Deep Brain Stimulation for Alzheimer’s Disease

Angelo Lavano*, Attilio Della Torre, Giusy Guzzi, Federica Deodato, Francesco Lavano and Giorgio Volpentesta
Department of Neurosurgery, School of Medicine and Surgery, University “Magna Graecia” of Catanzaro, Italy

Abstract

Alzheimer’s disease (AD) is a debilitating neurological illness of increasing prevalence. Accumulations of abnormal proteins (beta amyloid and tau protein), inflammatory cascades, abnormal responses to oxidative stress and alteration in oxidative metabolism have been implicated in AD. There are few therapeutic options available for this disorder. Latest research indicates that deep brain stimulation (DBS) may be a method for improving cognitive functions. Many aspects remain unclear, particularly with regard to the optimal target structure. In this review the pathophysiology, neural circuitry and potential neuromodulation options in patients with AD are resumed.

Keywords: Deep brain stimulation; Alzheimer’s disease; Dementia; Cognition; Memory; Animal models; Target structures; Fornix; Nucleus basalis of Meynert

Introduction

Alzheimer’s disease (AD) was first described by Dr. Alzheimer in 1901 in a 51-year-old woman with progressive memory loss [1]. AD affects approximately 35 million people worldwide and its incidence is expected to increase over the next decade, posing significant challenges for public health and allocation of health care resources [2,3]. Current medical therapy includes acetyl cholinesterase, NMRA receptors blockers, vitamin E, without improving the symptoms. The modest efficacy and adverse effects of current medications led to exploration of alternative treatment options for AD [4,5]. The application of DBS in neurodegenerative and neuropsychological conditions such as Parkinson’s disease, obsessive compulsive disorder and major depression is nearly demonstrated [6,7]. In the etiopathogenesis of AD accumulations of abnormal proteins (beta amyloid and tau protein), inflammatory cascades, abnormal responses to oxidative stress and alteration in oxidative metabolism are implicated [4,8-10]. At molecular level, these proteins are responsible of the loss of synaptic functions, defective metabolism, impaired cellular repair and cell death. These molecular alterations lead to neuronal loss and cerebral atrophy in different regions of the brain involving frontal, temporal, parietal, hippocampus and entorhinal cortex (EC). AD also disrupts the neuronal connections between the cortical and subcortical areas [4,7,9].

Targets Used in Patients with AD

Deep Brain Stimulation (DBS) is a proven therapy utilized for several neurological and psychiatric indications [11-14]. Targeting of memory circuits with deep electrodes in AD is a novel application of this surgical technique [15]. Anatomically AD affects many structures of the brain, but the most important circuitry is the limbic system. Current DBS targets used in patients with AD are fornix, nucleus basalis of Meynert (NBM), entorhinal cortex (EC), pedunculopontine tegmental nucleus (PPN), anterior thalamic nucleus (ATN) and anterior limb of internal capsule (ALIC/NAc).

Fornix

Based on the observation of unexpected memory improvement in a patient with bilateral hypothalamic DBS for obesity by Hamani et al., [16], the first phase I trial of DBS of the fornix was published in 2010 by Laxton et al., [17]. Six patients with early AD were treated with DBS of the fornix bilaterally, over 1 year, monitoring both neuropsychological assessments and FDG-PET scans. Monopolar stimulation was applied at 130 Hz, 90 μs pulse width, voltage between 1.0 and 10 V. The authors used positron emission tomography (PET) imaging to demonstrate that this therapy was effective in reversing impaired glucose utilization in the temporal and parietal lobes. Clinical evaluation with the Alzheimer’s Disease Assessment Scale-Cognitive Subscale (ADAS-COG) and the mini mental state examination (MMSE) suggested a decrease in the rate of cognitive decline. The follow-up PET studies after 1 year demonstrated an increase in cerebral glucose metabolism in frontal-temporal-parietal-striatal-thalamic circuit and frontal-temporal-parietal-occipital-hippocampal circuit that was subsequently associated with improved cognitive status and quality of life [18]. Fontaine et al., [19] demonstrated stabilization of memory scores and increased metabolism in the mesiotemporal lobe following bilateral DBS of fornix in a patient with mild to moderate AD at 52 months. Bilateral low frequency stimulation of fornix using in-depth electrodes has been shown to improve MMSE in 11 patients with intractable epilepsy over a period of 4 h [20].

After this published phase I clinical trial in which the safety and possible benefits of DBS were assessed, Sankar et al., observed with structural MRI bilateral hippocampal volume increases in two of six AD patients with the best clinical response to bilateral fornix DBS. In one patient, hippocampal volume was preserved three years after diagnosis. Mean hippocampal atrophy was significantly slower in the DBS group compared to the matched AD group. Hippocampal volume change correlated strongly with hippocampal metabolism and with volume change in the fornix and mammillary bodies, suggesting a circuit-wise effect of stimulation. Deformation-based morphometry in DBS patients revealed local volume expansions in several regions typically atrophied in AD. This is the first in-human evidence that, in addition to modulating neural circuit activity, DBS may influence the natural course of brain atrophy in a neurodegenerative disease [21].

