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Review

Deep brain stimulation in dementia-related disorders

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ABSTRACT

Memory loss is the key symptom of dementia-related disorders, including the prevalent Alzheimer's disease (AD). To date, pharmacological treatments for AD have limited and short-lasting effects. Therefore, researchers are investigating novel therapies such as deep brain stimulation (DBS) to treat memory impairment and to reduce or stop the progression of it. Clinical and preclinical studies have been performed and stimulations of the fornix, entorhinal cortex and nucleus basalis of Meynert have been carried out. The results of these studies suggest that DBS has the potential to enhance memory functions in patients and animal models. The mechanisms underlying memory enhancement may include the release of specific neurotransmitters and neuroplasticity. Some authors suggest that DBS might even be disease-modifying. Nevertheless, it is still premature to conclude that DBS can be used in the treatment of AD, and the field will wait for the results of ongoing clinical trials.

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1. Introduction

Dementia is the condition of severely impaired cognitive functioning in various domains and has a substantial negative effect on patients, families and caregivers. There are different types of dementia, amongst others Alzheimer's disease, vascular dementia, Parkinson's disease dementia, Huntington's disease, alcohol-related dementia and Creutzfeldt–Jakob disease. The most prevalent cause of dementia is Alzheimer's disease (AD), which accounts for an estimated 50–80% of all cases. AD is a progressive neurodegenerative disease, which has a detrimental impact on the quality of life of patients. The age-standardized prevalence of people aged 65 years or older of population-based studies in Europe suggests that 4.4% suffer from AD (Lobo et al., 2000). In the United States, the study of a national representative sample of people

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aged more than 70 years provided a prevalence for AD of 9.7% (Plassman et al., 2007). In the early-stage of AD, cognition and the ability to acquire new memories are impaired. In the later stages, symptoms include progressive cognitive deterioration, long-term memory loss, aphasia, apraxia and finally the inability to perform activities of daily living. Also behavioural and psychological symptoms, i.e. agitation, depression and aggressive behaviour, occur. Structural and functional imaging studies have shown generalized cerebral atrophy and fluordesoxyglucose-positron emission tomography (FDG-PET) studies found impaired metabolism in the frontal regions, the medial temporal lobe and the parietal regions (Buckner et al., 2005). The dysfunction and death of neurons is associated with cytoskeletal abnormalities, such as neurofibrillary tangles, as well as amyloid plaques (Dubois et al., 2010; Thies and Bleiler, 2011). The mean life expectancy following diagnosis is approximately seven years (Brookmeyer et al., 1998). Currently only symptomatic treatments are available for AD. There are no known treatments that cure or delay the progression of this neurodegenerative disease. Pharmacological therapies that are approved for the treatment of AD in North America and most European countries include memantine (an N-methyl-D-aspartate receptor antagonist) for severe AD and few acetylcholinesterase inhibitors for mild to moderate AD such as tacrine, donepezil, galantamine and rivastigmine (Thies and Bleiler, 2011).

These pharmacological treatments, however, are not effective for every patient and only improve symptoms temporarily. In some patients substantial side-effects such as gastrointestinal symptoms (nausea, vomiting, diarrhoea), eating disorder/weight loss, dizziness and muscle cramps are seen (Qaseem et al., 2008). Therefore, researchers are currently exploring the applicability of novel non-drug based therapies, such as deep brain stimulation (DBS) (Hamani et al., 2008; Hescham et al., 2013; Laxton et al., 2010), transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) (Boggio et al., 2011) to reduce or halt the progression of memory loss in AD and ultimately to improve the quality of life of patients and their caregivers.

