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BNST lesions aggravate behavioral despair but do not impair navigational learning in rats

Pınar Pezük [a], Didem Göz [b], Ayla Aksoy [a], Reşit Canbeyli [a,*]

[a] *Psychobiology Laboratory, Department of Psychology, Bogazici University, 34342 Bebek, Istanbul, Turkey*
[b] *Department of Biology, University of Virginia, Charlottesville, VA 22904-4328, USA*

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Abstract

The bed nucleus of the stria terminalis (BNST) is a basal forebrain structure involved in many motivational processes closely linked to stress regulation. The present study investigated the effect of bilateral lesions of the BNST in male Wistar rats on behavioral despair and navigational learning in the Morris water maze both of which present stressful challenges. Compared to controls, BNST-lesioned animals displayed longer duration of immobility in the second of two forced swim tests used to assess behavioral despair but performed similarly in the water maze task. The present results indicate strongly that the BNST is involved in the modulation of behavioral despair. Experimentally induced depression by BNST lesions does not impair learning and memory in the water maze suggesting a possible dissociation between BNST-mediated depression and cognitive performance.

Keywords: Bed nucleus of the stria terminalis; Depression; Learning; Memory; Morris water maze

1. Introduction

There is overwhelming evidence for an association between depression and impaired performance in learning and memory tasks [3,6,28,40]. Studying the relationship between depression and cognitive impairment is not only of interest for the elucidation of common central mechanisms, but has potential clinical implication in view of the often observed co-morbidity of depression and cognitive losses. Animal models of depression provide the means to investigate both the behavioral consequences and the central mechanism related to the effect of induced depression on consequent cognitive impairment. Additionally, such models can provide the means to assess how and to what extent cognitive impairment is causally related to depression.

As part of our investigation into the mechanisms that modulate immobility in forced swimming in rats [1,5,57], we reported earlier that bilateral destruction of the BNST aggravates behavioral despair [50], an animal model of depression based on two forced swim tests conducted 24 h apart [45]. Based on our earlier finding, the present study investigated the effect of experimentally induced behavioral despair on cognitive performance, specifically the effect of bilateral BNST lesions on behavioral despair and navigational learning as assessed in the Morris water maze.

The BNST is a limbic structure located within the basal forebrain adjacent to the septum and is neurally connected with many subcortical and cortical structures, particularly the amygdala and the PVN [2,13–15,25,33,36,48,53]. The BNST is implicated in many autonomic, neuroendocrine and motivational processes related, among others, to stress and fear [18,29–31,41,49,55]. In particular, the BNST modulates the activation and termination of the hypothalamo-pituitary-adrenal (HPA) axis response to stress that is critically involved in many aspects of memory, learning, and psychopathology [16,25,26,34,35,40,52,63].

Behavioral despair is an animal model of depression based on two forced swim tests conducted 24 h apart [45]; immobility in the second swim test is significantly longer in the second 5-min swim compared to the comparable period in the first 15-min swim test. Major classes of antidepressants and light exposure mimicking phototherapy shorten the duration

* Corresponding author. Tel.: +90 212 359 7129; fax: +90 212 287 2472.
E-mail address: canbeyli@boun.edu.tr (R. Canbeyli).

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of immobility in the second swim test compared to controls [11,32,37,45,47,62].

Several considerations suggest that the BNST lesions can modulate performance in the Morris water maze task. Since depression generally impairs memory and learning in both humans and animals [3,6,28,51,61], aggravation of behavioral despair by the BNST lesions can make the learning of the navigational task more difficult for the BNST-lesioned animals compared to controls. Furthermore, spatial learning in the water maze presents a stressful challenge to the animal [12,27,38]; both behavioral despair and the water maze test involve similar behaviors and challenges to the organism in the form of forced swimming. BNST-lesioned animals can therefore be expected to show impaired performance in the navigational learning task as well. Finally, Chen et al. [10] reported that pre- and post-training intra-BNST injections of prazosin, an α_1 adrenergic antagonist, impaired acquisition and retention in the Morris water maze task. In the light of the fact that BNST has the highest density of nor-epinephrine in the brain [4,9,19], and stressful situations can increase NE turnover in the BNST [41], Chen et al. study also suggests that BNST lesions can impair the acquisition of navigational learning in the present study.

