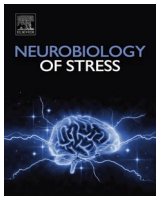
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Deep brain stimulation changes locus coeruleus responses to social stress from activation to inhibition

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ABSTRACT

Deep Brain Stimulation (DBS) of the subgenual cingulate cortex (SCC) stands as an innovative therapeutic approach for treatment-resistant depression. Previous preclinical investigations utilizing DBS targeted at the ventromedial prefrontal cortex (vmPFC), considered the rodent equivalent of the human SCC, have demonstrated antidepressant-like effects, as well as enhancement in the activity of the locus coeruleus (LC)-norepinephrine (NE) system and pontine-cortical network oscillations. Given the association between social stress and depression and other psychiatric disorders, we assessed the impact of vmPFC DBS on social stress-induced changes in LC neuronal activity in awake rats. Spontaneous and auditory-evoked LC single unit activity were compared between control and DBS male rats during the first (acute) and fifth (repeated) day of social defeat stress.

In stark contrast to LC activation observed in controls, both acute and repeated stress robustly inhibited LC neurons of DBS rats. While both groups experienced an acute stress-induced reduction in auditory-evoked LC discharge, the duration of the evoked response was only decreased in control animals. LC auditory-evoked activity was increased after repeated stress and DBS effectively counteracted these stress-induced alterations.

These findings suggest that DBS treatment shifts stress-induced regulation of LC activity such that it favors the engagement of inhibitory modulation. This may serve to promote resistance of the LC-NE system to stress-induced excitation and contribute to the mitigation of neuropsychiatric consequences of stress.

1. Introduction

Deep brain stimulation (DBS) serves as a surgical approach of administering adjustable stimulation for therapeutic purposes in neurological and psychiatric disorders. One noteworthy application involves the management of stress-related disorders, including treatment-resistant Major Depressive Disorder (MDD) (Lozano et al., 2019). The effectiveness of DBS, specifically delivered in the subgenual cingulate cortex (SCC), has been substantiated in patients with refractory MDD. These individuals exhibited a noteworthy improvement in depressive symptoms, reflecting a response rate ranging from 50 % to 60 % (Dandekar et al., 2018; Figee et al., 2022). Furthermore, the safety profile of DBS in the SCC region has been affirmed, as evidenced by the preserved cognitive function observed in MDD patients subjected to chronic treatment with SCC DBS (McNeely et al., 2008; Serra-Blasco et al., 2015).

Preclinical studies applying DBS in the ventromedial prefrontal cortex (vmPFC, the rodent counterpart to the human SCC (Ongur, 2000; Takagishi and Chiba, 1991)); showed the antidepressant-like effect of this technique. Similarly, other neuromodulatory techniques targeting the prefrontal cortex (PFC), such as transcranial direct current stimulation, have also shown antidepressant activity (Peanlikhit et al., 2017; Waye et al., 2021). Particularly, vmPFC DBS consistently demonstrated an antidepressant-like effect across various rodent models of depression (chronic unpredictable mild stress, social defeat or Flinders Sensitive Line (FSL) rat), alleviating behavioral despair and anhedonic-like behavior (Campos et al., 2023; Hamani and Nobrega, 2012). While the majority of these investigations have focused on elucidating the

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antidepressant effect of DBS at a behavioral level (Torres-Sanchez et al., 2017), the precise neurobiological mechanisms remain incompletely understood. Evidence suggests that vmPFC DBS enhances norepinephrine (NE) signaling. This is supported by the local NE release induced by DBS in awake animals and the increased climbing behavior in the forced swimming test (Jiménez-Sánchez et al., 2016), a behavior associated with higher NE bioavailability (Cryan et al., 2002; Detke et al., 1995). Additionally, in anaesthetized rats, it leads to elevated tonic and evoked activity of locus coeruleus (LC) neurons, desensitization of alpha2-adrenoceptors, increasing PFC-LC coherence in the delta frequency band and decreasing PFC-LC coherence in the theta band (Torres-Sanchez et al., 2018). These observed changes are likely pivotal in mediating the antidepressant-like effects.

The LC-NE functions as a central stress-response system and is significantly activated by stressors, leading to heightened arousal and adaptive behavioral changes (Valentino and Van Bockstaele, 2008). Acute stress exposure has been reported to increase LC neuronal activity and promote NE release in LC terminal regions (Abercrombie and Jacobs, 1987; Abercrombie et al., 1988; Britton et al., 1992; Curtis et al., 2001, 2012; Korf et al., 1973; Smagin et al., 1994; Zitnik et al., 2016). Interestingly, social stress has effects that are opposite those of DBS on PFC-LC coherence, decreasing coherence in the low frequency band and increasing coherence in theta frequencies (7–9 Hz) (Zitnik et al., 2016).

