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### **► To cite this version:**

Nathalie Mandaïron, Anne Didier. The brain's fight against aging. Proceedings of the National Academy of Sciences of the United States of America, 2010. <hal-02370299>

**HAL Id: hal-02370299**

**<https://hal.science/hal-02370299v1>**

Submitted on 19 Nov 2019

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# The brain's fight against aging

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**A**lterations of sensorial and cognitive performance appear with aging and affect quality of life. This is becoming an important societal and public health issue in our aging populations. The increasing number of elderly people in our society with their associated pathologies creates a need for better understanding of how the aged brain is different from the young brain. Surprisingly, very little is known about the cellular correlates of normal aging in the brain. Insights into structural alterations are essential to understanding the functional and cognitive changes associated with aging. In PNAS, Richard et al. (1), using the olfactory bulb (OB) as a simplified cortical model, show the overall stability of the structure and indicate that there is no neurodegeneration with aging. Interestingly, the results reveal fine synaptic alterations that affect selected cellular compartments, thereby opening perspectives for understanding the mechanisms of aging at the level of the cortical subcircuits. These data refute the view of aging as nonspecific homogeneous and regressive events and promote the view that more subtle alterations of brain circuitry could account for age-related functional changes.

The OB is an appropriate model for studying the effect of aging for several reasons. First, this sensory cortex has a well-known synaptic organization (2, 3). Second, olfaction is altered in normal (4–9) and pathological aging (10, 11), leading to food intake impairment, reduced quality of life, and altered health in the elderly. In addition, given the functional importance of olfaction in rodents and the similarities between the organization of the human and rodent olfactory systems, the mouse OB is relevant for studying aging in the brain.

## Overall Stability of the OB

A key finding of this study is that the anatomical features of the OB from its laminar organization to its cell numbers are strikingly stable in C57Bl6J mice. Indeed, using classical stereological methods associated with specific immunohistological staining of cell subpopulations, the authors find that the total volume of both the OB and its individual layers and the number of interneurons (granule and periglomerular cells) and relay cells (mitral cells) do not change across life. This finding is interesting with regard to the permanent supply of neurons, thanks to the

process of adult neurogenesis targeting both olfactory sensory neurons projecting from the olfactory epithelium to the OB and bulbar interneurons. Indeed, neurogenesis is known to dramatically decrease with aging (4, 12), and furthermore, ablation of bulbar neurogenesis has been shown to induce a reduction in the granule cell volume of the adult OB (13). One could thus expect that the volume of the OB and number of interneurons would decrease with aging. The structural stability of the OB shown by Richard et al. (1) is important in that it indicates that strong

## Richard et al. find that specific subsets of synapses are affected by aging.

compensatory mechanisms are at play during aging to maintain the integrity of the OB. These mechanisms will have to be assessed, but likely include a reduction in cell death within the renewed neuronal populations to compensate for the lower rate of formation of newborn neurons. This is a particularly interesting aspect, because it would show the ability of the aged brain to implement positive regulation to adjust for age-dependent alteration in neurogenesis. The aged brain would thus not only be degrading but also developing strategies to counteract aging. However, this view should be tempered. Indeed, despite these compensatory mechanisms, it is clear that the aged OB, even if it contains the same number of neurons, contains less newborn neurons. Because newborn neurons express facilitated synaptic plasticity (14), it is likely that the aged bulb would be less responsive to plasticity challenges, possibly accounting for deficits in perception.

A fundamental feature of the functional organization of the olfactory system is the convergent projections of sensory neurons expressing the same odor receptor to a few specific glomeruli at constant locations in the OB (15). This anatomofunctional organization is of primary importance, because it allows the construction of a spatial map of the activity in response to a given odorant at the entrance of the OB and distributes the olfactory inputs to the specific subpopula-

tions of mitral cells required for proper encoding of the odor. Because of the permanent renewal of olfactory sensory neurons, this organization is constructed during the development stage and needs to be permanently rebuilt. The study by Richard et al. (1) addresses the question of the maintenance of these axon-guidance mechanisms in the aged OB. They use transgenic mice expressing GFP protein under the control of the M72 olfactory receptor promoter to allow visualization of the axonal tracks from the epithelium to the OB. They find that the typical convergent projections of the olfactory sensory neurons expressing M72 onto their two specific glomeruli in the OB are conserved up to the age of 24 months. In addition to cellular numbers, mechanisms of axonal guidance are also conserved in the aged brain and contribute to the structural stability of the OB. The olfactory system is a unique niche in which development-like guidance mechanisms ignore aging.

