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Putting age-associated changes in neurogenesis in their place

Alexis M. Stranahan^{1,*}

¹Department of Psychological and Brain Sciences, Johns Hopkins University, Baltimore, MD, USA

Abstract

Individual differences in cognitive aging are, in some cases, correlated with changes in molecular markers at the neuronal level. However, the use of simple correlations to analyze data across multiple age groups has a number of potential pitfalls. When young animals differ from aged animals on both of the dependent variables being assessed with a correlation analysis, the age difference often accounts for the detection of a relationship between the two measures. When the age groups are analyzed discretely, the data may exhibit a completely different trend, as suggested in a recent Commentary. In addition to reconsidering the interpretation of recently published data on the relationship between age-related deficits in cognition and hippocampal neurogenesis, the demands of the task should be taken into account when evaluating the contributions of newly generated neurons.

Keywords

adult neurogenesis; hippocampus; water maze

Aging is associated with decrements in cognition, particularly on tasks that recruit the hippocampus and associated cortical structures. Because the hippocampus continues to generate new neurons throughout life, and the rate at which neurogenesis occurs declines with aging, multiple studies have addressed the possibility that age-related alterations in neurogenesis may be a mechanism for cognitive change. A recent study by Nyffeler and colleagues (*Neurobiol Aging*, 2008 in press) assessed the relationship between adult neurogenesis and learning at multiple time points over the life span of male Dark Agouti rats. This study suggests that individual differences in cognitive performance may be related to the extent to which neuronal maturation is delayed in the aging dentate gyrus. Nyffeler et al. used Pearson's correlations to assess the relationship between numbers of cells labeled with doublecortin, a marker of new neurons, and water maze escape latency during a specified range of training trials. The problem inherent with this method of analysis lies in the fact that age is a continuous variable tested at discrete intervals, and the dependent measures (number of doublecortin-labeled cells and latencies to the hidden platform) differ by age. Because young animals learn more efficiently and have more doublecortin-labeled cells, including them in the correlation analysis with aged animals that learn less effectively and have fewer doublecortin-labeled cells artificially inflates the probability of detecting correlation.

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*To whom correspondence should be addressed: Alexis M. Stranahan, Ph.D. Department of Psychological and Brain Sciences 3400 N. Charles St., Ames Hall Baltimore, MD 21218 Ph: (410)516-4142 Fax: (410)516-0494 alexis.stranahan@jhu.edu.

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In a recent Commentary, Lazic employed a data-extraction algorithm to re-analyze the data published by Nyffeler et al. Based on this re-analysis, Lazic interpreted the data in the context of an inverse relationship between doublecortin labeling and learning performance. Despite the small n-sizes (the study by Nyffeler et al used (n=4) 3-month-old rats, (n=4) 6-month-old rats, and (n=8) 24-month-old rats, which were further subdivided into two groups of (n=4) aged-impaired and (n=4) aged-unimpaired), there is a definite trend for higher levels of doublecortin labeling in rats that learn less effectively (relative to other rats of the same age). This casts doubt on the idea that prolongation of neuronal maturation in the aging brain may be linked to cognition, as suggested by Nyffeler et al.

Further examination of the report by Nyffeler and colleagues brings to light additional questions. Is the water maze really the best behavioral correlate of hippocampal neurogenesis? Adult-generated neurons have been suggested to contribute to multiple forms of hippocampus-dependent learning in rats, including trace eyeblink conditioning (Shors et al., 2001) and contextual fear conditioning (Snyder et al., 2009). Correlations between adult neurogenesis and behavior are less reliable when the task involves spatial navigation (Bizon and Gallagher, 2003, Merrill et al., 2003). Indeed, ablation experiments suggest that in rats, adult neurogenesis is not necessary for effective spatial learning (Shors et al., 2002; Wojtowicz et al., 2008), although new neurons do express immediate early genes preferentially relative to pre-existing neurons following water maze training (Snyder et al., 2009). Previous work suggests that the water maze is not the ideal behavioral readout for changes in adult neurogenesis in rats, which calls into question a central tenet in the manuscript by Nyffeler et al; namely, that the observed differences in adult neurogenesis contribute to behavior.

In summary, the Commentary by Lazic reinforces previous observations by Baxter and Gallagher (1996) regarding the appropriate design of analyses correlating neuronal alterations with behavior. If it were possible to correlate age-related phenomena with neuronal alterations and ascribe causation to this relationship, then it would be possible to say that gray hair 'causes' changes in neurochemistry and behavior. Epiphenomena and spurious correlations can be avoided by conducting discrete correlational analyses within different age groups. Moreover, the interpretation of behavioral observations in the study by Nyffeler et al. would benefit from further consideration of previous work on the role of adult neurogenesis in hippocampus-dependent memory.

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Figure 1. Hippocampus-dependent learning paradigms are not equally sensitive to changes in adult neurogenesis

Pharmacological ablation of adult neurogenesis impairs trace eyeblink conditioning without influencing plasticity in other hippocampal subfields (Shors et al., 2001). Contextual fear conditioning is impaired following irradiation-induced knockdown of adult neurogenesis (Wojtowicz et al., 2008; Snyder et al., 2009). In contrast, water maze learning is spared following inhibition of adult neurogenesis in rats (Shors et al., 2002; Wojtowicz et al., 2008). This suggests that the water maze is not the most sensitive measure for behavioral changes associated with adult neurogenesis.