Hence, modulation of the LC-NE system by vmPFC DBS could potentially yield an effective treatment strategy for stress-related disorders. Within this framework, the objective of this study was to assess the impact of vmPFC DBS on social stress-induced alterations in LC neuronal activity in awake, freely moving rats.

2. Material and methods

2.1. Animals

Experiments were performed on adult male Sprague-Dawley rats (300–400 g, Charles River, USA) individually housed under standard laboratory conditions (22 °C, 12h light/dark cycle, lights on at 08:00 a.m., food and water *ad libitum*). Male Long-Evans retired breeder rats (650–800 g, Charles River, USA) were not experimental subjects but were used exclusively as residents in the social stress (SS) protocol. Experimental animals were group-housed (3 to a cage) and acclimatized for seven days after arrival to the laboratory animal facility before the beginning of the experiments. Animals were single-housed after electrode implantation. All experiments were performed during the light cycle. Care and use of animals were reviewed and approved by the Children's Hospital of Philadelphia Institutional Animal Care and Use Committee and every effort was made to minimize animal suffering and to use the smallest number of animals possible. Two experimental groups of rats were established: Control animals had DBS electrodes implanted and retained in the vmPFC but received no DBS and were exposed to SS; DBS animals had electrodes implanted in the vmPFC and received DBS and were exposed to SS. Fig. 1A shows the timeline of the experimental protocol.

2.2. Stimulation and recording electrodes implantation

Animals were anaesthetized with isoflurane, positioned in a stereotaxic frame and prepared firstly for bilateral implantation of the DBS electrodes into the vmPFC (anteroposterior, AP +3.2 mm from bregma, midline, ML ±0.5 mm, dorsoventral, DV -4.0 mm from the dura mater (Perez-Caballero et al., 2014) by and partially cemented to secure them and allow us to continue with the recording electrodes implantation. Then, an 8-microwire electrode array (NB Labs, USA) was implanted into the LC following the procedure previously described (Curtis et al., 2012). Briefly, LC was firstly located by recording with a glass micropipette using the approximate stereotactic coordinates: AP -3.7 mm, ML -1.1 mm relative to lambda and 5.5–6.5 mm from the brain surface (Paxinos and Watson, 2009). Then, the implantation of the microwire electrode array was performed in a track in which LC activity could be