2. Methods

2.1. Animals

Twenty-two male Wistar rats raised in our breeding colony, weighing 260–275 g at the start of the experiment, were randomly assigned to lesion and sham groups. Fourteen rats were lesioned and eight were sham-operated. All animals were maintained in a temperature controlled room (22 ± 2 °C) on a 12 h light/12 h dark cycle (lights on at 07:00 h) Animals were group-housed with food and water available ad libitum.

2.2. Surgery

Bilateral BNST lesions were performed under ketamine anesthesia (160 mg/kg i.p., 50 mg/ml). Flat skull stereotaxic coordinates [44] relative to bregma were +0.7 mm anterioposterior (AP), ±1.1 mm mediolateral (ML), and −6.3 mm dorsoventral (DV) from dura for both BNST-lesioned and sham-operated animals. An anodal current of 1.5 mA was applied for 22 s on each side for BNST lesions. In sham operations the electrode was lowered into the brain for 22 s on each side but no current was applied.

2.3. Behavioral testing

All behavioral testing described below took place between 1000 and 1600 h and recorded on videotape.

2.3.1. Forced swim test

Two weeks after surgery, animals were tested in two forced swim tests (FSTs) separated by 24 h. FSTs were conducted in a vertical Plexiglas cylinder of 45 cm height and 30 cm diameter filled with water (25 °C) to a height of 15 cm. Animals were immersed individually in water and allowed to swim for 15 min in the first (FST1) and 5 min in the second (FST2) test. Total duration of immobility was measured in the second swim test. Immobility was defined as floating or lack of motion of the entire body without leaning against the wall of the cylinder.

2.3.2. Morris water maze

One week after the second forced swim test, animals were tested on a spatial navigation test using a Morris water maze (MWM) tank with a hidden platform that was surrounded by a large number of objects providing distinct cues. The tank was a circular Plexiglas pool (120 cm diameter, 60 cm height) filled to a height of 40 cm with water of approximately 20 °C temperature. A transparent platform (10 cm × 10 cm) was placed in a fixed quadrant throughout the training session submerged in water with the top 2 cm below water level. Animals received 7 days of training with five trials on each day with a 5–10 min intertrial interval. On each trial, the animal was randomly immersed into water from one of four designated starting points and was allowed to swim for 60 s or until it climbed onto the platform. The duration of this swimming interval was recorded as escape latency. Animals stayed on the platform for 15 s before being taken out. When an animal failed to reach and climb onto the platform within 60 s, it was gently guided by hand to the platform and allowed to stay there for 15 s. One day after the 7-day training period, animals received a single probe trial where each subject entered the pool from a fixed point and was allowed to swim for 2 min in the absence of the platform. The total time spent in the quadrant where the platform was placed in the acquisition phase of the experiment was recorded.

2.3.3. Open field (OF) test

Two weeks after the MWM task, animals were administered the open field test to measure activity in an unfamiliar environment [46]. The open field (OF) apparatus was a square box (80 cm × 80 cm × 40 cm) with the floor divided into 64 squares. Each subject was allowed to explore the field for 5 min and the number of squares entered with both fore- and hind-legs served as a measure of locomotor activity.

2.3.4. Histology

At the end of behavioral testing, animals were sacrificed with an overdose of ketamine and perfused intracardially with 0.9% saline followed by 4% paraformaldehyde in phosphate buffer. Brains were removed and fixed with the paraformaldehyde solution for several days. Vibratome sections of 50 μm thickness were stained with cresyl violet.

2.3.5. Statistics

One-way analysis of variance (ANOVA) was used to assess behavior in the forced swim and open field tests. For the Morris water maze test, a two factor (group × days) ANOVA with repeated measures was employed to evaluate performance over the 7 days of training while a one-way ANOVA was used to assess the time spent in the quadrant where the platform was placed in the training session.

