Medical Xpress

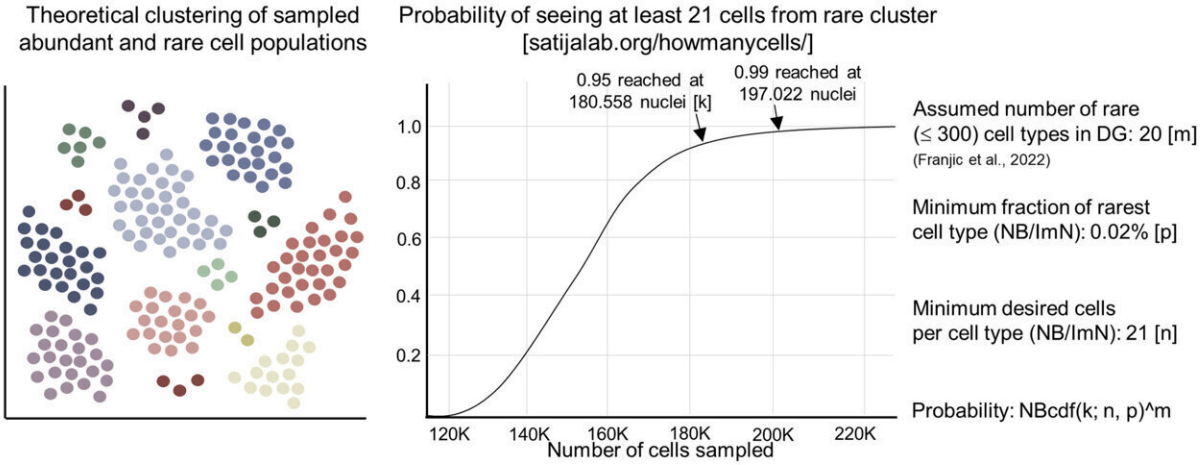
How do we know if our brain is capable of repairing itself?

April 3 2023

A

Brain region	Nr. donors	Age (years)	Nr. total nuclei (after QC)	Nr. DG granule cells	Sequencing depth (reads/nucleus)	Clinical documentation	Avg RIN	Avg PMD (hours)	Reference
Hippocampus Cortex	5	40-65	14 137	1453	10K	'Non-diseased'	7.3	12.4	Habib et al. 2017
Hippocampus	4	67-92	22 119	Unknown	85K	'Without neurological disorders'	Unknown	10	Wang et al. 2022
Hippocampus	5	26-60	129 908	~9K	20K	Temporal lobe epilepsy	Unknown	NA (fresh tissue)	Ayhan et al. 2021
Dentate gyrus	6	44-79	139 187	32 067	20K	'Clinically unremarkable' (5x) & status epilepticus (1x)	Unknown	15.6	Franjic et al. 2022
Hippocampus	38	0,1-88	152 184	35 187	23K	Free from neurological disorders & AD	Unknown	17.1	Zhou et al. 2022

B



C

Species	Detection	Cell proportion	Cell proportion	Cell proportion (of total DG	Expected # cells per 30.000 GCs	Total DG nuclei required to detect the same	Reference

Estimating the appropriate power for sc/snRNA-seq studies of human AHN(A) Summary of the published snRNA-seq studies in adult human hippocampus.(B) Probability estimation using How Many Cells|Satija Lab online software (https://satijalab.org/howmanycells/) assessing how many cells need to be sampled to detect at least n cells of each type. For a given cell type, the probability of seeing at least n cells in a sample of size k follows the cumulative distribution function of a negative binomial NBcdf (k; n, p), with p being the relative abundance.(C) Table reporting the proportions of putative NBs/ImNs per

total amount of DG cells, the expected numbers of NBs/ImNs per 30,000 GCs (number of GCs sequenced by the most powered published studies to date), and the number of cells that need to be sequenced to reach the same expected number of cells when using sc/snRNA-seq, according to different references. Avg, average; RIN, RNA integrity number; PMD, postmortem delay; NBs, neuroblasts; ImNs, immature neurons; GCs, granule cells. Credit: *Neuron* (2023). DOI: 10.1016/j.neuron.2023.03.010

Is our brain able to regenerate? And can we harness this regenerative potential during aging or in neurodegenerative conditions? These questions sparked intense controversy within the field of neuroscience for many years. A new study from the Netherlands Institute for Neuroscience shows why there are conflicting results and proposes a roadmap on how to solve these issues.