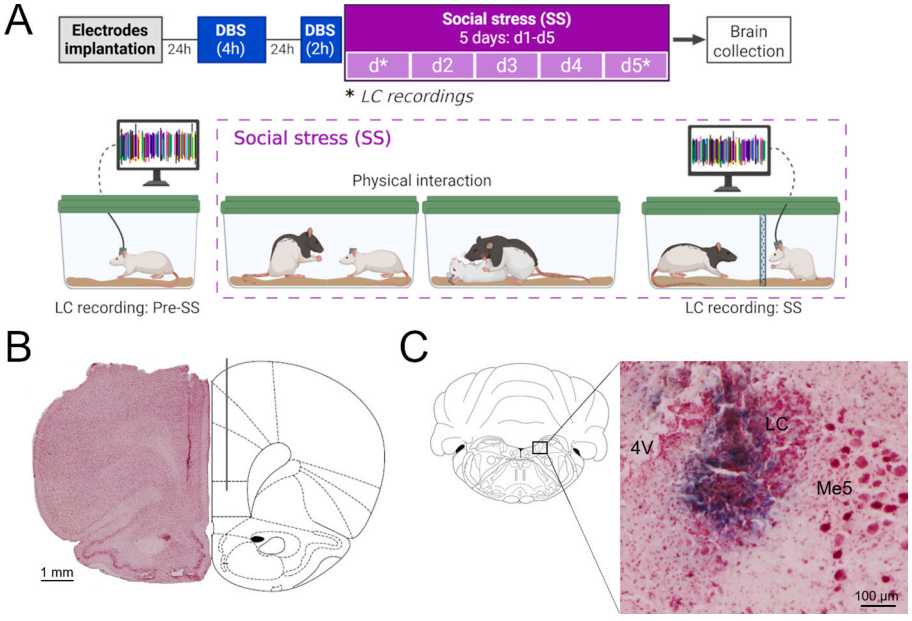


Fig. 1. Experimental design and histological verifications. (A) Schematic temporal representation of the experimental design followed in this study including the electrodes implantation surgery, the DBS protocol, the social stress (SS) exposition (5 days: d1-d5), the LC multiunit recording periods (Pre-SS and SS) on days 1 and 5 and finally the brain collection to perform histological verifications. Photomicrographs of coronal sections of the rat **(B)** prefrontal cortex and **(C)** brainstem stained with neutral red to show the placement of the stimulating electrodes in the vmPFC or the recording site in the LC (darkened region within the LC stained with Prussian blue produced by deposited metal ions reacting with potassium ferrocyanide), respectively. Abbreviations: 4V, fourth ventricle; DBS, deep brain stimulation; LC, locus coeruleus, Me5, mesencephalic trigeminal nucleus. Some elements of this figure were created with BioRender.com.

detected for at least 400 μm. Additionally, some holes were drilled to insert skull screws for fixing the DBS electrodes and the microwire electrode array to the skull with dental cement. To warrant proper animal recovery, isotonic sterile saline was administered subcutaneously (s.c.) to replace the lost fluids and the analgesic flunixin (1.1 mg/kg, s.c.) was administered two days post-surgery. This post-operative care preserved the normal animal aspect and typical behavior, minimizing weight loss and contributing to a successful recovery.

2.3. DBS procedure

The DBS electrodes consist of two bipolar stainless-steel enamel-coated wires (California Fine Wire, USA) with an 8–10 mm length and 1 mm exposed surface (without isolation) in the tips. The stimulation protocol involved monophasic square wave pulses delivered by a Master-8 pulse stimulator (AMPI, Israel), following parameters previously established: 100 μA, 130Hz and pulse width of 90μs (Hamani et al., 2010; Perez-Caballero et al., 2014; Torres-Sanchez et al., 2018). The stimulation protocol occurred over 2 days, with animals receiving two periods of stimulation: 4h block of stimulation occurred 24h after surgery and an additional 2h block of stimulation occurred 48h after surgery (Fig. 1A; Torres-Sanchez et al., 2018). This DBS protocol and stimulation parameters were previously shown to achieve an antidepressant-like effect in multiple behavioral assays (Hamani et al., 2010; Perez-Caballero et al., 2014). The two electrodes were implanted in control animals, connected to stimulation wires but they received no current pulses.

2.4. Social stress (SS)

Forty-eight hours after implantation surgery and after the end of DBS protocol, animals were exposed to the resident-intruder social stress using a protocol identical to our previously studies (Wood et al., 2010; Zitnik et al., 2016). Intruders (control or DBS rats) were introduced into the home cage of an unfamiliar Long-Evans resident. When the intruder assumed a defeat posture for 3s, a mesh wire barrier was placed to physically separate the two rats, for the remainder of a 30min session (Fig. 1A). If the intruder did not assume the defeat posture in the first 15min from the beginning of the test, then the barrier was inserted at this time until the end of the 30min session. At the end of each session rats were returned to their home cages. This procedure was repeated every day for 5 consecutive days and intruder rats were exposed to a different resident on each day.

2.5. Electrophysiological recordings

LC neurons were recorded on day 1 and day 5. Two session recordings were carried out each day: just before social stress (pre-SS) exposition (when animals were in their home cage) and during stress (SS) immediately after the physical interaction, while the intruder was in resident's cage but was physically separated from the resident by the wire barrier, which maintained visual, olfactory, and auditory communication between both (Fig. 1A). During these sessions, cables connected the headstage to the data acquisition system and multiunit activity on 8-microwires (channels) was recorded and monitored in real-time by the AlphaLab system (Alpha Omega, Israel), whereas unit discrimination was done offline (Curtis et al., 2012). The recording procedure was the same for all animals and each session consisted of recording spontaneous activity of LC for 300s followed by a 200s period of auditory stimulation (3 kHz tone, 50ms duration, 80 dB intensity, at 0.25Hz frequency, total 50 stimuli) that allowed for the study LC sensory-evoked responses. After the auditory stimulation trial, an additional 300s period of spontaneous activity was recorded (Zitnik et al., 2016). Then, the cables were disconnected and the animal was placed in the resident's cage or returned to its home cage (at the end of the experiment).