3. Results

3.1. Histology

Histological examination indicated that eight of the lesioned animals had symmetrical, bilateral damage restricted to the BNST; these animals constitute the BNST-lesion group (Fig. 1). The lesions were discrete with little invasion of adjacent tissue. In a few cases where there was such invasion, there was partial damage to the dorsal aspect of the septohypothalamic nucleus and to the stria terminalis. Tissue damage ventral to the BNST was rare and involved the dorsolateral aspect of the parastriatal nucleus. In some cases, there was restricted damage to the lateral aspects of the anterior commissure. Six other animals had sustained damage to nearby structures with only partial damage to the BNST; these are considered as the 'missed lesion' group. Statistical comparison of the six missed lesion and the eight sham animals revealed no significant difference in any of the behavioral measures to be described below. Hence, the missed lesion and the sham controls were combined in subsequent statistical analyses.

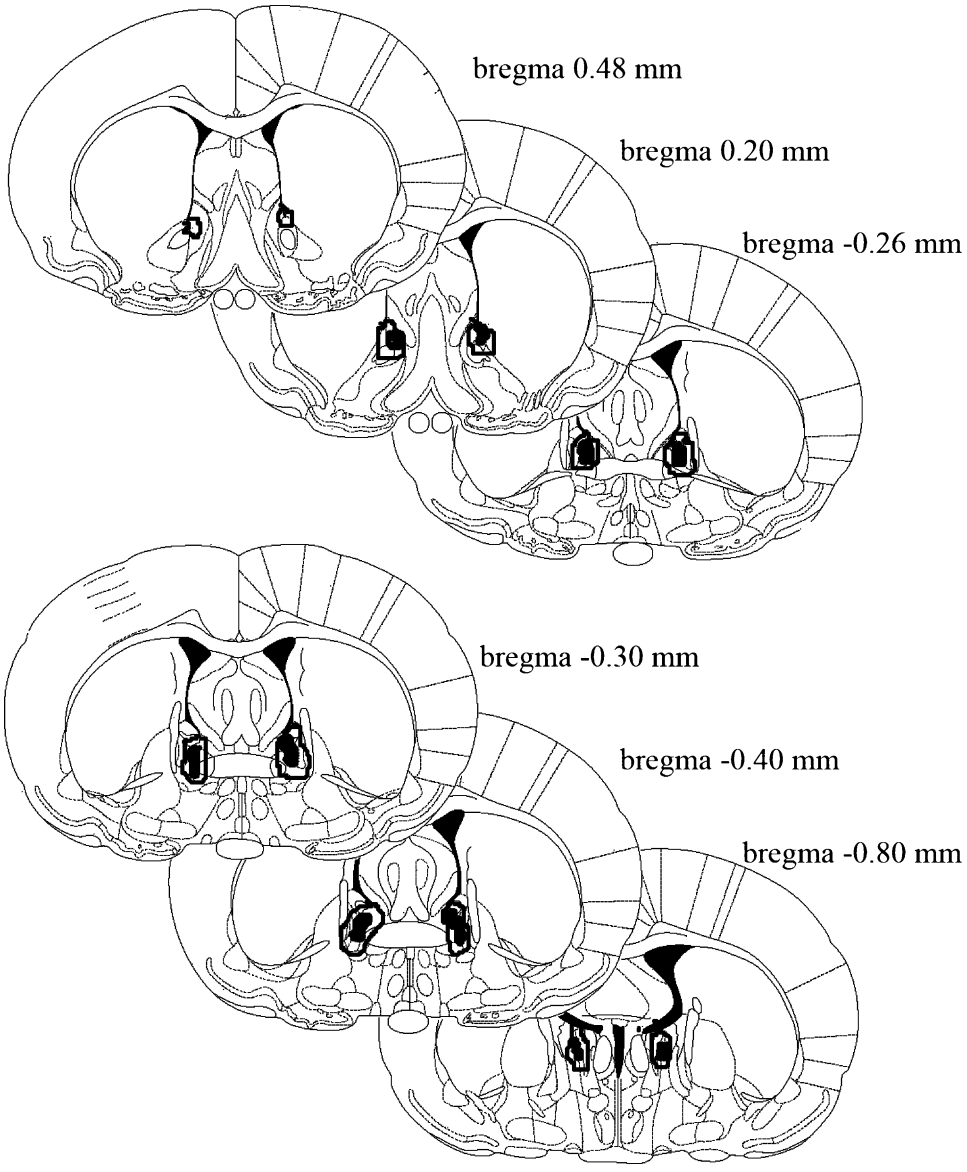

Fig. 1. Sections of the rat brain showing the smallest (in black) and the largest (depicted in outline) lesions of the bed nucleus of the stria terminalis (BNST). Brain maps are adapted from Paxinos and C. Watson [44].

3.2. Forced swim test

Fig. 2 shows the duration of immobility in the second of the swim tests for the lesioned animals and the control consisting of the sham animals and those with inappropriate lesions. ANOVA indicated that the BNST-lesioned group displayed significantly longer immobility than the controls [$F(1,20) = 6.97$, $p < 0.05$].