*Corresponding author: Angelo Lavano, Professor, Department of Neurosurgery, School of Medicine and Surgery, University “Magna Graecia”, Avenue Salvatore Ventuia-88100 Catanzaro, Italy, Tel +39 0961 3647389; E-mail: lavano@unicz.it, angelolavano@gmail.com

Received December 08, 2015; Accepted January 18, 2016; Published January 23, 2016


Copyright: © 2016 Lavano A, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
**Nucleus Basalis of Meynert**

The first case report describing DBS for dementia in a patient was performed nearly thirty years ago and targeted the Nucleus basalis of Meynert (NBM). In 1984 Turnbull unilaterally implanted a flexible electrode into the left NBM via a frontal approach in a 74-year-old patient with clinically moderate AD [22]. Based on animal studies, activation of NBM can enhance the behavioral state and thereby boost a range of mental faculties including memory, attention and perception. Patients suitable for NBM DBS trials are those who have already tried cholinesterase inhibitors, have minimal cortical atrophy on imaging, lack significant comorbidities and lucid intervals and capacity to consent. In one 71-year-old patient with Parkinsonian Dementia Disorder Freeman et al., [23] performed bilateral monopolar low frequency DBS of Ch4i subsector of NBM was (1 V, 20 Hz, 120 μs) associated with bilateral STN stimulation. NBM DBS improved markedly cognitive and memory functioning: after surgery score on Auditory Verbal Learning Test for immediate episodic memory and learning (AVLT-sum) demonstrated improvement of immediate and episodic memory and score on Auditory Verbal Learning Test for long term memory (AVLT-recog) amelioration of long term memory function. Cognitive benefits were sustained for 2 months during constant stimulation (time locked). This improvement in cognitive and behavior functions can be attributed to the potentiation of residual cholinergic projections in the memory circuits [24].

**Entorhinal Cortex/Hippocampus**

Neuropsychological data suggest that the left medial temporal lobe is better suited to verbal learning and that the right medial temporal lobe is better suited to nonverbal learning. Starting from this observation, in 2012 Suthana et al., tested the hypothesis that DBS of the hippocampus or entorhinal cortex alters memory performance, implanting intracranial depth electrodes in seven patients with epilepsy. An improvement of spatial memory with resetting of theta rhythm on EEG was observed when the medial temporal lobe was stimulated. This finding suggests that improvement could occur in patients with other memory impairments like Alzheimer’s disease [25]. Fell et al., conducted a pilot study to evaluate the effects of low frequency stimulation of EC and hippocampus in 11 patients with temporal lobe epilepsy. A linear correlation of stimulation on correctly remembered words was reported [26].

**Pedunculopontine Segmental Nucleus**

In a small cohort of six PD patients Stefan et al., pioneered the simultaneous implantation of both the subthalamic nucleus (STN) and the pedunculopontine tegmental nucleus (PPN). PPN-ON stimulation condition (25 Hz, 2.4 V and 60 μs PW) induced better performance in tests exploring both executive and attentive domains, which were coupled with increased glucose utilization in prefrontal and frontal bilateral cortical areas, including both lateral and more anterior-medial cortices. Moreover, during PPN-ON stimulation a surprising increase of FDG consumption was observed in the left ventral striatum. These data are consistent with the hypothesis of a positive effect of 25 Hz PPN-DBS on PD patients’ cognitive profile, probably due to a facilitatory effect exerted by PPN on both associative and limbic pathways [27].

**Anterior Thalamic Nucleus**

By the animal experience of Gao et al., bilateral Anterior thalamic nucleus (ATN) stimulation in rats reversibly increased glucose uptake in the target region, the thalamus and hippocampus, and decreased glucose uptake in the cingulate cortex and frontal cortex [28]. In 2011 Oh investigated the cognitive outcomes at least 12 months after bilateral DBS of ATN for controlling epilepsy in nine patients with intractable epilepsy who were not candidates for respective surgery. Bilateral ATN DBS directly activated the limbic memory circuit and the associated thalamo-cortical pathway, resulting in significant improvement in verbal memory or verbal fluency after chronic stimulation. The effects of ATN DBS on cognition represent an interesting collateral effect in the context of the antiepileptic treatment for intractable epilepsy. Thus, bilateral DBS of the ATN reversibly induces metabolic activation of the target area and modulates energy metabolism in remote brain regions via efferent or afferent fibers in non-epileptic rats [29].

