Experimental Neurology 303 (2018) 153–161

Contents lists available at ScienceDirect

Experimental Neurology

journal homepage: www.elsevier.com/locate/yexnr

Research Paper

The effects of bilateral, continuous, and chronic Deep Brain Stimulation of the medial forebrain bundle in a rodent model of depression

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ARTICLE INFO

Keywords:
Rodent depression-model
Deep Brain Stimulation
Behavior
Medial forebrain bundle

ABSTRACT

Background: Clinical trials of supra-lateral medial forebrain bundle (MFB) Deep Brain Stimulation (DBS) in treatment resistant major depressive patients have shown rapid and long-term benefits.
Objective/hypothesis: The study used Flinders Sensitive Line (FSL) rats with previously identified depressive-like phenotype to assess the range of behavior modification achieved by MFB DBS.
Methods: Male FSL and wild-type Sprague-Dawley rats as Controls were tested on mood/anxiety/exploration, cognitive and motor behaviors. The animals were implanted with bipolar stimulation electrodes in the MFB, and recovery was followed by 10 days of bilateral, chronic and continuous stimulation.
Results: Weight dynamics was assessed continuously and indicated similar growth rates although the FSL rats weighed approximately 20–25% less. MFB DBS had no impact on ultrasound calls emitted and the FSL rats continued to vocalize significantly less in the positive affect frequency compared to controls. Similarly, stimulation did not influence the FSL's exploration level (Elevated Plus Maze), nor locomotion (Open Field), although it reduced their freezing behavior (Open Field). Importantly, MFB DBS improved cognitive performance (Double-H) compared to Controls by reducing the time required and the number of errors committed to complete a spatial task.
Conclusion: MFB DBS in the FSL animals selectively affected certain types of behaviors. Exploration and vocalization remained unaltered, but cognitive performance such as speed and precision of memory recall improved compared to unstimulated and stimulated controls. Future studies should focus on the mechanisms of action of MFB DBS, and in particular on the role of dopamine in the stimulation-dependent phenotype changes.

1. Introduction

Major depressive disorder (MDD) has become a global epidemic, and is considered to be the leading psychiatric disorder today, impacting on quality of life, public health and multiple other socio-economic domains (DiLuca and Olesen, 2014). More than 300 Million people are affected directly by this disorder (many more if we consider relatives/carers) and it is the leading cause for work disability (WHO, 2012). If MDD is properly diagnosed and treated, the majority of patients will respond to the conventional therapies such as medication, psychotherapy, and electroconvulsive therapy. However, around 20% of the patients are considered to be treatment-resistant and are eligible for experimental therapies (Al-Harbi, 2012; Mayberg et al., 2005).

In an initial pilot series, the chronic, bilateral high frequency Deep Brain Stimulation (DBS) of the medial forebrain bundle (MFB) in treatment-resistant MDD patients has shown rapid and long-term benefits in the majority of the patients (Schlaepfer et al., 2013, 2014), which has been replicated by others (Fenoy et al., 2016). The MFB contains bi-directional, myelinated and unmyelinated projections of diverse neurotransmitter system connecting different regions of the brain that are associated with multiple functions such as motor, cognition and emotion/mood processing. In the context of the neurocircuitry of depression, a key component of the MFB is the limbic system that includes hubs such as the cingulate cortex, the nucleus

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https://doi.org/10.1016/j.expneurol.2018.02.002
Received 6 November 2017; Received in revised form 14 January 2018; Accepted 6 February 2018
Available online 08 February 2018

accumbens (NAc), and the ventral tegmental area (VTA), structures that are also part of the reward circuitry (Russo and Nestler, 2013). The MFB might be a legitimate target for neuromodulation using DBS on the grounds that a dysfunction of the reward circuitry is likely to play a significant role in anhedonia and reduced drive/motivational levels, two key symptoms of clinical depression.

The current study investigated the impact of bilateral MFB DBS on the behavioral phenotype of the Flinders Sensitive Line (FSL) rat, an animal model of depression. FSL rats are a selectively bred rat strain mimicking several depressive-like symptoms such as reduced motivation, locomotion and exploration, altered sleep rhythms and weight loss, impaired spatial orientation and learning and memory deficits and altered neurotransmitter and hormone levels (Overstreet, 1993; Thiele et al., 2016). The behaviors tested ranged from motor to cognitive, and were chosen based on earlier work showing that the deficits can be either transient (spontaneously recovering) or long-term (stable) (Thiele et al., 2016). Bilateral MFB DBS in the animals selectively affected certain types of behaviors. Explorative and vocalization behaviors were not changed, but some aspects of cognitive performance such as speed and precision of memory recall were significantly improved, suggesting a positive impact on attention. The data sheds light on the extent and nature by which electrical stimulation can modulate behavior in depression model.

2. Materials and methods

2.1. Study design

Flinders Sensitive Line (FSL) rats derived from a breeding colony received from Professor Rezvani (Duke University), and expanded in the animal facility of the Freiburg University Medical Centre were used in this study. Control animals were age and gender matched Sprague–Dawley (SD) rats (Charles River, Germany). All animals were single-housed with controlled temperature of 21 ± 1 °C and 50–60% relative humidity, and were weighed regularly. Animals had ad libitum access to food and water. The studies were approved by the veterinary board for animal research (University of Freiburg) and were carried out in accordance with the EU Directive 2010/63/EU concerning the protection of animals used for scientific purposes.

