Deep brain stimulation and memory functions

Valorization

According to the World Health Organization (WHO), globally 50 million people are suffering from dementia. This translates to 5-8 people out of 100 (1). The number of diagnosed cases is 10 million per year, and by 2030, it is expected that the total number of people who suffer from dementia will be 82 million; and 152 million by 2050 (1). Dementia is characterised by a disability of the patient's memory and cognition, and it can also affect sensory modalities. In progressed stages, the patients suffer from confusion, the inability to interpret sensations, the inability to speak or understand speech, and the inability to accept customs (2).

Dementia is considered as a major burden for both the patients and their families, and it causes a serious socioeconomic burden for the society. Increasing the elderly life span due to the improvement in the preventive measures as well as the medical improvement in the quality of the health care system, can be correlated to the increase in the number of people diagnosed with dementia and other chronic neurodegenerative diseases such as Alzheimer disease (AD) (3). The world population in 2017 was 7.6 billion, In Africa the people over the age of 60 years old is 5%, 25% in Europe. While this percentage is much higher in Asia due to the high distribution of the inhabitant in that continent (4). In Europe, the annual cost is around 32,000 Euros per person with dementia and the cost has increased in the USA to 42,000 Euros per person with dementia, while the world estimated cost is about 817 billion US dollars for a sample of 46 million people diagnosed with dementia. The progressed stage cost of dementia is higher than the early stage cost. The direct cost include in- or outpatient care, drugs and patients'travel cost while indirect cost varies from loss of productivity due to short- or long term sickness absence, increased morbidity, early mortality, family impact for taking care of people with dementia (5).

Currently, there is no cure or means of prevention for Dementia, the only available therapies that have been used are aimed to reduce the symptoms of Dementia. Because of the limited and short term symptomatic relief of these medications as well as their side-effects, there is a demand for the use of non-pharmacological therapies in order to reduce or delay the progress of dementia (6) or to improve long-term survival in some patients (7). Non-pharmacological Treatments currently being tested in an investigational stage to be safe and well tolerated for people with dementia are neuromodulation-based approaches such as deep brain stimulation (DBS) (8). DBS has been shown to be more beneficial for people 65 years or older who are suffering from early AD (9). The mechanisms of action of how DBS influences memory-related functions are not well understood, yet. I aimed in this thesis to generate data to identify the gaps in our knowledge by elaborating clinical and preclinical studies and provide an overview of the potential mechanisms of action of DBS on learning and memory. Synaptic placticity, neurogenisis and behavioral memory studies have been applied to detect the possible underlying mechanisms of action of DBS targeting the fornix and the nucleus basalis of Meynert (NBM) in rat models of dementia.

Based on the previous aforementioned social problem associated with epidemiological and socioeconomic impact of AD, we address the contribution of this thesis into three main goal targets. The first target group includes women and men who are diagnosed

with AD dementia, their caregivers and/or the daily activity informants. Reason for caregiver inclusion, because regularly, the level of caregiver burden is able to rate the patient's quality of life lower than AD patient's own rating (10). In addition, progression of AD is directly correlated with family: health, emotional well-beingand and life quality of patients and their caregiver. The of quality of life assessment of AD patients and their caregiversA depends on variety of important criterias such as cognitive and functional status, daily living pleasant activity and depression rating scale (11). The goals of DBS, as a potential non-pharmacological AD treatment, are focused to delay dementia progression, enhance cognitive and noncognitive behaviours including patient's quality of life. In literature, DBS has better impact on cognitive measures accompained by improvement in the quality of life of AD pateints which is positively reflected on their spouse/caregiver, 12 months after stimulation (12, 13). Therefore, in this thesis I have generated the primariy neuronal and behavoural effects of DBS on memory enhancement in experimental model of dementia. Enhancing memory performance is considered to be one of the cardinal signs and symptoms of improving life quality of AD demented patients.

The second target group includes the public society and their valuable cooperation impact in science researches. This group target can play a major role in delaying and limiting the political measures that aim to decrease or limit the researches on clinical and preclinical level. The prevalence of AD is expected to rise within the next 50 years not only among people who are 65 years and older but among people who are younger than 65 years old (14, 15). The direct and indirect service cost of AD urge society to support such a novel safe and tolerable minimal invasive DBS procedure. DBS is not only meant to improve the life quality and the social environment of AD sufferers, but is also meant to reduce the burden influence and the care service costs associated with this debilitating disease (16).

The third target group is the scientists who are working in neuromodulation field. The data generated from this thesis shed light on the beneficial use of DBS in such a devastating neurodegenerative disease. Since there is no cure for AD, this dissertation also can guide the academic community as well as the neuromodulation companies to work together to pursue and fund the future DBS clinical and experimental animal model researches of dementia. Two therapeutic targets have been selected so far in clinical trial for AD and still different promising targets have emerged within the memory circuits in preclinical studies. A good understanding of neuromodulation mechanisms in clinical and preclinical studies might help to attain optimal results, alleviate comorbid symptoms, and avoid intolerable side effects of drug-based treatment of dementia-related disorders.

