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Behavioral effects of deep brain stimulation of different areas of the Papez circuit on memory- and anxiety-related functions

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HIGHLIGHTS

- CA1 and enthorhinal cortex DBS reverse scopolamine-induced memory loss.
- DBS does not cause anxiety-related side effects in the open field and zero maze.
- CA1 DBS increases neural activity in the anterior cingulate gyrus.

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ABSTRACT

Deep brain stimulation (DBS) has gained interest as a potential therapy for advanced treatment-resistant dementia. However, possible targets for DBS and the optimal stimulation parameters are not yet clear. Here, we compared the effects of DBS of the CA1 sub-region of the hippocampus, mammillothalamic tract, anterior thalamic nucleus, and entorhinal cortex in an experimental rat model of dementia. Rats with scopolamine-induced amnesia were assessed in the object location task with different DBS parameters. Moreover, anxiety-related side effects were evaluated in the elevated zero maze and open field. After sacrifice, we applied c-Fos immunohistochemistry to assess which memory-related regions were affected by DBS. When comparing all structures, DBS of the entorhinal cortex and CA1 sub-region was able to restore memory loss when a specific set of stimulation parameters was used. No anxiety-related side effects were found following DBS. The beneficial behavioral performance of CA1 DBS rats was accompanied with an activation of cells in the anterior cingulate gyrus. Therefore, we conclude that acute CA1 DBS restores memory loss possibly through improved attentional and cognitive processes in the limbic cortex.

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1. Introduction

Dementia is a debilitating neurological condition with deterioration in more than one domain of cognitive function. The most prevalent cause of dementia is Alzheimer's disease (AD), accounting for 50–80% of all cases. In the United States, 9.7% of the population over 70 years of age, on average, suffers from AD [1]. In Europe, the age-standardized prevalence of people aged 65 years or older of population-based studies suggests that 4.4% is affected [2]. Symptoms include loss of memory, problems with communicating and reasoning, as well as changes in personality and behavior. After diagnosis the expected life span is approximately seven years [3]. Whilst there have been advances for symptomatic treatments for AD [4,5], there are currently neither cures nor treatments that delay or reverse the effects of AD. Thus, care and pharmacological interventions for dementia are mainly of palliative nature [6,7].

Against this background of limited progress in dementia treatment, researchers have been exploring non-drug based therapies as alternative treatment strategies to reduce or delay the progression

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of memory loss in AD. One such treatment is deep brain stimulation (DBS). The basic principle of modern DBS is the use of implanted electrodes connected to an internal pulse generator to deliver electrical stimuli to specific brain regions [8,9]. This method has mainly been applied in the field of Parkinson's disease in the last two decades, but has been found to produce therapeutic effects in a wide range of neurological [10–12] and psychiatric diseases [13–16]. In line with these developments, evidence from recent preclinical and clinical case studies suggests that DBS of the fornix, entorhinal cortex, and nucleus basalis of Meynert might have memory improving properties [17–22].

The rationale for choice of brain regions to improve memory functions in dementia using DBS is based on the classical circuit of Papez [23]. In this circuit, memory-related information flows through the perforant pathway from the entorhinal cortex to fields of the hippocampal formation, including the dentate gyrus, subiculum, CA1, and CA3. The information is then carried through the fornix to the mammillary bodies and thereafter to the anterior nucleus of thalamus via the mammillothalamic tract. The anterior nucleus of the thalamus in turn projects to the cingulate gyrus, and the memory circuit is completed by projections of the cingulate gyrus to the entorhinal cortex of the parahippocampal region [23].

Much of the above circuitry makes a relevant target for DBS. Because we already reported beneficial memory effects following fornix DBS [19], we wanted to explore the applicability and efficacy of other target regions within the circuit of Papez. Therefore, we compared the memory enhancing effects of DBS of the CA1 sub-region of hippocampus, mammillothalamic tract, anterior nucleus of thalamus, and entorhinal cortex in a spatial memory task and several anxiety tasks. In addition, we mapped memory-related brain regions affected by DBS using the early immediate gene c-Fos (K-25). C-Fos is expressed when neurons fire action potential and can be even used to map long-term activation. In particular, we investigated areas related to memory processes, i.e., the medial prefrontal cortex and hippocampus.

2. Materials and methods

2.1. Subjects

Sprague–Dawley (SD) rats from Charles River (Sulzfeld, Germany) were used, their weight ranging between 300 and 350 g at the time of surgery. The temperature of the colony room was maintained at a temperature of $21 \pm 1\,^{\circ}C$ and rats were individually housed in Makrolon™ cages with rat chow and water available ad libitum. Furthermore, the rats were exposed to a reversed 12:12 h light dark cycle. All experimental animal procedures were executed during the dark phase under red light.