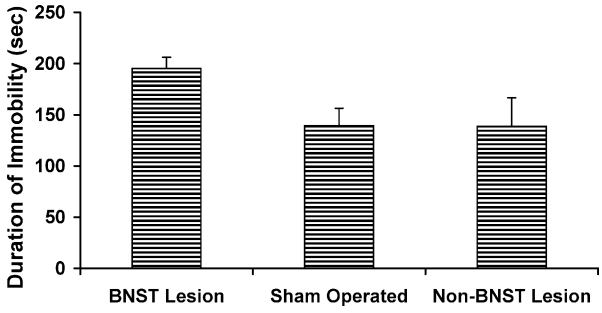

Fig. 2. Duration of immobility (mean ± S.E.M.) in the second of two swim tests separated by 24 h. The sham and non-BNST lesioned groups were combined as the control for statistical analysis.

3.3. Morris water maze

Fig. 3 summarizes the performance of the two groups on the 7 days of water maze test and the subsequent test without the hidden platform. ANOVA revealed main effect for days of testing [$F(6,120) = 36.5$, $p < 0.0001$] but not for groups [$F(1,20) = 0.18$, $p > 0.05$]. There was no significant group × days interaction. ANOVAs for time spent in the quadrant where the platform

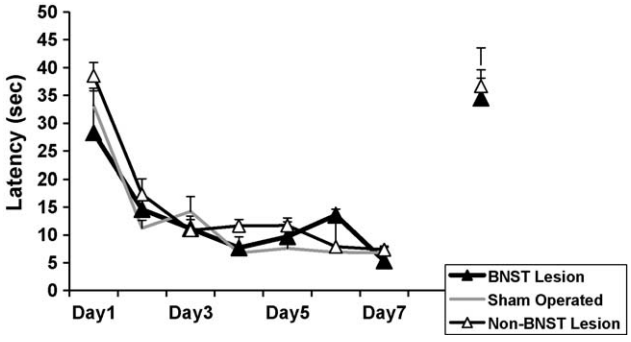

Fig. 3. Latency (mean ± S.E.M.) to reach the hidden platform in the Morris water maze over the 7 days of training. The platform was removed in the probe trial and the value shown denotes the time (mean ± S.E.M.) spent in the quadrant where the platform was placed in the previous acquisition days. The sham and non-BNST lesioned groups were combined as the control for statistical analysis.

was previously indicated no effect of treatment [$F(1,20) = 1.34$, $p > 0.05$].

3.4. Open field

The means and S.E.M.s of the number of squares crossed in the 5-min tests were 55.5 ± 9.6 and 58.0 ± 13.0, respectively, for the lesioned and the control groups. There was no significant difference between the groups [$F(1,20) = 0.035$, $p > 0.05$].

4. Discussion

The present study found that bilateral destruction of the BNST results in longer duration of immobility in forced swimming compared to controls, but does not affect navigational learning as tested in the Morris water maze.

