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SPECIAL ISSUE-EDITORIAL

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Neurogenesis in the adult brain: is there an association with mental disorders?

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Within the last two decades, our view of the mature mammalian brain has changed. The brain is far from being fixed and immutable, as a multitude of factors such as environmental stimulation, learning, growth factors, glucocorticoids and sexual hormones, stress, aging, and neurotransmitters such as glutamate and serotonin regulate generation of new neurons; also many drugs have an impact on neurogenesis in selected brain regions such as the subgranular zone of the hippocampal dentate gyrus and the subventricular zone of the lateral ventricles. This newfound capacity has forced a new look at plasticity of the brain, an organ previously considered to have a stable structure. The term neural plasticity summarizes dynamic processes that constitute the capacity of neural systems, single neurons, glia cells, synapses, receptors, and other components to adapt and change their structural or functional repertoire in response to alterations in the internal and/or external environment. Neural plasticity is mandatory for adequate functioning of an individual in the continuously changing environment. However, as demonstrated e.g., in brains of patients with mood disorders it became clear that neural plastic processes are not always beneficial.

The discovery of stem cells in the adult brain and of adult neurogenesis has added new dimensions to neuroplasticity research. Moreover, it raises questions regarding the underlying mechanisms of the newly generated neurons, and how they influence the functioning of established neuronal networks. The magnitude and ubiquity of adult neurogenesis across vertebrates suggests that it is an essential process and not merely a residue of development. The functional implications of adult neurogenesis are still a matter of debate, but several reports provide evidence, although so far only correlational, that neurogenesis in the adult dentate gyrus might be involved in learning and memory processes. Moreover, new theories have linked neuropsychiatric disorders such as depression, schizophrenia, dementia, and drug addiction to a failure of adult neurogenesis.

The hippocampus is one of the brain structures that has been extensively studied with regard to the consequences of stress, depression, and antidepressant actions. Recent imaging studies in humans revealed that the hippocampus undergoes selective volume reduction in stress-related neuropsychiatric disorders such as recurrent depressive illness.

Today there is compelling experimental evidence that reduced dentate neurogenesis and hippocampal volume loss in animal models of depression can be reversed by antidepressant treatment. These findings caused the formulation of the novel concept that reduced neurogenesis may contribute to the pathogenesis of depression. However, the exact mechanisms responsible for the hippocampal volume loss in major depression are so far unclear. In their article Czéh and Lucassen state that neuronal loss can be excluded as cause for the volume loss. As apoptosis and reduced neurogenesis contribute only to a very limited extent to the observed volume loss other factors such as alterations in the glial, dendritic, axonal, and synaptic compartments are discussed to contribute to the hippocampal shrinkage. Together with shifts in both the extracellular space and fluid volume theses factors may provide a mechanistic explanation for the ob-

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served reversibility of the reduction in hippocampal volume after therapeutic interventions in patients and animal models of depression.

The discovery that the reduced dentate neurogenesis can be reversed by antidepressant treatment have excited many researchers and supported the concept that altered cytogenesis and neurogenesis are regarded as a gold standard in animal models of depression. However, others vigorously disputed the functional significance of the newly generated neurons in the pathophysiology of mood disorders. In their review Vollmayr et al. provide evidence that neurogenesis in the dentate gyrus of experimental animals does not correlate with depressive-like behavior per se, but rather with factors modulating this behavior such as stress and antidepressant treatment.

The most convincing evidence for the central role of reduced neurogenesis in depression requires the direct examination of these processes in the brains of depressed patients. Until now the only study that addressed this question has been published recently by Reif et al. [3]. The authors compared the level of neural stem cell proliferation in human *post mortem* brain samples from patients with major depression, bipolar affective disorder, schizophrenia as well as control subjects. They could not find any evidence of reduced neurogenesis in the hippocampi of depressed patients. Furthermore, antidepressant treatment did not increase neural stem cell proliferation. Unexpectedly, significantly reduced numbers of newly formed cells were found only in schizophrenic patients. Although this study was based on a relatively small sample size, and further studies are warranted, so far there is no clinical evidence that an altered rate of adult dentate neurogenesis is critical to the etiopathology of major depression.

In continuation of their recent paper Reif et al. review current data on the neurogenesis hypothesis of schizophrenia which is supported by clinical studies (neuroimaging), as well as by several genetically modified mouse models. Moreover, a number of genes regulating adult neurogenesis are reported to be associated with schizophrenia by case–control studies in patients. These findings lead to the suggestion that reduced adult neurogenesis may contribute to the development of schizophrenic disorders, but may not be a critical risk factor in affective disorders such as depression.

The studies of Landfield and co-workers [2] were among the first to call attention to how aging impacts the hippocampus. In their contribution Klempin and Kempermann discuss aging as a central cofactor in the control of adult dentate neurogenesis. Based on the hypothesis that adult neurogenesis is one of the key mechanisms of structural plasticity in the hippocampus they conclude that age as a co-variable in the regulation of neurogenesis will be of relevance to many age-related changes that affect the hippocampus such as cognitive decline or neurodegenerative diseases.

With the discovery of neurogenesis in the adult brain, researchers had new hopes that neurodegenerative conditions observed in Alzheimer's disease and related dementias could be at least ameliorated by the generation of new neurons. In their review Kuhn et al. summarize and analyze the conflicting data on altered progenitor activity and neurogenesis with respect to Alzheimer's disease and related experimental animal models. Obviously the complex changes that occur in the course of Alzheimer's disease are likely to disturb the microenvironment in which new neurons can be generated from neuronal progenitor cells. Currently it is a matter of discussion whether changes in neurogenesis are functionally relevant, and whether a pharmacological intervention which stimulates neurogenesis could also make a difference for the progression of Alzheimer's disease. Despite the difficulty to prove functional relevance of neurogenesis, the authors conclude that pharmacological improvement of neuroplastic processes, including increased neurogenesis, is worth pursuing in order to ameliorate the cognitive deficits of severe neurodegenerative disorders such as Alzheimer's disease.

During the last decade evidence has accumulated that psychoactive substances including most abused drugs negatively influence neurogenesis in the adult hippocampal dentate gyrus. These finding have stimulated new approaches for exploring the neurobiological basis of drug addiction. In his contribution Juan J. Canales reviews current findings showing that psychomotor stimulants, opioids, psychedelic compounds, and alcohol influence one or several steps of adult neurogenesis (rate of progenitor proliferation, survival of newly generated cells, maturation, migration, and acquisition of cellular phenotype). Given the role of the hippocampal formation in learning and memory he discusses the hypothesis that impaired neurogenesis in the dentate gyrus could contribute to addiction by disrupting associative learning. Further investigations, however, are required to elucidate how modified neurogenesis interacts with cognitive, motivational, and affective aspects of addictive behavior and thus will help to understand the process of addiction.

The contributions to this Special Issue represent an interdisciplinary approach discussing selected aspects from basic research to the clinic and are meant to be an invitation for discussion. For interested readers a comprehensive and integrated overview of neurogenesis, one of the most exciting fields of today's neuroscience, can be found in a recent monograph by Kempermann [1].

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