## Fine Synaptic Alterations

Despite the stability of the epithelium-bulbar connections and the bulbar laminar structure, a decline in olfactory function is observed with aging. This highlights the need for investigation at the synaptic level into what could account for the perceptual deficit. Richard et al. find that specific subsets of synapses are affected by aging. Indeed, whereas the number of synapses in the granule cell layer is unaffected by aging, a decrease of the total synapse density is reported in the glomerular layer. Although equivalent findings are reported in other cortices (16, 17), this study reports layer-specific synaptic alterations in the OB (1). This finding is interesting, because it further points out the differential susceptibility to aging of two functional compartments of the mitral cells (apical versus lateral dendrites) that future experiments will have to explain. Neuromodulatory systems (cholinergic and noradrenergic, for instance) differentially target glomerular and granule cell layers. Their degeneration in brain diseases such as Alzheimer's or Parkinson's is well documented (18, 19); this is accompanied

Author contributions: N.M. and A.D. wrote the paper.

The authors declare no conflict of interest.

See companion article on page 15613.

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by olfactory deficits (20), but little is known about their status in normal aging. In this context, exploring the normal aging of these systems could shed light on the layer-specific loss of synapses. Synaptic alterations are currently difficult to relate to impairments in particular olfactory functions, such as detection, dis-

crimination, or memory, but will without doubt guide interpretation of future experiments.

In summary, the work of Richard et al. (1) highlights the complex mechanisms of cortical aging involving a determined effort to maintain structural integrity, although this does not prevent fine synaptic

alterations. These data suggest that efforts to better understand aging mechanisms and develop future therapies should be directed to (i) how the normal aged brain is able to maintain its pool of neurons and (ii) what molecular mechanisms are altered in neurons that subsequently lead to synaptic loss.

1. Richard MB, Taylor SR, Greer CA (2010) Age-induced disruption of selective olfactory bulb synaptic circuits. *Proc Natl Acad Sci USA* 107:15613–15618.
2. Schoppa NE, Urban NN (2003) Dendritic processing within olfactory bulb circuits. *Trends Neurosci* 26:501–506.
3. Shepherd GM (1972) Synaptic organization of the mammalian olfactory bulb. *Physiol Rev* 52:864–917.
4. Enwere E, et al. (2004) Aging results in reduced epidermal growth factor receptor signaling, diminished olfactory neurogenesis, and deficits in fine olfactory discrimination. *J Neurosci* 24:8354–8365.
5. Prediger RD, De-Mello N, Takahashi RN (2006) Pilocarpine improves olfactory discrimination and social recognition memory deficits in 24 month-old rats. *Eur J Pharmacol* 531:176–182.
6. Patel RC, Larson J (2009) Impaired olfactory discrimination learning and decreased olfactory sensitivity in aged C57Bl/6 mice. *Neurobiol Aging* 30:829–837.
7. Schoenbaum G, Nugent S, Saddoris MP, Gallagher M (2002) Teaching old rats new tricks: Age-related impairments in olfactory reversal learning. *Neurobiol Aging* 23:555–564.
8. Prediger RD, Batista LC, Takahashi RN (2005) Caffeine reverses age-related deficits in olfactory discrimination and social recognition memory in rats. Involvement of adenosine A1 and A2A receptors. *Neurobiol Aging* 26:957–964.
9. Mandaïron N, et al. (2010) Compensatory responses to age-related decline in odor quality acuity: Cholinergic neuromodulation and olfactory enrichment. *Neurobiol Aging*, 10.1016/j.neurobiolaging.2009.12.024.
10. Guérin D, Sacquet J, Mandaïron N, Jourdan F, Didier A (2009) Early locus coeruleus degeneration and olfactory dysfunctions in Tg2576 mice. *Neurobiol Aging* 30:272–283.
11. Wesson DW, Levy E, Nixon RA, Wilson DA (2010) Olfactory dysfunction correlates with amyloid-beta burden in an Alzheimer's disease mouse model. *J Neurosci* 30:505–514.
12. Weiler E, Farbman AI (1997) Proliferation in the rat olfactory epithelium: Age-dependent changes. *J Neurosci* 17:3610–3622.
13. Imayoshi I, et al. (2008) Roles of continuous neurogenesis in the structural and functional integrity of the adult forebrain. *Nat Neurosci* 11:1153–1161.
14. Nissant A, Bardy C, Katagiri H, Murray K, Lledo PM (2009) Adult neurogenesis promotes synaptic plasticity in the olfactory bulb. *Nat Neurosci* 12:728–730.
15. Mombaerts P (2006) Axonal wiring in the mouse olfactory system. *Annu Rev Cell Dev Biol* 22:713–737.
16. Burke SN, Barnes CA (2010) Senescent synapses and hippocampal circuit dynamics. *Trends Neurosci* 33:153–161.
17. Dickstein DL, et al. (2007) Changes in the structural complexity of the aged brain. *Aging Cell* 6:275–284.
18. Bartus RT, Dean RL 3rd (1982) Beer B, Lippa AS (1982) The cholinergic hypothesis of geriatric memory dysfunction. *Science* 217:408–414.
19. Marien MR, Colpaert FC, Rosenquist AC (2004) Noradrenergic mechanisms in neurodegenerative diseases: A theory. *Brain Res Brain Res Rev* 45:38–78.
20. Hawkes C (2006) Olfaction in neurodegenerative disorder. *Adv Otorhinolaryngol* 63:133–151.