The contribution of this thesis is still often under the preclinical therapeutic escalation of DBS in experimental rat model of dementia. DBS of the fornix was found to be effective in long-term memory enhancement and that memory enhancement was not supported by long-term formation of new functional hippocampal neuronal cells or even long-term synaptic plasticity. This experiment was applied in wild type rats and that might explain the cellular and molecular effect of DBS which appear to be more effective in AD animal models rather than in wild type animal subjects. Moreover, Intermittent

DBS targeting the NBM emerged a superior memory performance in experimental rat model of dementia when compared to sham animals. We hypothesized and we proved with evidence that tailored intermittent stimulation paradigm seems to be an effective factor to reverse the memory deficit induced by scopolamine as well as increases the formation of new cells in the hippocampal dentate gyrus. These preclinical new concept findings of memory restoration could hold a promising future for the use of DBS for treating patients suffering from dementia. Since promising preclinical findings face major difficulties and uncertainties to be translated from preclinical to clinical experiences, we think DBS has a promising future towards patients with cognitive impairments diseases.

In this thesis we try to cover a well understanding of the stimulation effects on memory-related function, and still there is a vital gap in our understanding which needs to be addressed. First, we reported the neuromodulation effect of fornix DBS on long-term changes in synaptic plasticity in a wild type rats (17). Therefore, studies in animal model of AD to uncover the connectivity mechanisms among the existing neurons are needed to be addressed further. For instance, short- and long-term effect on synaptic plasticity in response to fornix and NBM DBS, are necessary to be addressed. Second, In addition to synaptic plasticity mechanism, molecular mechanism in preclinical researches also needs to be validated. For example, our research group has observed hippocampal neurotransmitter release of Ach in response to fornix DBS (18). Therefore, further research is recommended to investigate the hippocampal release of glutamate and Ach using NBM DBS in wild type and AD rat models. Third, in the present thesis we found NBM DBD enhanced hippocampal neuroplasticity in experimental rat model of dementia. Whereas, our research group outlined in a previous study that fornix DBS induce long-term memory enhancement independent of hippocampal neurogenisis (19). Consequently, hippocampal neuroplasticity needs to be investigated in response to fornix in AD rat models and in response to NBM DBS in both wild type and AD rat models. Fourth, in this thesis we addressed that intermittent stimulation paradigm of NBM enhance recognition memory in experimental rat model of dementia. In view of that, this intermittent stimulation paradigm can be applied as well in fornix DBS in both wild type and AD rat models. Finally, are behavioral, cellular, molecular and neurogenic changes dependent on stimulation protocols e.g. continuous versus intermittent stimulation? This is what has to be proven in further future preclinical studies in alternative regions to induce memory-restoring effects in response to DBS.

Safe and effective non-drug based treatment to alleviate dementia symptoms with neuromodulation in both translational models and patients are the 21st century neuroscientist mission. In this thesis, we have outlined various behavioral and plastic changes following electrical stimulation. More advanced modulating techniques targeting different brain areas for AD and other neurological disorders, with high degree of selectivity and specificity to increase efficacy and intolerable side effects used in translational models, will be developed and approved. These techniques enhances brain microcircuitry in normal and deceased states for instance, opto- and chemo-genetics and magnitothermal neuromodulation (20).

Society and other academic disciplines shed more light on the importance of DBS field on aging, especially the cardinal decline in learning and memory that is associated with an individual's increase in their life expectancy. While dementia's cause is still not fully understood, the genetic and environmental factors are currently hypothesized. The intolerable drug-based dementia treatment increases the level of society's pressure towards physicians, academic researchers and scientists to find safe and effective alternative treatments such as electrical neuromodulation. This kind of electrical modulation induce a remarkable and fruitful results on patients with Parkinson's disease and luckily ongoing clinical and preclinical trials are currently worldwide evaluated for dementia. In this thesis we have shared our knowledge with other academic disciplines for better understanding of the effects of DBS on memory-related function in response to society's demands. With more preclinical studies to understand the essential mechanism of action of DBS in memory restoration, we can confidently implement DBS in clinical practice for patients suffering from dementia and other cognitive impairment diseases.

In conclusion, we have tried to provide in this dissertation some answers to the essential gaps in our knowledge regarding the cellular and behavioral mechanisms of action of fornix and NBM DBS to restore memory loss in experimental rat models of dementia. With this in mind, we will pursue further researches on the therapeutic effect of fornix and NBM DBS using behavioral, molecular, cellular and different stimulation protocol assessments. Furthermore, for better understanding of the molecular pathogenesis of dementia, synaptic- and neuro-plasticity, new mechanisms of DBS should be studied in a multi-methodological approach for better alternative treatment of patients suffering from dementia and other cognitive impairment diseases in the future.