The longer immobility in forced swimming after BNST lesions observed in the present study confirms our previous finding that BNST lesions aggravate behavioral despair [50] implicating the BNST in depression in rats. There was no difference between the groups in activity as measured in the open field test suggesting that the present results are not likely to be due to motor impairment or anxiety engendered by an unfamiliar environment [46] consequent to BNST lesions. Furthermore, the fact that the non-BNST lesioned rats did not differ from sham controls indicates that the present results are specific to bilateral damage to the BNST. Increased immobility during forced swimming due to BNST lesions is likely to reflect emotional and behavioral deficits as seen in depression, since a variety of antidepressant treatments are known to alleviate immobile behavior [11,32,45,47]. In contrast to studies which reported no effect of BNST lesions on controllable stress [23,58], BNST-lesioned rats in the present study demonstrated increased sensitivity to uncontrollable stress in the form of forced swimming in agreement with studies that attribute a role to BNST in uncontrolled/unconditioned stress and fear [8,17,31,55,59,60].

Our finding that navigational learning in the Morris water maze is not affected by BNST lesions provides new insight into the role of the BNST in learning situations involving stress. In the 7 days of training, both lesioned and control animals displayed similar patterns of acquisition. This indicates that bilateral destruction of the BNST had no differential effect on memory or learning processes that can be detected at any time during the 7 days of trials. In the probe trial conducted without the hidden platform, time spent in the quadrant where the platform was placed in the acquisition phase of the experiment was similar for the lesion and control groups. This suggests that destruction of the BNST did not impair memory for the learned place. In the only other study we know of in the literature that has investigated the role of the BNST in navigational learning in the water maze, Chen et al. [10] reported that pre- and post-training intra-BNST injection of prazosin, an α_1 adrenergic antagonist, impaired acquisition and retention in the Morris water maze task and counteracted the facilitatory effect of norepinephrine on learning of the task. It is noteworthy that Chen et al. [10] comment that suppression of BNST function with lidocaine failed to affect the expression of previously acquired navigational learning in the water maze.

The present findings indicate that increased behavioral despair as a result of BNST lesions is not accompanied by impaired performance in spatial learning in the Morris water maze. Our findings do not support the small number of studies that report impaired spatial learning in the water maze due to induced depression in rats: for instance, bulbectomy in rats, an animal model of depression [21,54] results in deficiency in spatial learning as tested in the eight-arm radial maze or the Morris water maze [20,21]. Depressive behavior as indicated by reduced mobility in an open field swimming test has been reported to impair learning and memory in rats in a spatial water maze task as well as in a multi-trial passive avoidance task [56]. Recently, it was reported [39] that rats that consistently displayed long immobility in forced swim tests were more impaired in a spatial task but not in an object recognition test compared to those with shorter duration of immobility. These last two studies and ours have in common the fact they all used forced swimming to induce depression. The present study, however, is not alone in reporting dissociation between depression and lack of impairment in spatial learning. The Flinders sensitive line (FSL) is a genetic model of depression and has contrasting behavior compared to the Flinders resistant line (FRL). FSL animals did not show any memory impairment in tasks involving the eight-arm radial maze and matching-to-position/visual discrimination (in a visual discrimination task) [7,42,43].

The dissociation between induced behavioral despair and cognitive impairment as in the present study may arise because of the fact that stress regulatory mechanisms in general [24] and the BNST, in particular, are activated differentially by the nature of the stressful situation [9,22,23,29,55,58–60]. While globally similar in that both involve swimming in a restricted environment, the two behavioral treatments in the present experiment nevertheless present different challenges to the animals. In fact, Walker and Davis [59] have proposed that while the central nucleus of the amygdala is involved in short-duration responses to stress, the BNST mediates long-duration responses to long-duration conditioned and unconditioned aversive situations. The forced swim tests used in our study present a prolonged inescapable situation (15 min in the first and 5 min

in the second swim test) whereas in the water maze, the stressful situation lasts 60 s or less for the acquisition phase and 2 min in the probe trial.

In conclusion, our findings strongly suggest a role for the BNST in behavioral despair in rats while indicating that spatial learning is not impaired after bilateral lesions of the BNST. The present results suggest that the BNST may belong to a pathway that modulates depression but may not be primarily involved in spatial learning.

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