Animals (FSL, n = 6; control, n = 6; male, 8–10 weeks old at start of the study) received baseline behavioral testing on numerous behavioral tests as described later. Next, bipolar electrodes were implanted bilaterally into the medial forebrain bundle and the animals received chronic and continuous stimulation as described later on and elsewhere (Furlanetti et al., 2015b). Post-stimulation, the behavior tests were repeated and the animals sacrificed. The experimental design is summarized in Fig. 1.

2.2. Electrode implantation

The animals were anesthetized using isoflurane at 4% with an oxygen flow of 2 L/min, and placed in the stereotactic frame under constant anesthesia. All coordinates were taken from a flat skull. As described previously, bipolar electrodes (125 μm diameter each, 90% platinum/10% iridium, 15-mm-length Teflon-coated shaft, World Precision Instruments, Sarasota, USA) were stereotactically bilaterally implanted into the medial forebrain bundle (MFB) and permanently fixed to the skull surface with micro-screws and bone cement (Furlanetti et al., 2015b). Anterior–posterior (AP) and mediolateral (ML) coordinates were used taken from bregma, and DV coordinate from dura. (AP: −2.8; L: ± 1.7; DV: −8.8) Buprenorphine (75 μg/kg, i.p.) was given to all animals for postoperative analgesia.

2.3. Stimulation parameters

Following electrode implantation surgery the animals were given 10–14 days of recovery time before reconnection to the pulse generator (STG 2008, Multichannel Systems, Germany) for stimulation. The stimulation parameters used have been described before: square-wave biphasic stimulation, 130 Hz, 100 μs and 250 μA average constant current (Furlanetti et al., 2015a). The current was individually titrated for each cerebral hemisphere incrementally in 50 μA steps beginning with 50 μA and reaching maximum 350 μA. If side effects (e.g. rotational behavior, dystonic movements) occurred, the current was reduced until the unwanted phenotype disappeared. Bilateral, chronic and continuous MFB-DBS was performed for 10 consecutive days.

2.4. Behavior testing

The tests used probed mood/anxiety/exploration and cognitive behaviors. The animals were regularly weighed as part of monitoring their health. All behavior tests had been recorded by a digital video camera (Sony Corporation, Japan) and the analysis was performed using Viewer2 (Biobserve, Germany).

2.4.1. Forced Swim Test (FST)

Depressive-like behavior in rodents is assessed using the FST. The test measures the duration of immobility while rodents are exposed to an inescapable situation. The rats were placed in a plastic cylinder (40 cm high, 20 cm in diameter) filled until 10 cm from the top with water (21–23 °C) deep enough to avoid the rats touching the bottom of the cylinder with their tails. The immobility was assessed the following day with a single 300 s (5 min) trial. Activity was recorded with a digital video camera (Sony Corporation, Japan) connected to the workstation (Viewer2, Biobserve, Germany), and the time spent in a posture of immobility was calculated. In accordance with the literature,

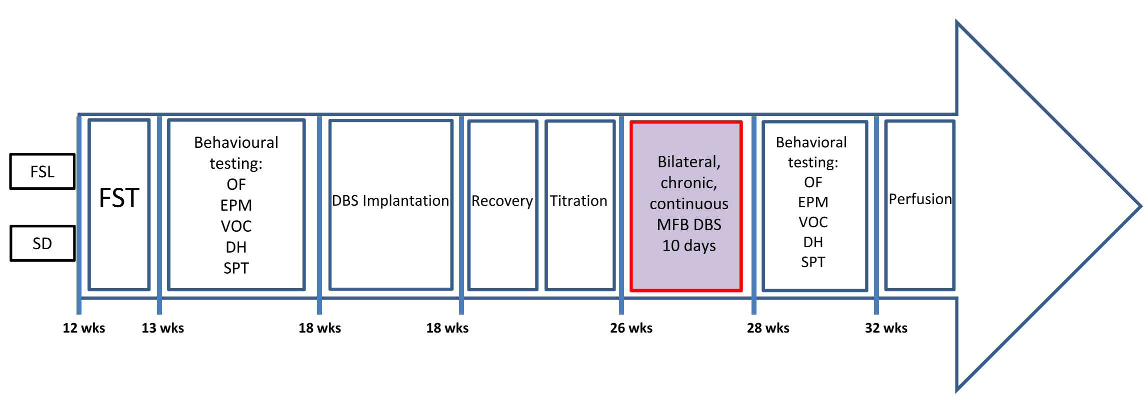

Fig. 1. Timeline of the behavioral tests. FST, Forced Swim Test; OF, Open Field; EPM, Elevated Plus Maze; VOC, ultrasonic vocalization; DH, Double-H Maze; SPT, sucrose preference test; MFB, medial forebrain bundle; DBS, deep brain stimulation. FSL, Flinders Sensitive Line; SD, Sprague-Dawley (Control).