2.2. Experimental groups

Rats were randomly assigned to one of the following experimental groups: Sham ($n = 11$), CA1 DBS ($n = 10$), mammillothalamic tract DBS ($n = 13$), anterior thalamic nucleus DBS ($n = 14$), and entorhinal cortex DBS ($n = 15$).

2.3. Surgical procedure

DBS electrodes were implanted bilaterally in the target areas using a rodent stereotactic apparatus (Stoelting, Wood Dale, IL, USA, model 51,653). Isoflurane (IsoFlo®, Abbott Laboratories Ltd., Berkshire, Great Britain) was used as inhalation anesthesia. After exposure of the rat skull, two burr holes were made either at the level of the CA1 (coordinates from bregma according to the rat brain atlas of Paxinos and Watson [24]: AP: −3.6 mm; ML: 1.8 mm; DV: −2.6 mm), mammillothalamic tract (AP: −1.8 mm; ML: 1 mm; DV: −6.2 mm), anterior thalamic nucleus (AP: −1.6 mm; ML: 1.5 mm; DV: −5.2 mm), or entorhinal cortex (AP: −6.7 mm; ML: 4 mm; DV: −8 mm). More detailed information about electrodes and surgical procedures is given in previous publications from our group [25,26]. Shams also underwent electrode implantation in the same brain targets, but were never stimulated. All rats were given a 2 week recovery period after surgery.

2.4. Drugs

Scopolamine hydrobromide (Acros Organics BVBA, Geel, Belgium) was dissolved in vehicle solution (saline; 0.9% NaCl) and injected intraperitoneally at a dose of 0.1 mg/kg (in 1 ml/kg) 30 min before the first trial in 6 consecutive sessions of the Object Location Task (OLT). The chosen dose of scopolamine has been described to affect spatial and recognition memory [27].

2.5. Deep brain stimulation

The following experimental conditions were tested: (i) saline injection with attachment of the stimulation cable (no stimulation) and (ii) scopolamine injection with DBS at various amplitudes (50 μA, 100 μA, and 200 μA) and frequencies (100 Hz or 10 Hz) at a pulse width of 100 μs. Stimulation was bipolar and monophasic in all cases. A randomized stimulation paradigm was applied between animals on the different testing days of the OLT. Stimulation was performed using a World Precision Instrument digital stimulator (DS8000, WPI, Berlin, Germany) and two stimulus isolators (DLS100, WPI, Berlin, Germany). Each animal was given a 24 h stimulation-off period between testing sessions. Prior to perfusion, the animals were stimulated for 1 h and were given 1 h of rest before sacrifice in order to observe expression of c-Fos [28].

2.6. Behavioral testing

2.6.1. Object location task

A full description of the OLT can be found in our previous publication [19]. In short, rats were placed in a circular arena (83 cm diameter) with 40 cm high walls. Half of the surrounding walls were made of grey polyvinyl chloride and the other half of transparent polyvinyl chloride. In total, four different sets of objects were used (A) a standard 1 L glass bottle (diameter 10 cm, height 22 cm) filled with water, (B) plastic cups (diameter 7.8 cm, height 9 cm), (C) aluminum containers (7.5 cm, 7.5 cm, 10 cm), and (D) ceramic pyramids (11.5 cm × 11.5 cm × 9.5 cm).

Objects were presented in a counterbalanced order to avoid preferences for particular objects or locations. In the first trial (T1), two identical objects were placed in a symmetrical position in the center of the arena and the rat was allowed to explore these objects for 3 min. After an inter-trial delay of 90 min, the second trial (T2) followed. In T2, one of the objects presented before was moved to a novel position (either left or right object was moved 10 cm to the front or to the back in a counterbalanced order). Using different sets of objects on each day per animal, as well as novel positions in T2 prevented habituation effects.

Two pre-tests with vehicle injections but without stimulation were carried out in order to establish a baseline. Following this, rats were given scopolamine injections 30 min before T1. Stimulation started 2 min before placing the rat into the testing arena (for both T1 and T2) and continued while the rats were in the arena for 3 min. Sham rats underwent the same procedures but were not stimulated.

Exploration time in T1 and T2 was measured manually by pressing keys on a custom-made computer program. During T1 and T2, total exploration time was considered as the sum of time spent at both objects. Discrimination performance was calculated by sub-

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