Deep Brain Stimulation and memory restoration

Valorization Addendum

Dementia is a cognitive impairment or cognitive decline that affects an individual's independent life, which will interfere with professional, family or social functions. A new case of dementia occurs every four seconds around the world [1]. According to statistics, the prevalence of dementia among people over 65 years old is as high as 7% around the world. The higher prevalence of dementia in developed countries (8-10%) may be due to longer life expectancy [2]. In today's society, dementia and its most common cause is AD, which has an imminent impact on the public health sector. According to the latest estimate, the global prevalence of dementia will increase to 115.4 million dementia patients by 2050 [2, 3]. It is difficult for any country in the world to bear the inherent cost of the burden of this disease. The most common early symptom is memory loss. As the disease progresses, symptoms may include language problems, disorientation, lack of motivation, difficulty speaking and writing and behavioral problems [4]. According to records, the global cost of dementia treatment in 2010 was US $818 billion. It is estimated that by 2030, this figure will reach $2 trillion [5]. Because AD patients have serious cognitive impairment, they need nursing and other care, which will affect family members emotionally and economically, and increase the cost of treatment and care [6, 7].

Given the limited efficacy of drugs associated with Alzheimer's disease and the occasional significant side effects associated with use, there is increasing interest in the use of non drug treatments, such as deep brain stimulation (DBS). In 1984, Turnbull et al. first used DBS of nucleus basalis of Meynert (NBM) for the treatment of AD patient. Even though there was no improvement in memory or cognition, researchers found some cortical glucose metabolic activity and limited arrest of deterioration [8]. After that, Hamani et al.found memory enhancement when using fornix DBS to treat obesity in 2008 [9]. Based on that study, a Phase I trial of DBS in the fornix of 6 patients with early AD was investigated. Bilateral stimulation of the fornix proved to be feasible and safe, having no serious adverse events [10]. Two patients experienced autobiographical experiential phenomena during surgery. Moreover, after 12-month DBS treatment, the patients exhibited improved memory and cognitive function, increased glucose metabolism [11]. And they also found enlarged bilateral hippocampal volume and slowing of mean hippocampal atrophy [12]. However, the sample size of six patients is small and the hippocampal enlargement was only found in two patients which may represent a chance finding. The stimulation parameters applied to AD patients may not be disease-specific. The mechanism of action and long-term efficacy evaluation of DBS need to be further studied.

Therefore, this thesis aims to study the most favorable effects of the target structure and stimulation parameters of DBS in an experimental model of dementia. In addition, this thesis describes the potential mechanism of DBS in memory recovery. To further study the mechanism of the process of DBS in the nucleus basalis of Meynert (NBM) inneurochemical changes hippocampus, synaptic plasticity and neurophysiology.

In view of the epidemiology and socio-economic impact of AD mentioned above, we divide the contribution of this paper into the following three main targets.
Consistent with this, by studying the experimental model of DBS in dementia, we may have found that this treatment scheme is not only suitable for patients with dementia, but also for patients with other central nervous system diseases with cognitive impairment. For example, obsessive-compulsive disorder, depression and addiction often suffer from cognitive impairment. Therefore, this paper provides preliminary evidence to help clarify how DBS may improve cognitive function in dementia and other neurological and mental diseases.

The second target group includes the public, society and the state. According to records, the global cost of dementia treatment in 2010 was US $818 billion. It is estimated that by 2030, this figure will reach $2 trillion [5]. The direct and indirect economic burden caused by AD has a significant impact on society and the country. Dementia seriously affects every health system in the world. A large number of resources and funds are used for dementia patients and their caregivers. There is evidence that the economic burden of middle-income countries is just beginning to appear [13-15]. DBS aims not only to improve the quality of life and physical health of AD patients, but also to reduce the related economic and social impact.

The third target group includes doctors and scientists in relevant disciplines in medicine and science. Neurologists and neurosurgeons are interested in the most favorable effect of specific brain targets of DBS on memory recovery. The scientific community and neuromodulation companies may benefit from the findings of this thesis and find future clinical and experimental animal models of DBS in the treatment of dementia. For example, this thesis found that intermittent stimulation may be an effective stimulation mode for DBS to improve memory, which coincides with the latest progress of adaptive DBS system in the treatment of epilepsy.

The main findings of this thesis are the preclinical treatment upgrading of DBS in the experimental dementia rat model and its possible mechanism. The results of this thesis provide evidence that intermittent DBS targeting NBM shows better memory performance in dementia experimental rat model, and can reverse the memory defect caused by scopolamine and increase the formation of new cells in hippocampal dentate gyrus.