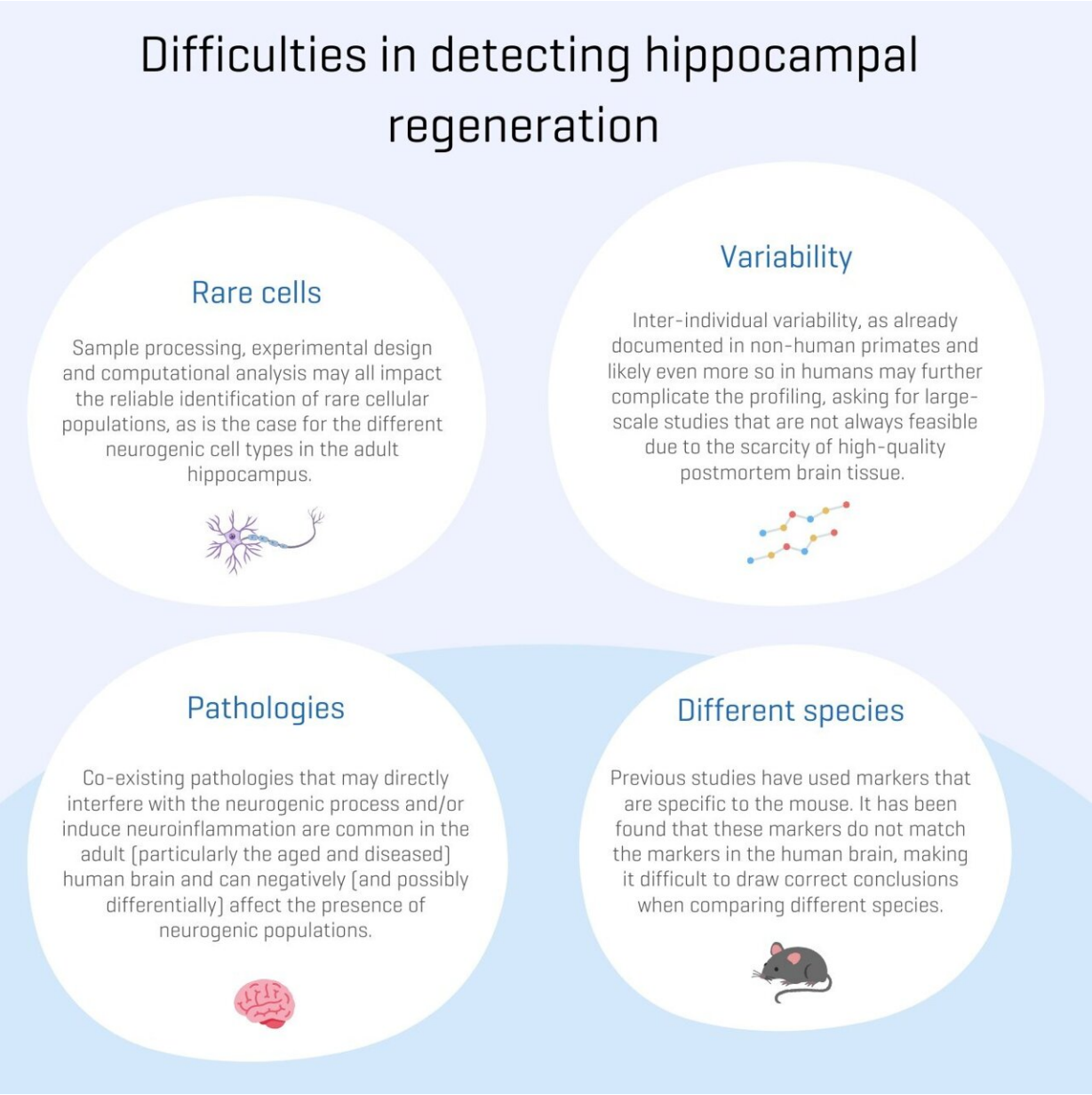
The notion of exploiting the regenerative potential of the human brain in aging or neurological diseases represents a particularly attractive alternative to conventional strategies for enhancing or restoring brain function, especially given the current lack of effective therapeutic strategies in neurodegenerative disorders like Alzheimer's disease.