**Anterior Limb of Internal Capsule/Nucleus Accumbens**

Modulation of ventral capsule, ventral striatum and nucleus accumbens are implicated in motivation and is a part of reward circuitry. Modulating these neural circuits might improve the cognitive and behavior functions in patients with AD [30]. The initial results of the study involving bilateral DBS of Anterior limb of internal capsule/ nucleus accumbens (ALIC/NAc) in patients with AD are promising and yet to be published.

**Discussion**

Several animal studies have shown that delivery of nerve growth factor (NGF) – a member of neurotrophin family that plays a role in cholinergic synaptic remodeling in the adult CNS-in basal forebrain (anterior part of the brain, cerebral hemispheres, thalamus and hypothalamus) by encapsulated cell biodelivery (ECB) could arrest or even reverse the neuronal degeneration process [31,32]. In 2012 Wahlberg et al., evaluated the safety and the clinical efficacy of ECB for use in humans [32]. Based on these promising results, Laxton and colleagues conducted an open-label study of DBS for AD [17]. The fornix is part of the so-called circuit of Papez. The circuit of Papez is one of the major pathways of the limbic system and is primarily involved in the cortical control of emotions and in storing memory. The stimulation activates medial temporal lobe structures like the hippocampus and the parahippocampal gyrus and thus improves hippocampus-dependent memory performances. The stimulation of the fornix drives its output and triggers the activity of the hippocampus and/or the anterior nucleus of the thalamus. The anterior thalamic nucleus is an important relay in the Papez circuit. Previous studies in rats have shown that ATN stimulation at relatively high current disrupted the acquisition of contextual fear conditioning and impaired performance on a spatial alternating task. Stimulation of this area also modulates regional cerebral metabolism as detected by FDG-microPET [28]. DBS of the nucleus basalis of Meynert (NBM) should improve or stabilize memory and cognitive functioning in patients with AD. The hypothesized mechanism involves a facilitation of neural oscillations and the synthesis of NGFs [33]. Medial temporal structures, including the hippocampus and the entorhinal cortex, have long been known to be important in memory formation and recall [25]. Previous studies in refractory epileptic patients have shown that entorhinal stimulation enhanced the memory of spatial information when applied during learning. The CA1 region of the hippocampus is another interesting target area and modulates energy metabolism in remote brain regions via efferent or afferent fibers in non-epileptic rats [29].
alterations in memory circuits, it is reasonable to expect that external stimulation of subareas within the circuitry will ameliorate symptoms. Restoration of functional connectivity and induction of hippocampal neurogenesis may be triggered by DBS. Independently of the target structure being stimulated, patients recovered quickly from surgery and only rarely experienced cognitive deterioration caused by the operation. Generally chronic stimulation was well tolerated, except for sensations of warmth, flushing and sweating. The neuropsychological results were highly variable both in validity and content, but might be interpreted with considerable reserve as indicating a stabilization of the disease progression after surgery. Although we rely on a small number of cases, the fornix is currently the target most frequently chosen for treating dementia [16,17]. As to a further potential target structure, there is one investigation dealing with the effects of low-frequency (20 Hz) DBS in the NBM for treating a patient with Parkinsonian Dementia Disease, stressing patient safety and technical feasibility of this method and also results regarding memory and other cognitive realms, such as attention, visual processing or practical symptoms [20]. NBM DBS also improves memory performance, as a result of ACh release from the NBM. Gratwicke et al., believe that especially the afferent and efferent projections of the NBM, the 90% cholinergic neurons and the early degeneration in AD make the nucleus basalis of Meynert a promising target structure in dementia [24,34-37]. Other potential DBS targets which might warrant evaluation in patients with dementia are the entorhinal cortex [25], the pedunculopontine tegmental nucleus [27] and the anterior thalamic nucleus (supported by animal studies), because at least in some areas of cognition such as spatial orientation, executive functions and attention, slight improvements appeared to occur in humans. Currently there are six clinical trials for DBS in AD that are listed by the National Institutes Health of Clinical Trial registry. One of these is a double-blind design, which should prove to be very informative in evaluating the effectiveness of DBS as a therapeutic technique in AD [32].

Conclusion

AD is a complex disease with significant financial and health-care burden. Medical therapy is of modest benefit and associated with significant side effects. To date, there is no evidence that DBS counteracts progressive neurodegeneration in any particular disorder. In selected patients with AD, DBS can delay cognitive decline, enhance memory functions and improve overall quality of life. Fornix is the most promising target for DBS in AD in terms of delaying and reversing the cognitive deterioration; other targets like NBM, PPN, EC, ATN are under investigation with good promising results. However long-term randomized controlled trials are required to validate the efficacy of neurostimulation and to determine the most optimal target for AD.

References

27. Stefani A, Pierantozzi M, Cervolo R, Brusa L, Galati S, et al. (2010) Deep brain stimulation of pedunculopontine tegmental nucleus (PPTg) promotes cognitive...
and metabolic changes: a target-specific effect or response to a low-frequency pattern of stimulation? Clin EEG Neurosci 41: 82-86.


