Novel insights towards memory restoration

CHAPTER 11

GENERAL DISCUSSION AND CONCLUSION

GENERAL DISCUSSION

Cognitive disorders are a major societal burden. In an ever-growing and aging population, these conditions demand urgent attention, in order to alleviate healthcare resources as well as provide a good quality of life for patients and caregivers. Although memory impairments are relatively common conditions in the elderly, few treatments are available to arrest or slow down the progression of memory loss. By targeting specific structures within known circuits, deep brain stimulation (DBS) can have beneficial effects across memory and cognitive networks, and is therefore a potentially promising avenue for non-drug based dementia treatments.

The application of DBS in psychiatry has emerged in the past 50 years [1-3]. To understand state-of-the-art applications of DBS in psychiatric conditions which potentially include memory impairments, I have reviewed relevant clinical studies on neuromodulation (Chapter 2). Non-invasive neuromodulation therapies, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), can produce short-term beneficial effects on refractory psychiatric symptoms [4, 5]. However, the effects on long-term treatment modalities are unknown. A main disadvantage seems to be that transcranial stimulation mainly targets cortical structures and does not reach deeply situated brain regions. Deep brain stimulation, on the contrary, enables focused stimulation of specific brain targets. At present, an increasing number of studies investigate the safety and efficacy of DBS, showing significant therapeutic effects in patients with different refractory psychiatric disorders [6].

With regard to memory-related disorders, DBS of the fornix and nucleus basalis of Meynert have been investigated as potential treatments for dementia in clinical trials (Chapter 3). The studies that were carried out, however, were mostly safety studies, with small sample sizes and no control group [7, 8]. As a result, this encouraging therapy has not been approved in the clinics, yet. In order to conduct standardized clinical trials, more preclinical research is warranted. Preclinical animal models are crucial to examine relevant brain targets and can accelerate the development of clinical applications of DBS. In addition, animal models are essential to increase our understanding of the underlying neural substrates of memory enhancement after DBS [3].

To further investigate the behavioral effects and mechanisms of DBS, we used a scopolamine-induced rat model of dementia. Scopolamine, a non-selective acetylcholine antagonist, has been used as a standard drug to induce memory impairments associated with aging and dementia in animals and humans [9]. Chronic scopolamine administration indeed has a widespread effect on brain depressant activity, which corroborates the variety of behavioral effects of this drug (Chapter 4). The dose I chose for the subsequent behavioral studies has been validated to impair recognition and spatial memory [9].

Thus, I have used the scopolamine-induced rat model of memory impairment and applied DBS to one of the potential targets in dementia-treatment, namely the fornix (Chapter 5). The fornices are white matter bundles, which reciprocally connect the bilateral hippocampi to the septal nuclei, nucleus accumbens (precommissural fornix) and hypothalamus (postcommissural fornix) [10]. In this study, I found that DBS of the fornix was able to restore memory loss in a spatial memory task when specific set of stimulation parameters was used. In particular, DBS of the fornix was not frequency dependent, but rather dependent on high current densities. With the investigated stimulation parameters, I found no evidence on anxiety-related side effects [11].

I have also investigated the efficacy of DBS in an aged animal model (Chapter 6). In particular, I aimed to investigate DBS of the input and output of the hippocampus and have stimulated the fornix and entorhinal cortex, respectively. In 24-months-old rats, I found that DBS of the fornix improved short-term memory in a spatial memory task. Entorhinal cortex DBS had beneficial effects on long-term recognition memory. Again no evidence for anxiety- related side effects were found. Taken together, these results support the notion that the fornix and entorhinal cortex are involved in different memory domains. This is in line with lesion studies, showing the involvement of the fornix in spatial [12-14] and the entorhinal cortex in recognition memory [15, 16], respectively.

