Title

Comment on "Impact of neurodegenerative diseases on human adult hippocampal neurogenesis".

Journal

Science (New York, N.Y.), 376(6590)

ISSN

0036-8075

Authors

Alvarez-Buylla, Arturo
Cebrian-Silla, Arantxa
Sorrells, Shawn F
et al.

Publication Date

2022-04-01

DOI

10.1126/science.abn8861

Peer reviewed

HHS Public Access

Author manuscript

Science. Author manuscript; available in PMC 2023 May 10.

Published in final edited form as:

Science. 2022 April 15; 376(6590): eabn8861. doi:10.1126/science.abn8861.

Comment on "Impact of neurodegenerative diseases on human adult hippocampal neurogenesis"

Arturo Alvarez-Buylla[1,2,*], **Arantxa Cebrian-Silla**[1,2], **Shawn F. Sorrells**[3], **Marcos Assis Nascimento**[1,2], **Mercedes F. Paredes**[1,4], **Jose Manuel Garcia-Verdugo**[5], **Zhengang Yang**[6], **Eric J. Huang**[1,7]

[1]Eli and Edythe Broad Institute for Stem Cell Research and Regeneration Medicine, University of California, San Francisco, CA 94143, USA.

[2]Department of Neurological Surgery, University of California, San Francisco, CA 94143, USA.

[3]Department of Neuroscience, University of Pittsburgh, Pittsburgh, PA 15260, USA.

[4]Department of Neurology, University of California, San Francisco, CA 94143, USA.

[5]Laboratorio de Neurobiología Comparada, Instituto Cavanilles de Biodiversidad y Biología Evolutiva, Universitat de València–Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Valencia, Spain.

[6]Department of Neurology, State Key Laboratory of Medical Neurobiology and Institutes of Brain Science, Zhongshan Hospital, Fudan University, Shanghai 200032, China.

[7]Department of Pathology, University of California, San Francisco, CA 94143, USA.

Abstract

Terreros-Roncal *et al.* investigated the impacts of human neurodegeneration on immunostainings assumed to be associated with neurogenesis. However, the study provides no evidence that putative proliferating cells are linked to neurogenesis, that multipolar nestin$^+$ astrocytes are progenitors, or that mature-looking doublecortin$^+$ neurons are adult-born. Their histology-marker expression differs from what is observed in species where adult hippocampal neurogenesis is well documented.

Work in juvenile and adult rodents has documented radial astrocytes (radial glia–like cells) that generate new neurons in the dentate gyrus (DG) of the hippocampus. Whether a similar process continues in the adult human brain remains controversial [see (2, 3)]. In their recent article (1), Terreros-Roncal *et al.* claim that neurogenesis is a robust process in aged humans, including patients with amyotrophic lateral sclerosis (ALS), Huntington's disease, α-synucleinopathies, or frontotemporal disorder (FTD). However, the authors do not acknowledge the limitations of their staining or discuss discrepancies with other studies that have observed immature neurons and proliferating progenitors rapidly decreasing during infancy, with few, if any, present in adults (4–6). Several claims of this study are based on inferences that remain speculative:

*Corresponding author. abuylla@stemcell.ucsf.edu.

1. The authors provide no evidence that doublecortin $(DCX)^+$ cells were born in adults. Multiple studies suggest caution interpreting DCX^+ neurons as evidence of neurogenesis: (i) DCX is expressed by neurons in non-neurogenic regions of the adult human brain (3, 7, 8); (ii) DCX can be reexpressed in neurons during aging or neurodegeneration (9, 10); (iii) transcriptomic data support the idea that mature neuron and glial cells can express DCX (3). DCX^+ cells presented are large and distributed throughout the granule cell layer, consistent with having been born during development. Note also that calretinin (CR) can be expressed by local inhibitory neurons and is not a marker of immature neurons.

2. Terreros-Roncal *et al.* present images of multipolar astrocytes [$nestin^+$/S100 calcium-binding protein B $(S100\beta)^-$], including some with thick and thin processes, as evidence of neural stem cells. These astrocytes have as many as seven processes, oriented in multiple directions, with none shown to cross the DG and ramify in the molecular layer [e.g., figure 1A and quantification in figure S3 of (1)]. These morphologies do not correspond to that of radial astrocytes. Several astrocytes identified as “radial” [e.g., figures 1A and 2A of (1)] display a rod-like expansion that does not traverse the granular cell layer or have other characteristics shown in the summary diagram [figure 6 of (1)]. $Nestin^+$ (unclear whether $S100\beta^-$) astrocytes in neurodegenerative cases are also not radial [e.g., figures 3A or 4A of (1)]. $Nestin^+/S100\beta^-$ cells could correspond to non-neurogenic astrocyte subtypes described in the DG (11, 12); this should be investigated and discussed. Were $nestin^+/S100\beta^-$ astrocytes found in other brain regions outside the DG? The proliferative capacity of the majority of these astrocytes, including those quantified, remains unknown. Their summary illustration [figure 6 of (1)] uses a schematic of classical radial astrocytes in the rodent DG; on the basis of their observations and those of others (4–6), this does apply to adult humans.