2.6. Electrophysiological data analysis

LC single-unit waveforms were discriminated and sorted using the WaveMark template-matching algorithm in the Spike2 software (Cambridge Electronic Design, UK) as previously described (Curtis et al., 2012). Briefly, this algorithm identified a set of waveforms that were verified as templates from a single LC unit by the principal component analysis (PCA) and autocorrelograms. In this way, waveform templates were considered single LC units if clusters generated by the PCA with an ellipsoid representing 1.5 standard deviation did not overlap, and if their autocorrelograms indicated that no spikes occurred during an absolute refractory period of 2ms. These terms were considered for multiunit recordings as verification that those events were from separate LC single units.

Spontaneous activity of LC neurons was measured as the mean firing rate (Hz) and the auditory-evoked activity was recorded as peristimulus time histograms (PSTHs) of activity recorded during repeated auditory stimulation. PSTHs were generated for each single unit using 8ms bins beginning 0.5s before to 1.5s after the auditory stimulation (Curtis et al., 2012). Thus, the sensory-evoked response was defined as that period after the stimulus when LC discharge rate exceeds 2 standard deviations above the mean tonic rate (calculated in the first 0.5s) and until three consecutive bins below the onset. Sensory-evoked activity was quantified as the total number of spikes and as the duration of the evoked response (ms).

2.7. Histological verification

At the end of the experiment, all animals were deeply anaesthetized with isoflurane and current (20 μA, 30s) was passed through the wires on which single unit activity was observed. Rats were perfused with a 6 % solution of potassium ferrocyanide in phosphate-buffered saline to induce a Prussian blue reaction product at the electrode site. Additionally, the histological verification of the DBS electrode placement was performed. Brains were frozen and 40 μm sections were cut on a cryostat, stained with neutral red and examined microscopically (Fig. 1B–C).

2.8. Statistical analysis

All the data are represented as the mean ± S.E.M. The results were analyzed using STATISTICA 10.0 (StatSoft, USA) or GraphPad Prism version 9.4.0 (GraphPad Software, USA). To evaluate the effects of DBS under stress conditions within the same neurons, separate two-way repeated measures (RM) ANOVAs were conducted for stress day 1 and day 5. In these analyses, "DBS" (control vs. DBS) was included as a between-subjects factor, and "Stress" (pre-SS vs. SS) as a within-subjects factor. Where appropriate, Bonferroni-corrected post hoc tests were used for multiple comparisons. To assess the impact of DBS on the percentage of change in LC activation across stress sessions (day 1 vs. day 5) in distinct neuronal populations, a two-way ANOVA was performed with both "DBS" (control vs. DBS) and "Stress-day" (day 1 vs. day 5) treated as between-subjects factors. Bonferroni post hoc tests were again applied where necessary to explore significant interactions or main effects. Statistical significance was set at $p < 0.05$. A detailed summary of the statistical results is provided in Supplementary Table 1.

3. Results

The single-unit discrimination process successfully identified a combined total of 43 LC units of 4 control rats and the same number of neurons of 4 DBS rats on day 1 of SS. On day 5, the same process revealed 27 LC units of 3 control rats and 22 LC units of 3 DBS rats. For each unit, both spontaneous activity and sensory-evoked responses to repeated auditory stimulation were recorded. Latencies to defeat were recorded in each subject. On day 1 the mean latency to assume the defeat posture was 103.3 ± 52.09s for controls and 506.7 ± 236.7s for DBS rats

respectively ($p > 0.05$, two-way ANOVA; Supplementary Fig. 1). On day 5 the mean latency to defeat was 473.8 ± 246.4s for controls and 392.0 ± 254.3s for DBS rats ($p > 0.05$, two-way ANOVA; Supplementary Fig. 1).

3.1. Spontaneous activity of LC neurons

LC spontaneous activity was recorded in both control and DBS animals before (pre-SS) and during stress (SS) after resident intruder interaction both on day 1 and 5 (Fig. 2 and Table 1). Fig. 2 shows representative discriminated single units and the mean of LC discharge rate expressed over time for each recording session on days 1 (Fig. 2A–B) and 5 (Fig. 2C–D) for control and DBS groups.

Neurons were recorded both before and during stress exposure on day 1, a two-way RM ANOVA with Stress as the within-subject factor revealed a significant main effect of DBS ($p < 0.01$) and a significant DBS × Stress interaction ($p < 0.001$; Supplementary Table 1). Bonferroni's post hoc analysis showed that baseline (pre-SS) spontaneous firing rates of LC neurons were comparable between control and DBS groups (control: 1.92 ± 0.19 Hz vs. DBS: 1.83 ± 0.21 Hz), indicating that DBS did not affect LC activity in the absence of stress (Fig. 2A–B; E; Table 1).