Deep brain stimulation (DBS) is a minimal invasive surgical treatment involving the implantation of electrodes, which deliver electrical impulses to specific parts of the brain. It has been shown that DBS has substantial therapeutic effects in a range of neurological disorders, including Parkinson's disease, Tourette's syndrome and severe forms of epilepsy (Andrade et al., 2006; Houeto et al., 2005; Savica et al., 2012; Temel and Visser-Vandewalle, 2006; Wichmann and DeLong, 2006). In the past years, the applicability of DBS in psychiatry has been evaluated in affective disorders. DBS of 'key' regions within the limbic system resulted in therapeutic effects in patients with treatment-resistant depression (Bewernick et al., 2010; Lozano et al., 2008; Malone et al., 2009) and obsessive–compulsive disorder (Denys et al., 2010). In this respect, recent clinical (Hamani et al., 2008; Laxton et al., 2010) and preclinical (Hamani et al., 2011; Hescham et al., 2013; Stone et al., 2011) studies have suggested that DBS can be used as a tool to enhance memory functions. TMS and tDCS, on the other hand, are non-invasive techniques that can induce significant and long-lasting changes in cognitive function in both healthy volunteers and patients with neurological disease (Boggio et al., 2006; Fregni et al., 2005; Köhler et al., 2004; Luber et al., 2007). To date, there are few reports about the effects of rTMS and tDCS on memory. Most of them investigate focal and non-focal neuroplasticity changes in subjects with mild AD disease (Bentwich et al., 2011; Boggio et al., 2009; Cotelli et al., 2011). For a detailed review on TMS and tDCS on AD see Boggio et al. (2011). Here, we will focus on DBS and address the question whether there is a place for DBS as a treatment of memory-related disorders. We will review relevant preclinical and clinical literature.

2. Outline of the review

This review was based on articles identified by a PubMed search with the terms "Alzheimer's disease", "deep brain stimulation", "dementia" and "memory" as the main keywords. Relevant articles were also identified from the reference lists of articles, review papers, and book chapters. Only original data has been included in this review, giving preference to behavioural studies investigating memory performance of subjects. Review papers were utilized for background information and discussions throughout the text.

The outline of the review is as follows: in the first section, the neuroanatomical circuit responsible for memory functions is summarized in order to provide background information for the choice of the different targets for DBS. In the second section, preclinical studies, experimental findings in humans and clinical studies which have applied DBS to modulate memory functions are outlined. Finally, we provide an overall discussion of the evidence available thus far.

3. The memory circuit

The selection of the brain regions for DBS is mainly based on the so-called memory circuit of the brain. The major pathway for memory, including long-term storage and recognition memory, is located in the medial temporal lobe (i.e. hippocampus, rhinal cortices and amygdala) and diencephalic structures (i.e. mammillary bodies, thalamus). In the classical memory circuit, the entorhinal cortex projects to the hippocampus via the perforant pathway. The perforant pathway is considered the main afferent pathway to the hippocampus, where glutamatergic fibres from the entorhinal area reach the granule cell layer of the dentate gyrus. Moreover, the perforant pathway also projects to the subiculum as well as to the CA3 and CA1 subfield of the hippocampus (Witter et al., 2000). From the dentate gyrus connections are made to the pyramidal neurons in the CA3 subfield via mossy fibres. Lastly, CA3 neurons project to pyramidal neurons in the CA1 through Schaffer collaterals. It is known that pyramidal neurons contain glutamatergic and GABAergic synapses (Megías et al., 2001).

From the hippocampus the information proceeds through the subiculum to the fimbria and the fornix. The precommissural branch of the fornix projects amongst others to the anterior cingulate cortex via the septal nuclei and ventral striatum. Cholinergic fibres from the basal forebrain, including the septal nuclei and the nucleus basalis of Meynert (NBM), run through the fornix. Some fibres from the fornix also pass through the anterior commissure to the contralateral hippocampus. The postcommissural branch of the fornix projects to the anterior nuclei of the thalamus and the mammillary bodies. Because the mammillothalamic tract couples the mammillary bodies and the anterior thalamic nucleus, the hippocampus can have a direct as well as indirect effect on the thalamus (Aggleton and Mishkin, 1986; Neave et al., 1994). Findings from several electrophysiological studies indicate that the anterior nucleus of the thalamus is the primary source of glutamatergic input to cingulate neurons (Gemmell and O'Mara, 2002; Hedberg and Stanton, 1995). Thus, the postcommissural branch of the fornix reaches the cingulate gyrus through the anterior thalamic nucleus. This memory circuit is completed by projections of the cingulate gyrus to the entorhinal cortex of the parahippocampal region.

Experimental approaches have contributed to a nuanced view of understanding the different structures of the memory circuitry, since lesions in the memory circuit can mimic some of the typical memory deficits seen in ageing and dementia. Hippocampal and anterior thalamic nuclei lesions predominantly affect episodic (Aggleton and Brown, 1999; Aggleton et al., 2010) and spatial memory (Aggleton et al., 1996; Moser et al., 1995). To some extent