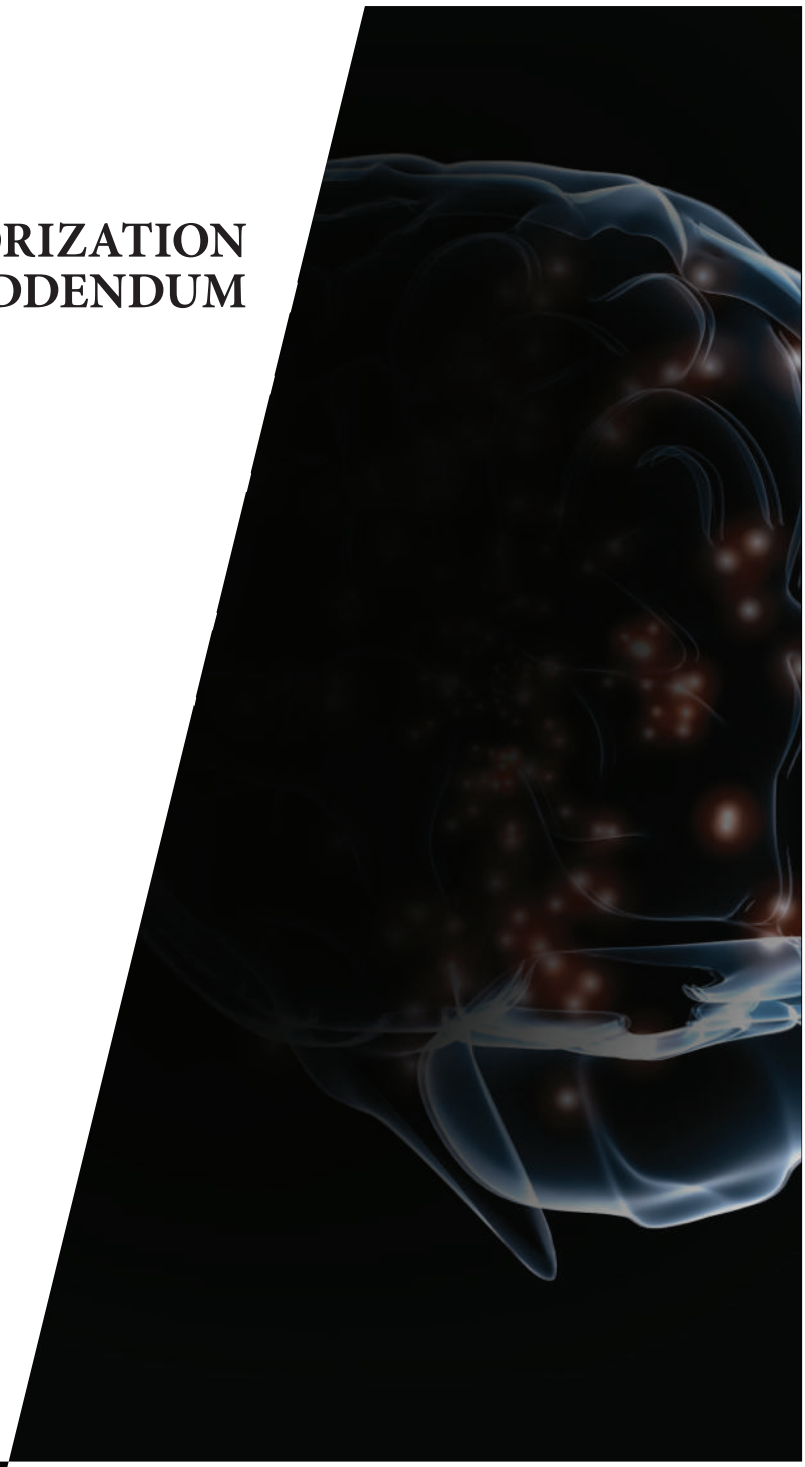
Novel insights towards memory restoration

VALORIZATION ADDENDUM



RELEVANCE FOR SOCIETY

Today, more than 44.4 million people suffer from dementia [1]. This number will increase to about 135.5 million in 2050. Every year 7.7 million new cases of dementia are diagnosed, implying that there is a new case of dementia somewhere in the world every four seconds. Dementia has emerged as one of the leading health problems of our time and has been recently recognized as one of the major threats to world population [2]. Symptoms include progressive loss of memory, impaired reasoning and judgement, difficulties paying attention, communication problems and various non-cognitive symptoms, ultimately leading to disability and need for care.

Most individuals diagnosed with dementia are 65 years or older, although there is a growing awareness of cases that start before the age of 65 [1]. Demographic ageing is a worldwide process resulting from constantly improving health care systems. The fastest growth in the elderly population is taking place in China, India, and their South Asian and Pacific neighbors. In 2010, the total estimated worldwide cost of dementia was US$604 billion, which equals to around 1% of the world's gross domestic product [3]. About 70% of the costs occur in Western Europe and North America. Statisticians even claim, that if dementia care would represent a country, it would be the world's 18th largest economy, ranking between Turkey and Indonesia [1].

Unfortunately, despite decades of research, we are still in need of an effective therapy for dementia, symptomatic or curative. There are 5 approved drugs on the market, which either modulate the cholinergic system by inhibiting acetylcholinesterase or reduce glutamate by antagonising specific glutamate receptors [4]. These pharmacological interventions, however, have limited efficacy and severe-side effects for patients; therefore, we are in need of new, effective, and safe alternative treatment options.