Importantly, stress exposure produced opposing effects on LC neuronal firing between experimental groups. In control animals, stress significantly increased the LC discharge rate ($p < 0.001$), whereas in DBS-treated rats, it led to a marked reduction in firing rate ($p < 0.001$ vs. both pre-SS values and the stressed control group; Fig. 2A–B, E, Table 1). On day 5, recordings from another population of LC neurons showed a significant main effect of Stress and a significant DBS × Stress interaction (both $p < 0.001$; Supplementary Table 1). At baseline, LC firing rates were significantly higher in DBS-treated rats compared to controls ($p < 0.05$; Fig. 2C–E; Table 1). During stress exposure, the DBS group showed a robust reduction in firing rate ($p < 0.001$), whereas no significant change was observed in the control group.

Further analysis using a two-way ANOVA on the percentage change in LC activation indicated a robust main effect of the DBS factor ($p < 0.001$, Supplementary Table 1). Specifically, stress exposure led to an increase in LC activation in the control group by 40.06 ± 9.03 % on day 1 and 24.56 ± 10.24 % on day 5. In contrast, DBS treatment significantly reduced LC activation by 61.27 ± 3.49 % and 61.96 ± 5.04 % on days 1 and 5, respectively, compared to controls ($p < 0.001$; Fig. 2F; Table 1).

