Pathol*. 2005;167(1):151-159. doi:10.1016/S0002-9440(10)62962-8.
  22. Hamilton LK, Aumont A, Julien C, Vadnais A, Calon F, Fernandes KJ. Widespread deficits in adult neurogenesis precede plaque and tangle formation in the 3xTg mouse model of Alzheimer's disease. *Eur J Neurosci*. 2010;32(6):905-920. doi:10.1111/j.1460-9568.2010.07379.x.
  23. Hattiangady B, Rao MS, Shetty AK. Chronic temporal lobe epilepsy is associated with severely declined dentate neurogenesis in the adult hippocampus. *Neurobiol Dis*. 2004;17(3):473-490. doi:10.1016/j.nbd.2004.08.008.
  24. Varma P, Brulet R, Zhang L, Hsieh J. Targeting seizure-induced neurogenesis in a clinically-relevant time-period leads to transient but not persistent seizure reduction. *J Neurosci*. 2019. doi:10.1523/JNEUROSCI.0920-19.