Most DBS studies of mental diseases are first carried out in humans. Due to the similarity between clinical data and animal research results, the animal model in this paper is of great value for finding new DBS targets and memory recovery settings. These preclinical studies on memory recovery may bring a new direction for DBS in the treatment of dementia patients, and have a good prospect for patients with cognitive impairment diseases. Intermittent NBM DBS with optimal stimulation parameters has the potential to improve memory function, and has no side effects on anxiety level and general motor activities. In addition, there were significant differences in stimulation induced adult neurogenesis between NBM DBS group and sham operation group. And intermittent NBM DBS may induce long-term potentiation related mechanisms. NBM DBS activates the hippocampus and regulates the expression of neurotrophic factors and synaptic plasticity markers, which play a key role in memory processing. In addition, this paper also found that intermittent STN DBS seems to be an effective and safe treatment for cognitive impairment in PD patients. In this paper, we outline various behavioral and plasticity changes after electrical stimulation. These are safe and effective neuromodulation techniques with high selectivity and specificity, which provide ideas for improving the efficacy and reducing side effects in the transformation model.

Due to the relevance of the project to patients, society and the scientific community, the knowledge and new insights generated will be shared with relevant organizations, medical and scientific communities. Relevant research results have been or will be published in peer-reviewed international journals and presented at national and international conferences.

References

1. Duthey B: **Background paper 6.11: Alzheimer disease and other dementias**. *A public health approach to innovation* 2013, **6**:1-74.
2. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP: **The global prevalence of dementia: a systematic review and metaanalysis**. *Alzheimer's & dementia* 2013, **9**(1):63-75. e62.
3. Organization WH: **Dementia cases set to triple by 2050 but still largely ignored**. 2012.
4. Burns A, Iliffe S: **Alzheimer's disease**. *BMJ* 2009, **338**:b158.
5. Ernst RL, Hay JW: **The US economic and social costs of Alzheimer's disease revisited**. *American Journal of Public Health* 1994, **84**(8):1261-1264.
6. Black CM, Fillit H, Xie L, Hu X, Kariburyo MF, Ambegaonkar BM, Baser O, Yuce H, Khandker RK: **Economic burden, mortality, and institutionalization in patients newly diagnosed with Alzheimer's disease**. *Journal of Alzheimer's Disease* 2018, **61**(1):185-193.
7. Kiecolt-Glaser JK, Dyer CS, Shuttleworth EC: **Upsetting social interactions and distress among Alzheimer's disease family care-givers: A replication and extension**. *American Journal of Community Psychology* 1988, **16**(6):825-837.
8. Turnbull IM, McGeer P, Beattie L, Calne D, Pate B: **Stimulation of the basal nucleus of Meynert in senile dementia of Alzheimer's type**. *Stereotactic and Functional Neurosurgery* 1985, **48**(1-6):216-221.
9. Hamani C, McAndrews MP, Cohn M, Oh M, Zumsteg D, Shapiro CM, Wennberg RA, Lozano AM: **Memory enhancement induced by hypothalamic/fornix deep brain stimulation**. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society* 2008, **63**(1):119-123.
10. Laxton AW, Tang-Wai DF, McAndrews MP, Zumsteg D, Wennberg R, Keren R, Wherrett J, Naglie G, Hamani C, Smith GS *et al*: **A phase I trial of deep brain stimulation of memory circuits in Alzheimer's disease**. *Ann Neurol* 2010, **68**(4):521-534.
11. Laxton AW, Tang-Wai DF, McAndrews MP, Zumsteg D, Wennberg R, Keren R, Wherrett J, Naglie G, Hamani C, Smith GS: **A phase I trial of deep brain stimulation of memory circuits in Alzheimer's disease**. *Annals of neurology* 2010, **68**(4):521-534.
12. Sankar T, Chakravarty MM, Bescos A, Lara M, Obuchi T, Laxton AW, McAndrews MP, Tang-Wai DF, Workman CI, Smith GS: **Deep brain stimulation influences brain structure in Alzheimer's disease**. *Brain stimulation* 2015, **8**(3):645-654.
13. Association As: **2010 Alzheimer's disease facts and figures**. *Alzheimer's & dementia* 2010, **6**(2):158-194.
14. Wimo A, Jonsson L, Winblad B: **An estimate of the worldwide prevalence and direct costs of dementia in 2003**. *Dementia and geriatric cognitive disorders* 2006, **21**(3):175-181.
15. Canada ASo: **Rising tide: The impact of dementia on Canadian society**. *Executive Summary* 2010:1-24.