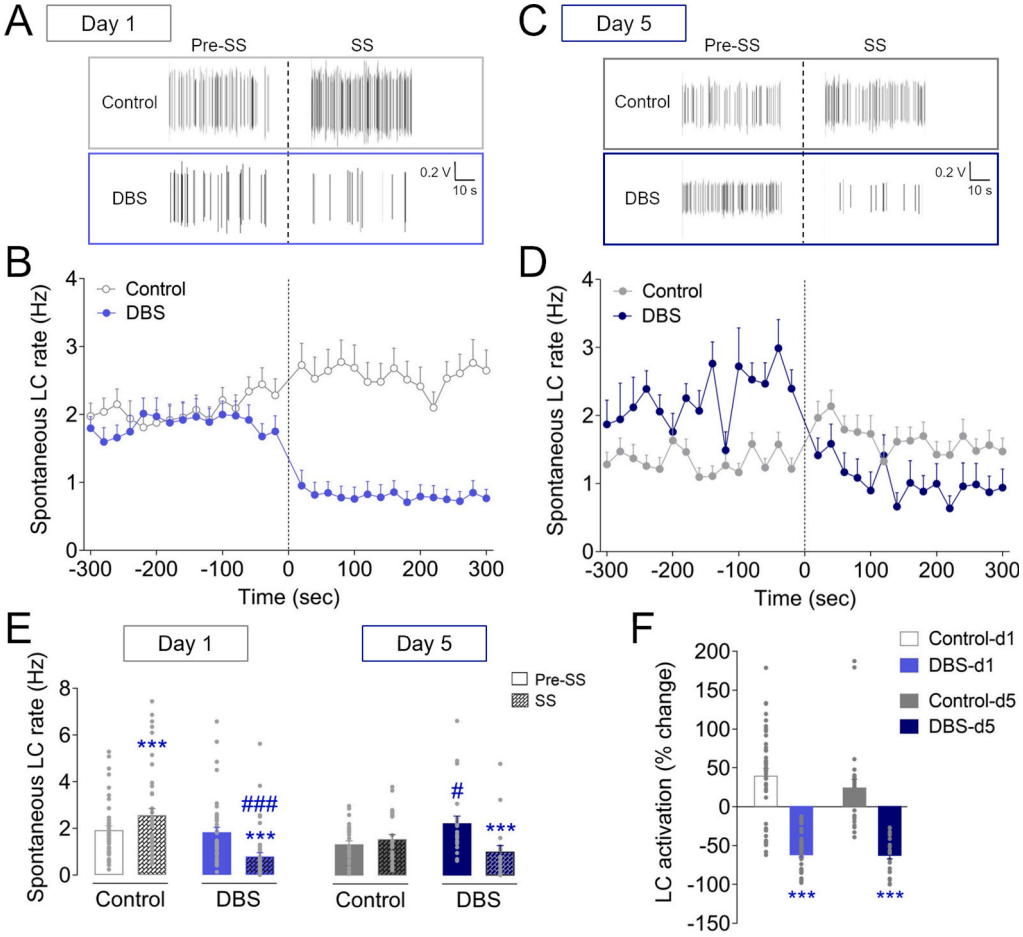


Fig. 2. Effect of DBS and social stress on spontaneous activity of LC neurons. Spontaneous spikes discharged in 50 s periods of a representative LC neuron from either a control or a DBS freely moving animal recorded before (Pre-SS) and during social stress (SS) on **(A)** day 1 and **(C)** day 5 of social stress. Spontaneous LC firing rates (Hz) of control or DBS rats are expressed over time on **(B)** day 1 (control: white circles, n=43 cells; DBS: light blue circles, n=43 cells) and **(D)** day 5 (control: grey circles, n=27 cells; DBS: dark blue circles, n=22 cells). Each point represents the mean firing rate averaged over 20-second intervals. Time zero represents the start of recording after physical interaction during SS (SS period). **(E)** Bars represent the mean spontaneous firing rates (Hz) of LC neurons recorded over the 300 s before (Pre-SS) and 300 s during social stress (SS) on day 1 and day 5 ± SEM. ***p<0.001 vs. Pre-SS; #p<0.05, ###p<0.001 vs. control animals; two-way RM ANOVA, Bonferroni's post hoc test. **(F)** LC activation induced by SS on day 1 and day 5 expressed as the percentage change from basal firing rate. The data represent the mean ± SEM. ***p<0.001 vs. control animals; two-way ANOVA, Bonferroni's post hoc test.

Table 1
Effect of DBS on spontaneous activity of LC neurons before and after acute (day1) and repeated (day5) social stress (SS).

Spontaneous activity	Pre-SS (day1)	SS (day1)	*LC activation (% change)*	Pre-SS (day5)	SS (day5)	*LC activation (% change)*
Firing rate (Hz)						
Control	1.92 ± 0.19	**2.56 ± 0.29*****	*40.06 ± 9.03*	1.33 ± 0. 16	1.56 ± 0.20	*24.56 ± 10.24*
DBS	1.83 ± 0.21	**0.79 ± 0.16*****$^{\#\#\#}$	***−61.27±3.49***$^{\#\#\#}$	**2.24 ± 0.31**$^{\#}$	**1.03 ± 0.26*****	***−61.96±5.04***$^{\#\#\#}$
Evoked activity	Pre-SS (day1)	SS (day1)		Pre-SS (day5)	SS (day5)	
Spikes						
Control	17.98 ± 2.35	**11.16 ± 1.85***		9.92 ± 1.70	**16.62 ± 2.65***	
DBS	24.05 ± 3.14	**11.53 ± 1.97*****		**28.17 ± 7.85**$^{\#}$	25.33 ± 6.26	
Duration (ms)						
Control	46.88 ± 5.42	**23.81 ± 2.92*****		30.15 ± 4.81	40.62 ± 4.92	
DBS	52.28 ± 5.46	**45.58 ± 5.84**$^{\#}$		49.33 ± 6.52	50.67 ± 9.20	

Data are expressed as the mean ± S.E.M. *$p < 0.05$, ***$p < 0.001$ vs Pre-SS (day1 or day5), $^{\#}p < 0.05$, $^{\#\#\#}p < 0.001$ vs control.

3.2. Auditory-evoked activity of LC neurons

The sensory-evoked activity of LC neurons was assessed through repeated auditory stimulation on days 1 and 5 of the stress protocol (Fig. 3, Table 1). Representative PSTHs of auditory-evoked LC activity before (pre-SS) and during SS sessions for control and DBS-treated rats are shown in Fig. 3A (day 1) and Fig. 3B (day 5).

On day 1, a two-way RM ANOVA with Stress as the within-subject factor revealed a significant main effect of Stress ($p < 0.001$), but no significant effects of DBS or the interaction factor (Supplementary Table 1) on the number of evoked spikes. Bonferroni post hoc comparisons indicated that stress significantly reduced the number of auditory-evoked spikes in both control and DBS groups compared to pre-SS values ($p < 0.05$ and $p < 0.001$, respectively; Fig. 3A, C; Table 1). Analysis of the duration of the auditory-evoked response on day 1 revealed significant effects of DBS ($p < 0.05$), Stress ($p < 0.001$), and their interaction ($p < 0.05$) (Supplementary Table 1). Post hoc testing showed a significant reduction in response duration in control animals following stress ($p < 0.001$), whereas the duration in DBS animals remained unchanged (Fig. 3A, D; Table 1). Notably, the response duration in the DBS group during stress was significantly longer than that of the stressed control group ($p < 0.05$; Fig. 3A, D; Table 1).

