ALZHEIMER DISEASE

Birth of hippocampal neurons declines in Alzheimer disease

> new neurons are added to the dentate gyrus in AD but fail to mature

Generation of new neurons in the hippocampus continues into old age but is impaired in Alzheimer disease (AD), according to a new study published in *Nature Medicine*. The results suggest that the decline in neurogenesis begins early in AD progression, raising the possibility that targeting this process has therapeutic potential.

The dentate gyrus of the mammalian hippocampus is known to continue to produce new neurons in adult animals. Some evidence indicates that this process takes place in humans but, in contrast to work in rodents, investigation of neurogenesis in human hippocampi has been limited by the quality of available tissue samples. This limitation has led to contradictory evidence and a lack of consensus about the existence of adult hippocampal neurogenesis in humans.

Immature neurons in the dentate gyrus can be identified by their expression of the neuronal migration protein doublecortin. This expression begins at cell division and continues throughout the maturation process. In the new study, tight control of the conditions under which post-mortem brain samples were obtained and processed enabled María Llorens-Martín and colleagues to identify thousands of doublecortin-expressing dentate gyrus neurons in neurologically healthy subjects. The findings were consistent with neurogenesis taking place throughout the adult lifespan, into the ninth decade, with a modest reduction in numbers of immature neurons with age. Further probing of these newborn neurons for expression of markers related to maturation stage enabled the team to piece together the first model of the differentiation stages in human adult hippocampal neurogenesis.

Llorens-Martín and colleagues then tested whether neurogenesis in the dentate gyrus was affected differently in pathological ageing. "My personal interest was to study this process in patients with AD and to compare it with what occurred in neurologically healthy controls during physiological ageing," notes Llorens-Martín.

To do this, the researchers studied post-mortem tissue from 45 patients with AD who died between the ages of 52 and 97 years. Progression of AD in these individuals was determined according to Braak staging, a commonly used system based on the distribution pattern of tau pathology. The cohort included patients at each of the six Braak stages of AD.

A marked reduction in the number of doublecortin-positive neurons was seen in the hippocampi of patients with AD compared with neurologically healthy individuals. "Adult hippocampal neurogenesis was dramatically impaired in patients with AD," explains Llorens-Martín. "We observed a sharp decrease in the number of immature neurons even at Braak tau stage I."

As well as beginning early — before plaques or tangles are commonly found in the dentate gyrus — the reduction in neurogenesis was also progressive, with less evidence of neurogenesis at each of the six successive Braak stages.

To determine whether the decline resulted from reduced addition or survival of newborn neurons, Llorens-Martín and colleagues evaluated the expression of maturation-stage-related markers in the tissue. The percentage of doublecortin-positive cells that also expressed markers of maturation was lower in patients with AD than in controls. The reduction was observed from Braak stage III onwards. This finding indicates that new neurons are added to the dentate gyrus in AD but fail to mature.

The early onset of the decline in neurogenesis opens up diagnostic and therapeutic possibilities for AD. "If we were able to detect the levels of adult hippocampal neurogenesis in living individuals by means of non-invasive methods, we could start working on identifying novel biomarkers for disease progression," suggests Llorens-Martín. "Given that adult hippocampal neurogenesis can be positively modulated in rodents, if this could be done in humans, we could start working on therapeutic approaches based on regenerative strategies."

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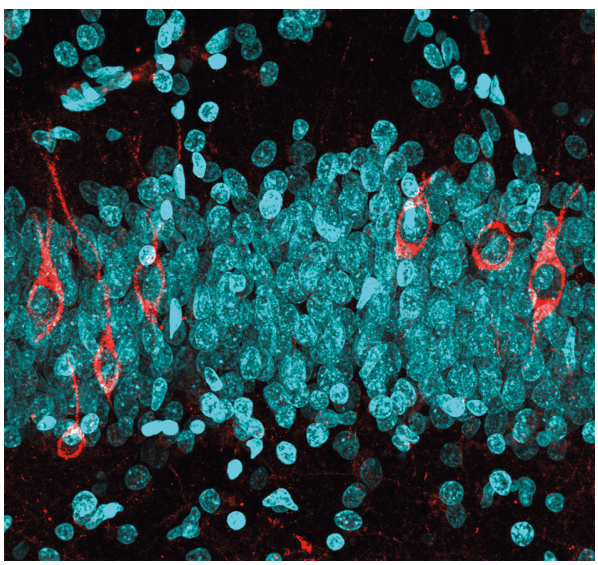

Credit: Image courtesy of M. Llorens-Martin, Llorens Lab, Spain.

ORIGINAL ARTICLE Moreno-Jiménez, E. P. et al. Adult hippocampal neurogenesis is abundant in neurologically healthy subjects and drops sharply in patients with Alzheimer's disease. *Nat. Med.* https://doi.org/10.1038/s41591-019-0375-9 (2019)