Age-dependent impairments in spatial learning in mice with reduced BDNF levels

The protein BDNF (brain-derived neurotrophic factor) belongs to the family of nerve growth factors (neurotrophins). Therefore, one of its major functions is related to the maturation and differentiation of developing nerve cells in the brain. But BDNF is not only important for the developing brain; it is also crucially involved in learning and memory processes in the adult brain. These learning-related functions are mainly mediated by binding of BDNF to TrkB (tropomyosin receptor kinase B) receptors. Both BDNF and TrkB receptors are highly prevalent in the hippocampus, a brain region that is very important for learning and the formation of memories in mammals. It has been shown by several studies that BDNF is also required for many hippocampus-dependent learning tasks, like spatial or emotional learning.

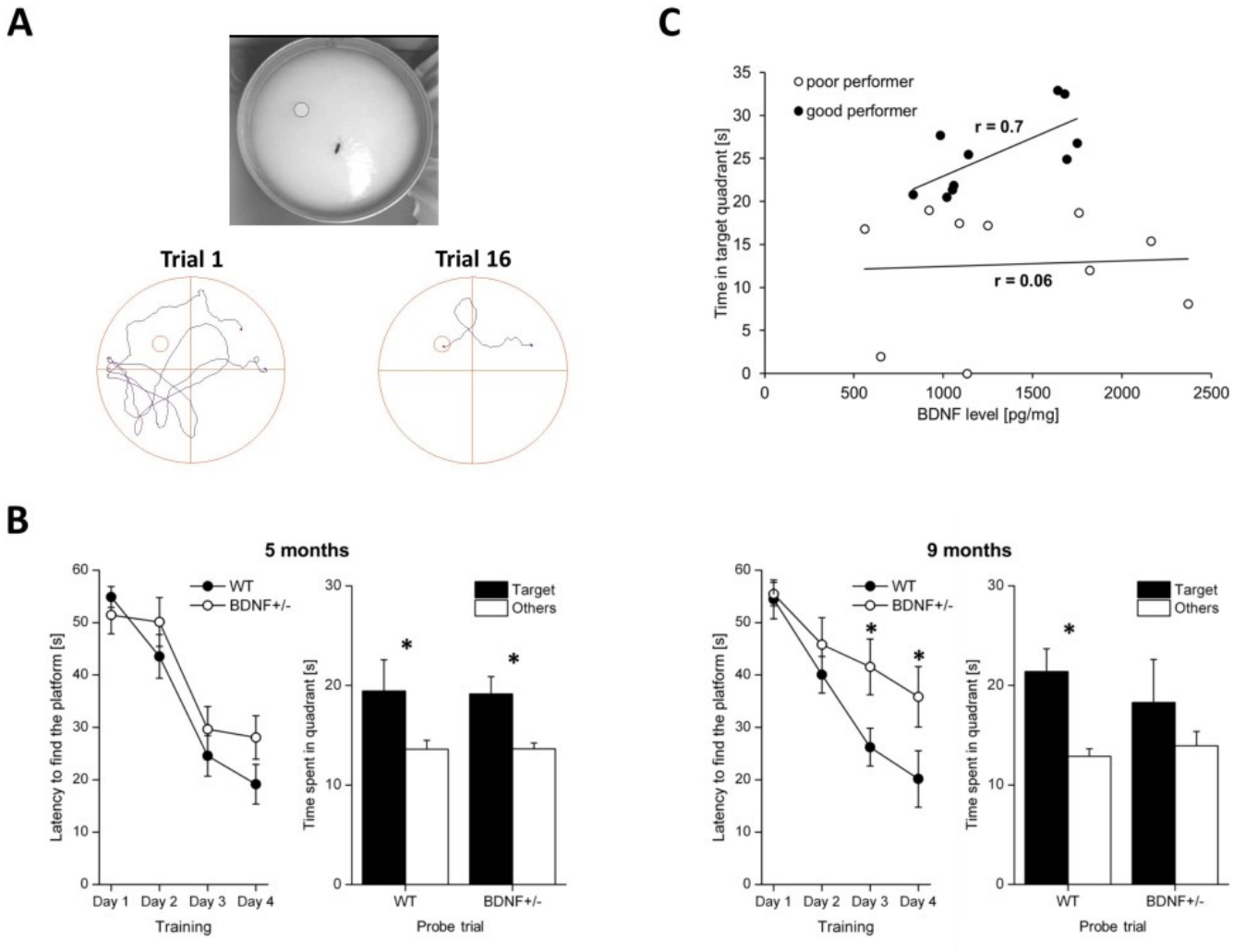

Fig. 1. A: Morris water maze task: during training sessions animals had to learn navigating to a

