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Research report

Subthalamic nucleus modulates social and anxogenic-like behaviors

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HIGHLIGHTS

- In Parkinson's disease, global social maladjustment and anxiety are frequent after subthalamic nucleus (STN) stimulation.
- We examine the impact of a STN lesion upon anxiogenic-like behavior and social behavior in a rat model.
- Lesioned rats showed impairments in their social behaviors.
- Lesioned rats showed an increase in anxiogenic-like behaviors.

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ABSTRACT

In Parkinson's disease, global social maladjustment and anxiety are frequent after subthalamic nucleus (STN) stimulation and are generally considered to be linked with sociofamilial alterations induced by the motor effects of stimulation. We hypothesized that the STN is per se involved in these changes and aimed to explore the role of STN in social and anxogenic-like behaviors using an animal model.

Nineteen male Wistar rats with bilateral lesions of the STN were compared with 26 sham-lesioned rats by synchronizing an ethological approach based upon direct observation of social behaviors and a standardized approach, the elevated plus maze (EPM). Comparisons between groups were performed by a Mann–Whitney–Wilcoxon test.

Lesioned rats showed impairments in their social ($P = 0.05$) and aggressive behaviors with a diminution of attacking ($P = 0.04$) and chasing ($P = 0.06$). In the EPM, concerning the open arms, the percentage of distance, time, inactive time, and entry were significantly decreased in lesioned rats ($P = 0.02$, $P = 0.01$, $P = 0.04$, and $P = 0.05$). The time spent in non-protected head dips was also diminished in the lesioned rats ($P = 0.01$).

These results strongly implicate the STN in social behavior and anxogenic-like behavior. In human, as DBS induces changes in the underlying dynamics of the stimulated brain networks, it could create an abnormal brain state in which anxiety and social behavior are altered. These results highlight another level of complexity of the behavioral changes after stimulation.

1. Introduction

Slight to severe global social maladjustment is frequent in patients suffering from Parkinson's disease (PD) after subthalamic nucleus (STN) deep brain stimulation. In these patients, the motor improvement after surgery is followed in some cases by the deterioration of conjugal relationships, which are triggered or aggravated postoperatively by the emergence of severe anxiety [1,2]. It has been hypothesized that these interpersonal conflicts were in line with an emergent property of systemic interactions between the patients, who suddenly regained their autonomy, and their devoted spouses, who lost their function after years of disease-related compassion and care. It has also been hypothesized that such psychological side-effects were due to sudden reduction in dopamine replacement therapy inducing a dopaminergic deficit in associativo-limbic areas of the brain [3].

Abbreviations: PD, Parkinson's Disease; STN, SubThalamic Nucleus; EPM, Elevated Plus Maze.

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Nevertheless, if the STN is a part of the basal ganglia which is well known to be involved in extrapyramidal control of movement [4–6], it is also linked with structures involved in the control of non-motor behaviors via different neural associative and limbic circuits [7]. These functional networks may be of interest in behavioral regulation and the STN deep brain stimulation (DBS) could be per se involved in social maladjustment and emergence of anxiety. Moreover, psychological side-effects described with DBS should differ regarding electrode target placement within different STN sub-territories. Despite the number of STN subdivisions and their anatomical localization is still uncertain [8], it has been suggested that the ventral part of the STN is closely involved in the emotional network [9]. Although the neuronal bases of the effects of DBS remain unclear [10], it was hypothesized that changes in the underlying dynamics of the stimulated brain networks may represent the core mechanism of DBS and those basic dynamical changes can be achieved via activation, inhibition, or lesion [11]. Concerning STN lesions in humans, subthalamotomy could be a stereotactic surgery performed in patients suffering from PD in circumstances when DBS is not viable [12]. Only one small prospective study including 10 patients found no change concerning anxiety following subthalamotomy [13] and, to our knowledge, no previous study has investigated its impact upon human social behavior.

Thus, animal models could provide an opportunity for experimental manipulations that are not possible in human and can allow for exploring our hypotheses. To our knowledge, there was no previous investigation of consequences upon social behavior of STN inactivation carried out in animals.

Thus, this study aimed to explore the role of STN on rat's social and anxogenic-like behaviors by synchronizing two complementary methods: an ethological approach based upon direct observation of a wide range of social behaviors [14], and a standardized approach using the elevated plus maze (EPM), a 'gold standard' test to explore anxiety-like behaviors [15].

2. Material and methods

2.1. Animals

Adults, male Wistar rats (CERJ), weighing 200–300 g at the beginning of the experiments, were kept 4 per cage in an approved animal house at 22 ± 2 °C, in 12-h light/dark cycle (light on at 08.00 h). Tap water and food pellets were available ad libitum. The animals were familiarized with the animal house at least 10 days before surgery. The researchers are approved by the Veterinary department of the French Ministry of Health (authorization number 35-01). All animal experiments were carried out in accordance to the European Communities Council Directive (86/609/EEC). The care provided to them before, during and after the protocol was in compliance with ethical standards and good laboratory practices.

