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Activity- and pharmacology-dependent modulation of adult neurogenesis in relation to Alzheimer's disease

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General Summary

The recent discovery of resident neural stem cells (NSCs) and their restorative potential has reversed earlier notions of the brain as a static and unchangeable structure. The process of adult neurogenesis, particularly generation of new neurons from NSCs located in the adult hippocampal dentate gyrus, has attracted considerable interest. This process is modifiable, conserved across mammalian species, and plays an important role in cognition and behavior, as measured experimentally e.g. in specific spatial memory and pattern separation paradigms. Although much less is known about its role in humans, neurogenesis appears to be important for maintaining cognitive function during aging. Neurogenesis decreases with age, which may reflect increased vulnerability to neuropathology, age-related memory deficits, and Alzheimer's disease. Research described in this thesis focused on proliferation and neurogenesis in the adult and aging brain, through postmortem studies of middle-aged primates, human Alzheimer's subjects, and interventional studies in mice that included behavioral analysis.

We studied changes in structural plasticity and neurogenesis in relation to psychosocial stress exposure in a primate model. In humans, we established that microglia proliferate in the hippocampus of aged individuals, with potential importance for hippocampal neurogenesis and neuroinflammation. We further experimentally tested whether activity and pharmacology can stimulate neurogenesis and behavior in inbred mice (young and old) and in a well-known mouse model of AD; studies performed to evaluate the therapeutic capacity of neurogenesis to modulate behavioral deficits and Alzheimer neuropathology.

In **Chapter 3** we studied the consequences of psychosocial stress on neurogenesis in two brain regions of the middle-aged common marmoset, a new world primate. We established that neurogenesis in the hippocampus of marmosets is not sensitive to psychosocial stress exposure when measured after a two-week recovery period. Surprisingly, large numbers of neuroblasts were found to be additionally present in the basal and lateral nuclei of the amygdala, at a dramatically higher density compared to the hippocampal dentate gyrus in animals this age. Stress failed to change the density of neuroblasts in the amygdala in this species. We further showed that

these DCX-positive, immature neurons co-express PSA-NCAM which strongly suggests the cells remain migratory. Similar cells were also seen in the entorhinal cortex. These results indicate that substantial populations of immature neurons are present in the amygdala and entorhinal cortex of the middle-aged marmoset. Whether these cells play a role in structural plasticity and behavior, possibly even emotional memory, has yet to be established.

In **Chapter 4**, we studied proliferation of glia cells in the aged human hippocampus (>70 years age) in relation to amyloid pathology and dementia. Our work followed up on our previous publication showing that proliferation was increased in the hippocampus of presenile AD patients, an increase that appeared to be largely due to proliferation in glia-rich regions of this brain region. However, the phenotype of these proliferating cells was not established.

In our study, we co-labeled the proliferation marker PCNA with GFAP-expressing astrocytes, and Iba1-expressing microglia. While astrocytes failed to co-express the proliferation marker PCNA, we could demonstrate that Iba1 expressing microglia cells that proliferate the AD brain. This phenomenon was observed across disease conditions and in the presence of A β plaques, indicating that A β plaques may spur microglial proliferation. This suggests that microglial proliferation occurs during the early stages of disease, and could make a so far unknown contribution to neuroinflammation in general and to the subsequent progression of cognitive decline and dementia in particular.

Regarding pharmacology-dependent neurogenesis, previous work had established that antidepressants from the selective serotonin reuptake (SSRI) class increased neurogenesis and neuronal maturation, leading to higher neuronal cell survival in young inbred mice. In **Chapter 5**, we first evaluated the ability of duloxetine hydrochloride, a dual-pharmacology SSRI/SNRI compound to induce neurogenesis. Duloxetine was compared with fluoxetine, a classic and commonly prescribed SSRI, and voluntary wheel running, to measure stimulation of neurogenesis in young female C57Bl6J mice.

Our findings indicate that neither drug was able to improve the survival of new neurons in the dentate, although increased neuronal differentiation was observed for fluoxetine. Behaviorally however,

fluoxetine and duloxetine treated mice demonstrated higher levels of anxiety compared to control animals. Compared to the minor effect of fluoxetine on neuronal differentiation, wheel running produced a profound increase in neuronal cell survival that would be the basis for our follow-up experiment in middle-aged mice.

In **Chapter 6** we tested the ability of prolonged i.e. 6 months physical activity to stimulate neurogenesis and hippocampal function in female C57Bl6J mice when started in middle age. Animals were tested in the Morris Water Maze to evaluate the ability of this intervention to prevent age-mediated declines in spatial learning and memory.

Our results show that wheel running in middle-aged mice preserved spatial memory performance. The mice further showed elevated neurogenesis and increased levels of BDNF protein, a neurotropic factor with known neuroprotective properties. Mice allowed to exercise through long-term wheel running further performed better in a spatial memory test. This indicates that prolonged wheel running reversed age-dependent deficits in spatial memory and in neurogenesis. They also show that BDNF likely plays an important role in mediating the effects of wheel running. These data sets reflect that prolonged exercise in mid-life has beneficial effects on both hippocampal structure and function.

In **Chapter 8** we report on a similar experimental paradigm as described in chapters 5 and 6 but applied to the 3xTg AD mouse model, harboring 3 mutant transgenes (APP, PS1, and tau) and recapitulating both A β and tau pathology, the main neuropathological hallmarks of AD. We explored the synergistic treatment of the 3xTg mice with fluoxetine and voluntary wheel running, with the expectation that combined intervention would have an additive effect in reversing deficits in neurogenesis and hippocampal-mediated behavior. Wheel running was shown to significantly increase neurogenesis in 3xTg mice but did not significantly elevate BDNF as was found before in the aging C57Bl6 mice. Surprisingly, the 3xTg mice never exhibited deficits in spatial learning and memory, disassociating the relationship between neurogenesis and spatial learning and memory performance. This finding is carefully reviewed, with special attention for the genetic background of the 3xTg mice, the phenotype of these animals, and the behavioral tests employed.

Our findings presented here provide insight into the complex regulation of neurogenesis and the difficulties encountered when attempting to stimulate stem cell proliferation in the brain for modifying age- and disease-associated behaviors. Our work further highlights the important role for glial cells during health and disease. This body of work implies that further scientific pursuit of adult neurogenesis and AD will result in better therapeutic options for treating Alzheimer's disease.