In this thesis we have identified several target groups (the general public, the scientists who are working in this field, scientific community and patients suffering from dementia who are affected by memory and cognitive decline). Some of the current material has been previously published or will be published in scientific j9ournals. This material has also been presented at scientific meetings promoted by patient's association and networks.

Reference

1. Lai NM, Chang SMW, Ng SS, Stanaway F, Tan SL, Chaiyakunapruk N. Animal-assisted therapy for dementia. Cochrane Database of Systematic Reviews. 2019(1).
2. Kandel ER, Schwartz JH, Jessell TM. Principles of Neural Science. New York, 4th Ed. 1414 pp: McGraw-Hill; 2000.
3. Cimler R, Maresova P, Kuhnova J, Kuca K. Predictions of Alzheimer's disease treatment and care costs in European countries. PLoS One. 2019;14(1):e0210958.
4. Alpopi C, Nica E, Oancea MDN, Balu PE. ASPECTS OF SUSTAINABLE DEVELOPMENT IN THE PERSPECTIVE OF THE POPULATION AGING PHENOMENON. Calitatea. 2019;20(S2):21-6.
5. Cantarero-Prieto D, Leon PL, Blazquez-Fernandez C, Juan PS, Cobo CS. The economic cost of dementia: A systematic review. Dementia. 2019:1471301219837776.
6. Zec RF, Burkett NR. Non-pharmacological and pharmacological treatment of the cognitive and behavioral symptoms of Alzheimer disease. NeuroRehabilitation. 2008;23(5):425-38.
7. McKinnon C, Gros P, Lee DJ, Hamani C, Lozano AM, Kalia LV, et al. Deep brain stimulation: potential for neuroprotection. Annals of clinical and translational neurology. 2019;6(1):174-85.
8. Hescham S, Lim LW, Jahanshahi A, Blokland A, Temel Y. Deep brain stimulation in dementia-related disorders. Neurosci Biobehav Rev. 2013;37(10):2666-75.
9. Lozano AM, Fosdick L, Chakravarty MM, Leoutsakos J-M, Munro C, Oh E, et al. A phase II study of fornix deep brain stimulation in mild Alzheimer's disease. J Alzheimers Dis. 2016(Preprint):1-11.
10. Logsdon RG, Gibbons LE, McCurry SM, Teri L. Assessing quality of life in older adults with cognitive impairment. Psychosom Med. 2002;64(3):510-9.
11. Logsdon RG, Gibbons LE, McCurry SM, Teri L. Quality of life in Alzheimer's disease: patient and caregiver reports. Journal of Mental health and Aging. 1999;5:21-32.
12. Laxton AW, Tang-Wai DF, McAndrews MP, Zumsteg D, Wennberg R, Keren R, et al. A phase I trial of deep brain stimulation of memory circuits in Alzheimer's disease. Ann Neurol. 2010;68(4):521-34.
13. Kuhn J, Hardenacke K, Lenartz D, Gruendler T, Ullsperger M, Bartsch C, et al. Deep brain stimulation of the nucleus basalis of Meynert in Alzheimer's dementia. Mol Psychiatry. 2015;20(3):353-60.
14. Lozano AM, Fosdick L, Chakravarty MM, Leoutsakos J-M, Munro C, Oh E, et al. A phase II study of fornix deep brain stimulation in mild Alzheimer's disease. J Alzheimers Dis. 2016;54(2):777-87.
15. Kuhn J, Hardenacke K, Shubina E, Lenartz D, Visser-Vandewalle V, Zilles K, et al. Deep Brain Stimulation of the Nucleus Basalis of Meynert in Early Stage of Alzheimer's Dementia. Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation. 2015;8(4):838-9.

16. Brookmeyer R, Gray S, Kawas C. Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. Am J Public Health. 1998;88(9):1337-42.
17. Aldehri M, Temel Y, Jahanshahi A, Hescham S. Fornix deep brain stimulation induces reduction of hippocampal synaptophysin levels. J Chem Neuroanat. 2019;96:34-40.
18. Hescham S, Jahanshahi A, Schweimer JV, Mitchell SN, Carter G, Blokland A, et al. Fornix deep brain stimulation enhances acetylcholine levels in the hippocampus. Brain Structure and Function. 2016;221(8):4281-6.
19. Hescham S, Temel Y, Schipper S, Lagiere M, Schönfeld L-M, Blokland A, et al. Fornix deep brain stimulation induced long-term spatial memory independent of hippocampal neurogenesis. Brain Struct Funct. 2017;222(2):1069-75.
20. Temel Y, Jahanshahi A. Treating brain disorders with neuromodulation. Science. 2015;347(6229):1418-9.