Recently, deep brain stimulation (DBS) has shown to have beneficial effects across memory and cognitive networks. A first evidence for this emerged when Hamani and colleagues stimulated the fornix/hypothalamus area in a patient suffering from morbid obesity [5]. In this specific case, DBS generated detailed autobiographical memories in the patient. Based on this case-observation, the same group performed a phase-I trial in patients with Alzheimer's Disease (AD) [6]. Indeed, memory tests confirmed possible improvements and/or slowing in the rate of cognitive decline in some patients following chronic DBS of 12 months.

Despite the encouraging results of the clinical trials presented above, basic neural and chemical mechanisms underlying DBS are still debated [7]. One approach to address these issues is to investigate the effects by stimulating homologous regions in experimental animal models [8].

Therefore, the studies described in this dissertation aimed at investigating which DBS target structures and stimulation parameters produce the most beneficial effects in an

experimental model of dementia. In addition, the present dissertation also describes potential mechanisms of action of DBS with regard to memory restoration. Only through understanding the mechanisms, DBS therapy in dementia patients can be fine-tuned to produce the best possible symptom relief currently available.

TARGET GROUPS

Target groups of the research presented in this dissertation are broad.

The first target audience entails the patients and their caregivers. As described above, effective dementia treatment represents a major unmet medical need at present. The quality of life of millions of patients as well as their caregivers significantly decreases in the progression of the disease. The consequences usually include a substantial decline in family's health and emotional well-being. Unfortunately, drug-based research activities in the last years have not resulted in breakthroughs in treating patients with dementia. In this respect, DBS might open new ways for alternative, non-drug based treatment in dementia-related disorders. In line with this, by examining the effects of DBS in an experimental model of dementia, we might have established the groundwork of new treatment options for not only for patients with dementia, but also for patients suffering from other cognitive impairing CNS diseases. In fact, many neurological and psychiatric conditions are constituted by cognitive disorders, for example patients with schizophrenia, attention-deficit hyperactivity disorder, depression and addiction often suffer from comorbid cognitive impairment. Thus, the present dissertation provides primary findings, which help to elucidate how DBS could potentially improve cognitive functions in dementia and other neurological and psychiatric diseases.

Coherent to this, the general public forms another target audience. Dementia has been defined as the most costly disease of our time. Treatment costs are covered by health insurances, affected individuals, their families and private insurances. In this respect, alleviating symptoms of dementia by means of DBS, would not only improve the quality of life of patients and caregivers, it would also provide a major financial relief for health care costs. Thus, delaying institutionalisation of patients by means of DBS can have an impact on economy and society, because patients function independently for longer, i.e. they can work, consume and invest for longer.

The third target group comprises the scientific critical mass. The findings of which brain region target for DBS produces most beneficial effects with regard to memory restoration might be of interest to neurosurgeons. Out of all structures within the circuit of Papez, the studies described in this dissertation, and other studies indicate that the fornix is the most relevant one for dementia therapy [9, 10]. Finally, the academic community as well as neuromodulation companies might profit from findings within

this dissertation. For example, there is an increasing awareness for the necessity to develop adaptive DBS systems (i.e., closed-loop), which prevent side-effects caused by overstimulation. Closed-loop feedback systems are latest advances in DBS therapy for epilepsy, but have not yet been developed for AD.

ACTIVITY/PRODUCTS

The major product/finding which can be derived by studies in this dissertation is that DBS might constitute an alternative treatment option for patients with dementia-related disorders. Results of the current dissertation provide evidence, that the fornix is the most suitable DBS target structure within the circuit of Papez to restore memory loss in an experimental rat model of dementia. The effects of fornix DBS are accompanied by selective neural activation in the hippocampus as well as increased hippocampal acetylcholine levels and no long-term neurogenic changes. In fact, the experiments in Chapter 9 have indicated that adaptive mechanism-based DBS might be necessary to maintain beneficial memory effects.

Chapter 3 of this dissertation also sheds light on the fact that up to now, most DBS studies in psychiatric disorders were first conducted in humans. Since the clinical data and the findings from animal studies show similarities, animal models can be of important value to find potential new DBS targets and settings for memory restoration. Close collaboration between basic scientists and clinicians has led to a successful implementation of preclinical findings to clinical DBS over the past years. For a successful treatment, such as DBS in patients with Parkinson's disease, a solid scientific base is needed. Increased understanding of basal ganglia function from studies in translational Parkinson's disease models [11, 12] paved the way for the clinical application of this method [13] and became the most successful application of DBS thus far.

INNOVATION

The studies of this dissertation have been innovative for several reasons. This work comprised in-depth investigation of the recently introduced concept of treating demented patients with DBS. This is a novel concept that might provide more rapid and robust therapies for patients with dementia. Furthermore, a multi-level, interdisciplinary approach was applied: bilateral DBS in freely moving animals, behavioral assessment, microdialysis and histology. This multi-level approach helped to understand if and how memory can be improved by DBS, in particular what the potential mechanisms

of action are. Novel mechanisms of DBS were identified, which might facilitate the treatment and management of patients with dementia in the future.

IMPLEMENTATION

In line with the abovementioned relevance of this project for patients, society and the scientific community, the implementation of the knowledge generated by this dissertation is again at various levels. Therefore, novel insights will be shared with patient organizations, health care professionals and scientific societies. From an academic perspective, results have been or will be published in peer-reviewed international journals and are presented at national and international conferences.

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