On day 5, a similar two-way RM ANOVA identified significant effects of both DBS and the interaction factor on the number of evoked spikes ($p < 0.05$; Supplementary Table 1). Post hoc analysis revealed that the number of spikes in the DBS group prior to stress exposure was significantly higher than in the control group ($p < 0.05$; Fig. 3B–C), and this value remained stable during the stress session. In contrast, stress significantly increased the number of evoked spikes in the control group ($p < 0.05$; Fig. 3B–C; Table 1). For the response duration on day 5, the analysis showed a significant main effect of DBS ($p < 0.05$; Supplementary Table 1), though post hoc comparisons did not reveal statistically significant differences between groups (Fig. 3B, D; Table 1).

4. Discussion

The present study demonstrates that while vmPFC DBS does not alter LC activity of unanesthetized rats under baseline, non-stress conditions, it markedly shifts the neural response to stress. Specifically, DBS reverses the typical stress-induced activation of LC neurons, instead promoting a pronounced inhibition of LC firing in unanesthetized, freely moving rats. Our findings align with previous reports indicating that acute social defeat stress increases LC neuronal discharge rates in adult male rats (Chaijale et al., 2013; Zitnik et al., 2016). Importantly, our results extend these observations by demonstrating that vmPFC DBS not only blocks this stress-induced activation but also induces a neurophysiological shift whereby both acute and repeated social stress lead to a pronounced suppression of LC activity. Given previous evidence for a coordinated engagement of both excitatory and inhibitory afferents to the LC by stress, the present results suggest that DBS alters network activity to favor stress-induced inhibition of the LC-NE system. The extent to which this would be adaptive is presently unknown although by promoting resistance to stress-elicited activation, it may be therapeutic.

The vmPFC DBS procedure itself did not impact subsequent spontaneous LC activity in unanesthetized Sprague-Dawley rats, in contrast to our earlier study where an increase in spontaneous LC firing rate was noted in anaesthetized Wistar rats (Torres-Sanchez et al., 2018), highlighting a potential influence of anesthesia or animal strain on LC activity.

Several studies have demonstrated that LC discharge rate as well as c-fos expression or NE release in forebrain targets are increased by acute exposure to diverse stressors including social stress (Curtis et al., 2001, 2012; Day et al., 2004; Hahn and Bannon, 1999; Melia et al., 1992; Page and Abercrombie, 1997, 1999; Reyes et al., 2015; Valentino and Van Bockstaele, 2008, 2015; Valentino and Wehby, 1988; Zitnik et al., 2016). The stress-related neuropeptide, corticotropin-releasing factor (CRF) has been implicated in stress-induced LC activation because administration of CRF antagonists can prevent these effects (Curtis et al., 2001, 2012; Valentino et al., 1991; Valentino and Wehby, 1988). Notably, CRF antagonist administration prior to stress unmasks a stress-induced inhibition that is naloxone sensitive, implying that endogenous opioids afferents to the LC are also recruited by stress (Curtis et al., 2001, 2012; Valentino and Van Bockstaele, 2001). These data support a mechanism whereby acute stressors engage both excitatory and inhibitory afferents to the LC, with a bias towards excitation initially that would increase behavioral arousal and followed by inhibition that would limit the response and promote recovery. The effects of DBS in the present study are reminiscent of those produced by CRF antagonists; DBS unmasked the stress-induced inhibitory modulation of the LC. DBS could do this by interfering with stress-induced excitatory regulation of the LC. This is likely to be CRF-mediated because DBS did not alter sensory-evoked LC activity in the pre-SS state, which is thought to be mediated by excitatory amino acid afferents. CRF from the central nucleus of the amygdala (CeA) has been implicated in LC activation by social defeat stress (Reyes et al., 2015). Given that vmPFC DBS reduces the electrical activity of the basolateral region of the amygdala, (a projection area of the mPFC neurons (McDonald, 1998; McDonald et al., 1996): in a preclinical model of post-traumatic stress disorder (PTSD) (Reznikov et al., 2018), vmPFC DBS could potentially decrease activity in the CeA and the CRF-CeA excitatory input to LC in response to stress. Alternatively, DBS may set up a condition that favors a robust