hidden platform (indicated by the dashed circle) by using spatial cues around the pool. The lower panel depicts two example traces of a mouse at the beginning (trial 1) and the end of the training (trial 16). B: Spatial learning in 5 and 9 months old BDNF+/- mice and their wildtype littermates. The left panels indicate the time the animals needed to find the platform during the four days of training. The right panels depict the time the animals spent in the previous target area on day 5, when the hidden platform was removed from the pool. 9 months old BDNF+/- mice needed more time to navigate to the platform and spent less time in the previous target quadrant (* indicates a significant difference). C: Positive correlation between BDNF protein levels in the hippocampus and the individual learning performance in animals that learned the task (“good performers”), while there was no such correlation in animals that didn’t learn the task (“poor performers”).

Interestingly, the levels of BDNF protein are declining throughout aging, suggesting that this decline could be one factor contributing to aging-related memory impairments in humans. In addition, several clinical studies reported that patients suffering from Alzheimer’s disease exhibit reduced BDNF levels in the blood and the brain. Since BDNF is not only important for cognitive processes but is also neuroprotective against cell toxicity induced by the Alzheimer-inducing amyloid-beta (A?) protein, a reduction in BDNF protein availability might be an important detrimental factor contributing to the pathology in Alzheimer’s disease.

To test the impact of reduced BDNF levels on aging related changes in learning and memory performance, animal models with reduced BDNF protein levels represent a valuable tool. The heterozygous BDNF knock-out ($BDNF^{+/-}$) mouse exhibits a chronic reduction in BDNF protein of around 50%. A commonly used test to assess hippocampus-dependent learning in laboratory rodents is the Morris water maze task. In this paradigm, animals are trained to navigate by spatial cues to a submerged platform in a larger circular pool. By measuring the time the animals need to swim to the platform (latency) we can assess the learning performance of the animals (Fig. 1A). On the last experimental day the platform was removed from the pool and the time the animals spent in the former platform region is measured as readout for the memory strength of the previously learned platform position.

If BDNF is important for hippocampus-dependent spatial learning, one would assume that these mice should exhibit an impaired spatial learning. Interestingly, previous studies from other labs that analyzed spatial learning of $BDNF^{+/-}$ mice in the Morris water maze reported conflicting results. Some studies reported BDNF dependent learning in this task while others did not. Possible reasons for these discrepancies could be the genetic background and the age of the tested animals. To address this issue, we performed the Morris water maze experiment with differently aged $BDNF^{+/-}$ mice that were backcrossed to the C57BL/6J genetic background, the best described genetic background in mice. Here, we observed an age-dependent deficit in spatial learning in $BDNF^{+/-}$ mice, starting at 9 months of age (Fig. 1B). To further pinpoint the cause for the observed learning deficit, we analyzed the level of BDNF protein in the hippocampus. To our surprise the

amount of BDNF protein was very stable in the tested age range. But we observed a positive correlation between hippocampal BDNF protein levels and the learning performance in animals that successfully learned the task. Thus, higher BDNF protein levels in the hippocampus resulted in an improved spatial learning performance (Fig. 1C).

Overall, our study demonstrates that $BDNF^{+/-}$ mice exhibit an age-dependent deficit in spatial learning. Furthermore, we observed a positive correlation between the level of BDNF protein in the hippocampus and the spatial learning performance, thus further stressing the important role of BDNF in hippocampus-dependent learning paradigms. In addition, our study suggests that the above mentioned discrepant findings regarding the role of reduced BDNF in spatial learning might result from the differences in genetic background and the age of the tested animals.

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Publication

Chronic BDNF deficiency leads to an age-dependent impairment in spatial learning.
Petzold A, Psotta L, Brigadski T, Endres T, Lessmann V.
Neurobiol Learn Mem. 2015 Apr