Next, I assessed whether DBS can have beneficial memory effects when applied to other structures within the circuit of Papez (Chapter 7). Therefore, I implanted electrodes in the CA1 subregion of the hippocampus, the mammillothalamic tract, anterior thalamic nucleus and enthorhinal cortex and again made use of the scopolamine-induced rat model of dementia. DBS of the CA1 and entorhinal cortex was able to restore memory loss when specific set of stimulation parameters were used. The conclusions, however, were twofold. Firstly, I have shown that within the circuit of Papez, only DBS of the CA1 subregion, entorhinal cortex and fornix is able to restore spatial memory loss. Nonetheless, secondly, from a stereotactic point of view, I concluded that a strategic target should be chosen for therapy. The hippocampus and entorhinal cortex are relatively large brain regions in rodents and primates [17]. Therefore, neuromodulation through a single electrode might be challenging, given the risk of not targeting the relevant region in a patient. Contrary to this, the fornix entails localized fiber bundles and its size is accessible in both, rodents and primates. Thus, within the circuit of Papez, the fornix might consequently represent a preferred target for the treatment of dementia-related disorders with DBS.

In the last 3 chapters of this thesis, I focused on mechanisms of action of DBS. In Chapter 8, I investigated brains of rats, which underwent DBS in the entorhinal cortex, mammillothalamic tract and anterior thalamic nucleus. When looking at dopamine, a neurotransmitter widely acknowledged as important for memory functions, I have not

found any difference between sham and entorhinal cortex DBS animals in the ventral tegmental area. Only DBS of the anterior thalamic nucleus, induced substantial higher numbers of TH-immunoreactive cells in the ventral tegmental area, while there was no difference in the number activated cells (measured by c-Fos). My findings suggest that DBS can induce a phenotypic switch, or GABA - dopamine neurotransmitter re-specification, in the ventral tegmental area [18].

With regard to fornix DBS, mechanisms of action were evaluated by immunohistochemistry and microdialysis experiments (Chapter 9). First, I performed c-Fos immunohistochemistry in the dorsal hippocampus and found that beneficial memory performance was accompanied with a selective activation of cells in the CA1 and CA3 subfields. In order to elucidate what types of neurons were activated in the hippocampus, additional rats were implanted with fornix DBS electrodes and hippocampal microdialysis probes. During stimulation, I observed a substantial increase in the levels of extracellular hippocampal acetylcholine in fornix DBS rats when compared to sham. Specifically, acetylcholine levels increased in the first 20 min of stimulation. No effects on hippocampal glutamate levels were found during or after DBS. Therefore, my findings provide first experimental evidence that beneficial memory effects following fornix DBS can be attributed to cholinergic modulation of the hippocampus.

Lastly, I assessed whether acute DBS of the fornix can produce long-term changes in memory and whether they can be linked to adult hippocampal neurogenesis (Chapter 10). Although, fornix stimulated rats showed superior memory performance 6 weeks after DBS when compared to sham, I did not find evidence for increased hippocampal neurogenesis. My findings suggest, that besides yielding immediate effects on memory (e.g., vivid autobiographical recall seen during initiation of stimulation in some clinical studies [8, 19] and improved memory performance in rodents [11]), fornix DBS might also induce long-term memory effects. These long-term effects, however, cannot be explained by neurogenesis and further studies are indicated, which investigate changes in other neuroplastic domains.

CONCLUSION

Clinical studies have shown that targeting key structures in memory and cognitive circuits for DBS therapy is safe and can activate these circuits. In particular, case studies or phase I trials of patients with Alzheimer's disease or other dementias suggest that DBS may be associated with stabilization or improvement in memory. In the present thesis, I have found the fornix to be the most optimal target structure within the circuit of Papez to improve short-term spatial memory. DBS of the fornix induces neuronal activation in the CA1 and CA3 subfields of the hippocampus and also enhances hippocampal

acetylcholine levels instantaneously. Moreover, acute fornix DBS produced long-term memory effects. Nonetheless, no evidence for stimulation-induced survival of newborn hippocampal neurons was found. Despite these findings, the exact mechanisms of action are yet to be explored. Moreover, the efficacy of nucleus basalis of Meynert DBS, which highlights another promising target in the treatment of Alzheimer's disease [20] needs further investigation. Also, the outcome of long-term DBS in animals could reveal interesting findings with respect to the effects on brain functions and the efficacy on memory enhancement. Ongoing preclinical work may help to find the most beneficial target structure and define the therapeutic value of DBS in dementia-related disorders. Ultimately, the outcomes of sham-controlled, randomized clinical trials will determine whether DBS will play a role in the management of memory and cognitive disorders.

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