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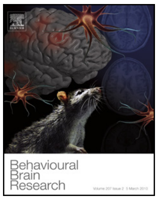

Research report

Intracranial self-stimulation also facilitates learning in a visual discrimination task in the Morris water maze in rats

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HIGHLIGHTS

- Self-stimulation (ICSS) facilitates the learning of a visual discrimination task.
- A direct, instead of a trial and error strategy is preferred by ICSS animals.
- *Number of errors* is a more sensitive measure than *latency* in visual discrimination.
- A strengthened implicit memory caused by ICSS, challenges reversal learning.

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ABSTRACT

Intracranial self-Stimulation (ICSS) of the medial forebrain bundle is a treatment capable of consistently facilitating acquisition of learning and memory in a wide array of experimental paradigms in rats. However, the evidence supporting this effect on implicit memory comes mainly from classical conditioning and avoidance tasks. The present work aims to determine whether ICSS would also improve the performance of rats in another type of implicit task such as cued simultaneous visual discrimination in the Morris Water Maze. The ICSS treatment was administered immediately after each of the five acquisition sessions and its effects on retention and reversal were evaluated 72 h later. Results showed that ICSS subjects committed fewer errors than Sham subjects and adopted more accurate trajectories during the acquisition of the task. This improvement was maintained until the probe test at 72 h. However, ICSS animals experienced more difficulties than the Sham group during the reversal of the same learning, reflecting an impairment in cognitive flexibility. We conclude that post-training ICSS could also be an effective treatment for improving implicit visual discrimination learning and memory.

1. Introduction

The electrical activation of the medial forebrain bundle (MFB) via Intracranial self-stimulation (ICSS) has been confirmed in our and other laboratories as a treatment capable of consistently facilitating the acquisition and retention in a wide array of experimental paradigms, for both implicit [1–4] and explicit memory [5,6], in rats. Several mechanisms of action have been proposed to explain these facilitating effects of ICSS on learning and memory. Stimulation of the MFB has been linked to activation of general arousal systems [7,8], due to activity of dopaminergic, noradrenergic and serotoninergic ascendant fibers [9,10]. Learning and memory facilitation has also been linked to structural plasticity induced by ICSS [11]. Recent work undertaken in our laboratory has shown an increase in the density of dendrite spines in the CA1 neurons of the hippocampus in rats that received ICSS after training in a spatial task [6]. These morphological modifications could be related to changes in the expression of several plasticity-related genes caused by the post-training ICSS treatment, with increased levels of Nurr1, c-Fos and Arc protein consistently being found in hippocampus, amygdala, dorsal striatum, lateral hypothalamus or retrosplenial cortex [12–15].

While most evidence supporting the facilitating effect of the post-training ICSS on explicit memory comes mainly from spatial learning tasks in T-mazes and the Morris Water Maze (MWM), the type of implicit memory that has been subjected to ICSS treatment effects is an amygdala-dependent emotional memory. Thus, the most commonly used tasks have been aversive classical condition-

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ing and avoidance learning. While some pioneering studies have looked into the effects of ICSS on other types of implicit tasks, such as appetitive classical conditioning [16], there are none that focus on tasks more related to perceptual learning and memory. Perceptual abilities of recognition and discrimination between stimuli are the foundation of most of the learning processes both in animals and humans and, therefore, if ICSS were able to facilitate visual discrimination conditioning and memory it would extend the range of cognitive processes – involving stimuli perception – that are improved by ICSS or the stimulation of reward pathways. Furthermore, since a deficit in implicit learning and memory related to visual discrimination are observed in both Parkinson's disease [17] and the later stages of Alzheimer's disease [18], the possibility of positively affecting this type of memory could also be interesting in the field of neurodegenerative diseases.

In order to study the possible effect of post-training ICSS on a simultaneous visual discrimination task in the MWM (SVD), we modified the configuration of the MWM based on the model presented by Packard and McGaugh [19] of a two-platform task, in a non-spatial version of the MWM task, in which two visible white rubber balls were painted with black horizontal and vertical stripes and used as cues attached to the escape/non-escape platforms. As ICSS treatment demonstrates a higher effectiveness on high difficulty conditions [20–22] a SVD task would present the appropriate setup, given that the task involves the need to identify and compare two similar stimuli in order to solve it. Moreover, this task in the MWM does not require caloric restriction in order for the animal to learn to find the platform, thus reducing the possible interference of the motivational states on learning [23]. This task is considered to be a non-declarative memory task [24], which also requires the animal to establish an association between a specific stimulus and the location of the platform, generating an instrumental escape response; this associative nature would also involve the use of relatively inflexible memory processes [25] which could mean that reversing or changing a well-consolidated memory would be extremely challenging. This suggests that, should the acquisition of the SVD task be facilitated by the ICSS treatment, the retention of the memory will be stronger while the reversal learning will be challenged.