The question of whether the human brain does possess the ability to regenerate or not has been at the center of a fierce scientific debate for many years and recent studies yielded conflicting results. A new study from Giorgia Tosoni and Dilara Ayyildiz, under the supervision of Evgenia Salta in the laboratory of Neurogenesis and Neurodegeneration, critically discusses and re-analyzes previously published datasets. How is it possible that we haven't yet found a clear answer to this mystery?

Previous studies in which dividing cells were labeled in postmortem human brain, showed that new cells can indeed arise throughout adulthood in the hippocampus of our brain, a structure that plays an

important role in learning and memory, and is also severely affected in Alzheimer's disease. However, other studies contradict these results and cannot detect the generation of new brain cells in this area.

Both conceptual and methodological confounders have likely contributed to these seemingly opposing observations. Hence, elucidating the extent of regeneration in the human brain remains a challenge.



Difficulties in detecting hippocampal regeneration. Credit: Netherlands Institute for Neuroscience

New state-of-the-art technologies

Recent advances in single-cell transcriptomics technologies have provided valuable insights into the different cell types found in human brains from deceased donors with different brain diseases. To date, single-cell transcriptomic technologies have been used to characterize rare cell populations in the human brain. In addition to identifying specific cell types, single-nucleus RNA sequencing can also explore specific gene expression profiles to unravel full the complexity of the cells in the hippocampus.

The advent of single-cell transcriptomics technologies was initially viewed as a panacea to resolving the controversy in the field. However, recent single-cell RNA sequencing studies in human hippocampus yielded conflicting results.

Two studies indeed identified neural stem cells, while a third study failed to detect any neurogenic populations. Are these novel approaches—once again—failing to finally settle the controversy regarding the existence of hippocampal regeneration in humans? Will we eventually be able to overcome the conceptual and technical challenges and reconcile these -seemingly- opposing views and findings?

Technical issues

In this study, the researchers critically discussed and re-analyzed previously published single-cell transcriptomics datasets. They caution

that the design, analysis and interpretation of these studies in the adult human hippocampus can be confounded by specific issues, which ask for conceptual, methodological and computational adjustments. By re-analyzing previously published datasets, a series of specific challenges were probed that require particular attention and would greatly profit from an open discussion in the field.

Giorgia Tosoni says, "We analyzed previously published single-cell transcriptomic studies and performed a meta-analysis to assess whether adult neurogenic populations can reliably be identified across different species, especially when comparing mice and humans. The neurogenic process in adult mice is very well characterized and the profiles of the different cellular populations involved are known."

"These are actually the same molecular and cellular signatures that have been widely used in the field to also identify neurogenic cells in the human brain. However, due to several evolutionary adaptations, we would expect the neurogenesis between mice and humans to be different. We checked the markers for every neurogenic cell type and looked at the amount of marker overlap between the two species."

"We found very little, if no, overlap between the two, which suggests that the mouse-inferred markers we have been long using may not be suitable for the human brain. We also discovered that such studies require enough statistical power: if regeneration of neuronal cells does happen in the adult human brain, we expect it to be quite rare."

"Therefore, enough cells would need to be sequenced in order to identify those scarce, presumably neurogenic populations. Other parameters are also important, for example the quality of the samples. The interval between the death of the donor and the downstream processing is critical, since the quality of the tissue and of the resulting data drops over time."

Reproducibility is key

Dilara Ayyildiz says, "These novel technologies, when appropriately applied, offer a unique opportunity to map hippocampal regeneration in the human brain and explore which cell types and states may be possibly most amenable to therapeutic interventions in aging, neurodegenerative and neuropsychiatric diseases. However, reproducibility and consistency are key. While doing the analysis we realized that some seemingly small, but otherwise very critical details and parameters in the experimental and computational pipeline, can have a big impact on the results, and hence affect the interpretation of the data."

"Accurate reporting is essential for making these single-cell transcriptomics experiments and their analysis reproducible. Once we re-analyzed these previous studies applying common computational pipelines and criteria, we realized that the apparent controversy in the field may in reality be misleading: with our work we propose that there may actually be more that we agree on than previously believed."

The study is published in the journal *Neuron*.

More information: Giorgia Tosoni et al, Mapping human adult hippocampal neurogenesis with single-cell transcriptomics: Reconciling controversy or fueling the debate?, *Neuron* (2023). DOI: 10.1016/j.neuron.2023.03.010

Provided by Netherlands Institute for Neuroscience