2.2. Surgical procedures

The animals were anesthetized with 350 mg/kg chloral hydrate injected intraperitoneally and secured into a Kopf stereotaxic apparatus (Phymep, Paris, France). Lesioned rats received bilateral injections of ibotenic acid [9.4 μg/μl (53 mM), in 0.1 M phosphate-buffered saline, 6.5 < pH < 7]. Sham-operated rats received vehicle alone (0.1 M phosphate-buffered saline). Initially, the volume injected was 0.5 μl per side and was slowly infused over 3 min using a 10-μl Hamilton syringe. The needle was left in place for 3 min after completion of the injection. Nevertheless, as a small proportion of rats showed substantial brain lesions after histological verification, it was decided to inject 1 μl per side.

The coordinates targeting the STN were determined according to Paxinos Watson's atlas [16] and were measured from bregma: anterior/posterior, – 3.7 mm; lateral, ± 2.4 mm; dorsal/ventral – 8.8 mm (from skull). Postoperatively, rats were housed individually in clear square plastic cages.

2.3. Behavioral testing

The same observer performed all the following behavioral testing.

2.3.1. Open-field

At day 12 after surgery, rats were individually placed in Plexiglas chambers (45 × 45 × 30 cm) at a light intensity of 30 lx. Their spontaneous motor activity was measured min per min for a total duration of 10 min, using a movement analysis system (Bioseb®, Chaville, France), which counts movements by scanning 2 × 16 pairs of infrared photobeams on the side walls and allows for measuring spontaneous activity in the open field in lower position and in upper position. Furthermore, as all animals were placed in the open field, this phase allowed for habituation to the testing apparatus used in social interactions test.

Table 1
Detailed description of behavioral rating.

Behaviors	Detailed description
Non social behaviors	
Non social exploration	- Exploring the open field.
Rearing	- Standing on its hind legs and appearing to be looking at something.
Resting	- Passive behavior in which the rat does not move and has a relaxed body posture.
Self-grooming	- Licking or biting its own fur. - Rubbing the forepaws over the head.
Social behaviors	
Contact behavior	- Grooming (chewing and licking the partner's fur). - Crawling over the social partner. (+) - Crawling under the social partner. (−)
Social exploration	- Anogenital investigation (sniffing or licking the anogenital area of the social partner). - Non-anogenital investigation (sniffing at any part of the partner's body, except the anogenital area).
Tail manipulation	- Grabbing and pulling the partner's tail.
Aggressive behaviors	
Pinning	- The social partner is lying on its back with the experimental animal standing over him. (+) - The experimental animal is lying on its back with the social partner standing over him. (−)
Attacking	- Boxing. (+) - Biting. (+)
Chasing	- Rapide pursuits. (+)
Evading	- Running, leaping or swerving away from the social partner. (−)

(+) Dominant behavior
(−) Submissive behavior

2.3.2. Social interaction test

The general design of the social interaction tests was adapted from File and Seth [17], Schneider *et al.* [18,19], and Rudebeck *et al.* [20]. Social interactions were assessed at three different time points (day 13, 14, and 15 after surgery) in the open field (under the conditions described above) wherein rats were exposed to an unfamiliar social partner for 10 min. Lines on the tail were drawn on sham and lesioned rats in order to recognize them from their congeners.

Partners used in social interaction tests were free of any surgical intervention. The test area was cleaned with a 5% alcohol solution after each trial. The two rats were recorded with a digital video camera and sequential elements of behavior were analyzed manually by a trained and blinded observer. The following behavioral elements were quantified (mean number of occurrences during the three sessions) in the experimental rats (sham or lesioned): non-social behaviors, social behaviors, and aggressive behaviors. Behaviors were also categorized as dominant or submissive. A detailed description of these behaviors is given in Table 1.

2.3.3. Elevated plus maze

This test was performed at day 16 after surgery. The EPM was made of wood and painted black. The apparatus consisted of two opposite open arms (45 × 10 cm) without side walls and two enclosed arms (45 × 10 × 30 cm) with sides and end walls, extending from a central square (10 × 10 cm). The maze was elevated to the height of 60 cm from the floor and placed in a moderately lit room (30 lx as measured at the center of the maze). At the test onset, the animals were placed at the center of the EPM, facing toward an open arm.

The Video-Track® system used for recording the animal behaviors was composed of a roof-handled camera connected to a computer. This apparatus measured activity or inactivity time and distances covered in each part of the maze in open or closed arms or center, minute per minute, for 5 min. The five following conventional parameters were recorded: total distance covered, number of entry in the open arms, percentage of distance and of time spent in the open arms, and percentage of inactive time spent in the open arms compared with total inactive time spent in the EPM as a whole. Furthermore, to minimize the possibility false-negative results [21], three ethological parameters were recorded on videotape and analyzed by a person not involved in the experimental procedure. The time devoted to the following behavioral activities was then recorded: risk assessment, the rat exiting an enclosed arm with the forepaws and head only and investigating the