2. Materials and methods

2.1. Subjects

A total of Forty-two Wistar male rats with mean age 90.35 days (SD = 2.20), and a mean weight of 390.57 g (SD = 20.83) from our laboratory's breeding stock were used. Three days before the stereotaxic procedure they were isolated and kept in individual cages (50 × 22 × 14-cm, plastic bottomed and sawdust-bedded). The animals were kept under conditions of controlled temperature and humidity, and subjected to an artificial 12-h light/dark cycle (light on at 08:00). The experimental work was carried out during the first half of the light cycle. All subjects were in an ad libitum regime of food and water. All procedures were carried out in compliance with the European Community Council directives for care and use of laboratory animals and were approved by the institutional animal care committee.

2.2. Surgery

Previous to the surgery, two sessions of handling took place in order to diminish emotional reactivity of the animals towards experimental manipulation. Under general anesthesia (150 mg/kg Imalgène® ketamine chlorhydrate (Merial, Lyon, France) and 0.08 mg/kg Rompun® xylazine (Bayer, Barcelona, Spain); i.p.), all rats were chronically implanted with a monopolar stainless steel electrode (150 μm in diameter) aimed at the right lateral hypothalamus (LH) into the fibers of the MFB, according to coordinates from the stereotaxic atlas of Paxinos and Watson [26], anterior: −1.8 mm from bregma, lateral: 2.0 mm (right hemisphere) and ventral: −8.5 mm with the cranium surface as the dorsal reference. In the post-surgery recovery period (7 days), the animals were weighed and handled daily.

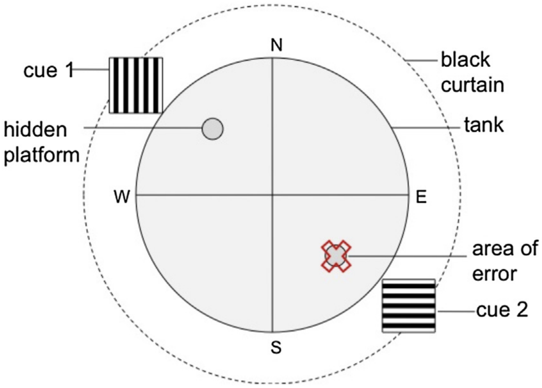

Fig. 1. Representation of one of the configurations for MWM in the simultaneous visual discrimination task. *Escape area* is associated to cue 1 and illustrated with a clear platform. *Area of error* represents the "no escape" associated to cue 2 and is signaled with a black X.

2.3. Group designation and ICSS behavior shaping

The rats were randomly distributed into two groups, Sham and ICSS, according to the independent variable "ICSS-treatment". Subjects in the ICSS group were taught to self-stimulate by pressing a lever in a Skinner box (25 × 20 × 20 cm). Electrical brain stimulation consisted of 0.3 s trains of 50 Hz sinusoidal waves at intensities ranging from 20 to 250 μA. The optimum intensity (OI), defined by the lowest intensity that led to a stable rate of about 250 responses in five minutes, was established.

2.4. Morris water maze apparatus

The MWM consisted of an elevated circular pool (2 m diameter; 60 cm above the pool floor) filled with water (45 cm height) maintained at 22 ± 2 °C. The pool was in the middle of a semi-dark room and surrounded by black curtains reaching from a false ceiling to the base of the pool forming a circular enclosure 2.4 m in diameter. In an adapted version of the two-platform task of Packard and McGaugh [19], four imperceptible nylon threads hung from the false ceiling at equal distances from one another to provide suspension for the two mobile cues throughout the training. These cues rested in the middle of the virtual quadrant in the tank, 45 cm above the water level, and consisted of identical squares (40 cm^2) with a vertical or horizontal black and white stripes pattern of 1 cm wide stripes, as represented in Fig. 1. For the escape task, a clear Plexiglas platform (11 cm diameter) was placed centrally in one of the four equal quadrants in which the tank was virtually divided, with its top 2 cm below the surface of the water. All swim paths were recorded using a closed-circuit video camera (Smart Video Tracking System, Version 2.5, Panlab) with a wide-angle lens was mounted 1.75 m above the center of the pool inside the false ceiling.