3. The study claims ~25,000 DCX^+ cells/mm^3 of human DG (average age ~65 years). If these are all new neurons as suggested, a robust and proliferative niche should be present in older patients. However, their images are consistent with previous studies showing that the “subgranular zone” (SGZ) has a cell density similar to that of the rest of the hilus without a clear layer of dividing progenitors. Quantifications of phosphorylated histone H3 $(pH3)^+$ cells in the “SGZ” are presented as evidence for proliferating progenitors, but the cell types being counted are unidentified and most of their $pH3^+$ cells are not in the SGZ [figures 1B, 2C, and 3B of (1)]. pH3 is only expressed during G_2/M phases of the cell cycle, so large numbers of $pH3^+$ cells suggest the presence of an even greater pool of progenitors. This is discordant with the cell density in the SGZ, or the few cells observed using Ki-67 (3), which labels cells in more stages of the cell cycle. If there are this many dividing progenitors in the DG of elderly patients, there should be a large population of immature migrating neurons, which is not evident in the data presented as the majority of DCX^+ cells have mature morphology. Terreros-Roncal *et al.* also use ELAV-like protein 4 (HuC/HuD) as

a marker of neuroblasts, but this marker can also be expressed in mature neurons and should also stain the cytoplasm (13).

4. FTD can result in a loss of granule neurons (14), but the FTD cases shown by Terreros-Roncal *et al.* appear to have preservation of DG and DCX^+ cells [figure 5, A and D, of (1)]. Yet the number of $pH3^+$ cells decreased by ~80%. Is this dysregulation of neurogenesis, as suggested, or evidence that pH3 staining is not linked to neurogenesis? For ALS, they report an increase in "radial glia–like" and DCX^+ cells, but no increase in the numbers of CR^+, HuC/HuD^+, or $pH3^+$ cells. These observations also strongly suggest caution interpreting CR^+ or HuC/HuD cells as new neurons or pH3 staining as a reflection of neuronal progenitor proliferation. An increase in $nestin^+/S100\beta-$ and sex-determining region Y-box 2 $(SOX2)^+$ cells in the DG of cases with α-synucleinopathies, with no effect on pH3 or DCX numbers, is again suggested to be due to dysregulation of neurogenesis. But this could indicate that $nestin^+/S100\beta-$ cells are not related to neurogenesis. Furthermore, their conclusion that "α-synucleinopathies differentially target the DG milieu and generate singular [adult hippocampal neurogenesis] signatures" is not supported by a large study with 95 cases of dementia with Lewy body showing no pathology in the DG (15). Given these limitations, it is premature to propose that neurogenesis continues in the adult human hippocampus or, if present, that it is affected by neurodegenerative diseases [figure 6 of (1)].

Whether adult neurogenesis continues in humans during adulthood remains of great interest to neuroscience and the general public. Terreros-Roncal *et al.* offer an intriguing cellular analysis of the DG in different neurodegenerative conditions but no evidence that the proteins investigated are markers of adult neurogenesis. Unless the human neurogenic niche is organized very differently, the absence of radial astrocytes and of a proliferative layer is consistent with the idea that proliferating neurogenic progenitors in the human DG are not present, or are very rare.

ACKNOWLEDGMENTS

Supported by NIH grants P01 NS083513 (A.A.-B., M.F.P., and E.J.H.), K08 NS091537 (M.F.P.), and R01 NS028478 (A.A.-B.); the Roberta and Oscar Gregory Endowment in Stroke and Brain Research (M.F.P.); the Valencian Council for Innovation, Universities, Sciences and Digital Society (PROMETEO/2019/075) and Red de Terapia Celular (TerCel-RD16/0011/0026) (J.M.G.-V.); and a Spanish Generalitat Valenciana and European Social Fund postdoctoral fellowship (APOSTD2018/A113) (A.C.-S.).

REFERENCES

1. Terreros-Roncal J, Moreno-Jiménez EP, Flor-García M, Rodríguez-Moreno CB, Trinchero MF, Cafini F, Rábano A, Llorens-Martín M, Impact of neurodegenerative diseases on human adult hippocampal neurogenesis. Science 374, 1106–1113 (2021). doi:10.1126/science.abl5163 [PubMed: 34672693]
2. Moreno-Jiménez EP, Terreros-Roncal J, Flor-García M, Rábano A, Llorens-Martín M, Evidences for Adult Hippocampal Neurogenesis in Humans. J. Neurosci. 41, 2541–2553 (2021). doi:10.1523/JNEUROSCI.0675-20.2020 [PubMed: 33762406]
3. Sorrells SF, Paredes MF, Zhang Z, Kang G, Pastor-Alonso O, Biagiotti S, Page CE, Sandoval K, Knox A, Connolly A, Huang EJ, Garcia-Verdugo JM, Oldham MC, Yang Z, Alvarez-Buylla

A, Positive Controls in Adults and Children Support That Very Few, If Any, New Neurons Are Born in the Adult Human Hippocampus. J. Neurosci. 41, 2554–2565 (2021). doi:10.1523/JNEUROSCI.0676-20.2020 [PubMed: 33762407]

4. Sorrells SF, Paredes MF, Cebrian-Silla A, Sandoval K, Qi D, Kelley KW, James D, Mayer S, Chang J, Auguste KI, Chang EF, Gutierrez AJ, Kriegstein AR, Mathern GW, Oldham MC, Huang EJ, Garcia-Verdugo JM, Yang Z, Alvarez-Buylla A, Human hippocampal neurogenesis drops sharply in children to undetectable levels in adults. Nature 555, 377–381 (2018). doi:10.1038/nature25975 [PubMed: 29513649]
5. Paredes MF, Sorrells SF, Cebrian-Silla A, Sandoval K, Qi D, Kelley KW, James D, Mayer S, Chang J, Auguste KI, Chang EF, Gutierrez Martin AJ, Kriegstein AR, Mathern GW, Oldham MC, Huang EJ, Garcia-Verdugo JM, Yang Z, Alvarez-Buylla A, Does Adult Neurogenesis Persist in the Human Hippocampus? Cell Stem Cell 23, 780–781 (2018). doi:10.1016/j.stem.2018.11.006 [PubMed: 30526879]
6. Cipriani S, Ferrer I, Aronica E, Kovacs GG, Verney C, Nardelli J, Khung S, Delezoide A-L, Milenkovic I, Rasika S, Manivet P, Benifla J-L, Deriot N, Gressens P, Adle-Biassette H, Hippocampal Radial Glial Subtypes and Their Neurogenic Potential in Human Fetuses and Healthy and Alzheimer's Disease Adults. Cereb. Cortex 28, 2458–2478 (2018). doi:10.1093/cercor/bhy096 [PubMed: 29722804]
7. Zhang X-M, Cai Y, Chu Y, Chen E-Y, Feng J-C, Luo X-G, Xiong K, Struble RG, Clough RW, Patrylo PR, Kordower JH, Yan X-X, Doublecortin-expressing cells persist in the associative cerebral cortex and amygdala in aged nonhuman primates. Front. Neuroanat. 3, 17 (2009). doi:10.3389/neuro.05.017.2009 [PubMed: 19862344]
8. Liu R-X, Ma J, Wang B, Tian T, Guo N, Liu S-J, No DCX-positive neurogenesis in the cerebral cortex of the adult primate. Neural Regen. Res. 15, 1290–1299 (2020). doi:10.4103/1673-5374.272610 [PubMed: 31960815]
9. Hagihara H, Murano T, Ohira K, Miwa M, Nakamura K, Miyakawa T, Expression of progenitor cell/immature neuron markers does not present definitive evidence for adult neurogenesis. Mol. Brain 12, 108 (2019). doi:10.1186/s13041-019-0522-8 [PubMed: 31823803]
10. Franjic D et al. , Molecular Diversity Among Adult Human Hippocampal and Entorhinal Cells. bioRxiv 2019.12.31.889139 (2020). doi:10.1101/2019.12.31.889139
11. Kosaka T, Hama K, Three-dimensional structure of astrocytes in the rat dentate gyrus. J. Comp. Neurol. 249, 242–260 (1986). doi:10.1002/cne.902490209 [PubMed: 3525618]
12. Eckenhoff MF, Rakic P, Radial organization of the hippocampal dentate gyrus: A Golgi, ultrastructural, and immunocytochemical analysis in the developing rhesus monkey. J. Comp. Neurol. 223, 1–21 (1984). doi:10.1002/cne.902230102 [PubMed: 6707248]
13. Okano HJ, Darnell RB, A hierarchy of Hu RNA binding proteins in developing and adult neurons. J. Neurosci. 17, 3024–3037 (1997). doi:10.1523/JNEUROSCI.17-09-03024.1997 [PubMed: 9096138]
14. Dickson DW, Kouri N, Murray ME, Josephs KA, Neuropathology of frontotemporal lobar degeneration-tau (FTLD-tau). J. Mol. Neurosci. 45, 384–389 (2011). doi:10.1007/s12031-011-9589-0 [PubMed: 21720721]
15. Adamowicz DH, Roy S, Salmon DP, Galasko DR, Hansen LA, Masliah E, Gage FH, Hippocampal α-Synuclein in Dementia with Lewy Bodies Contributes to Memory Impairment and Is Consistent with Spread of Pathology. J. Neurosci. 37, 1675–1684 (2017). doi:10.1523/JNEUROSCI.3047-16.2016 [PubMed: 28039370]