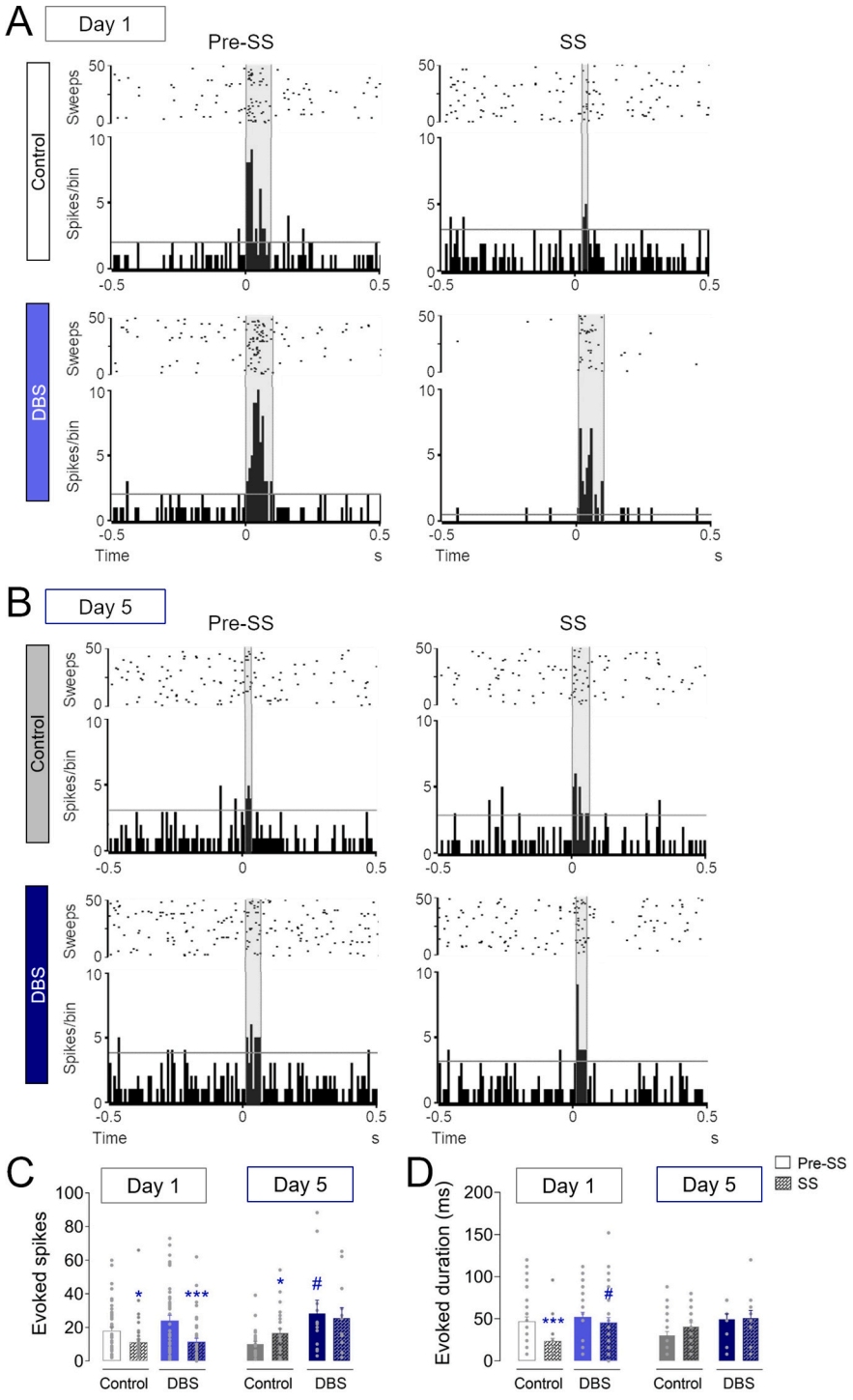


Fig. 3. Effect of DBS and social stress on evoked activity of LC neurons. Representative peristimulus time histograms (PSTHs) of a LC neuron in response to repeated auditory stimulation from either a control or a DBS animal, before (Pre-SS) and during social stress (SS) exposition on **(A)** day 1 and **(B)** day 5. The horizontal cursor placed in each PSTH represents the onset of the evoked response (2 standard deviations above the mean tonic rate that was calculated in the first 0.5 s). The evoked response is indicated by the grey area delimited by the two vertical cursors in each PSTH, showing the beginning and the end of the evoked response and therefore the duration of each response. The effect of DBS and SS on **(C)** the number of evoked spikes discharged and **(D)** the duration of the evoked response of LC neurons in response to repeated auditory stimulation on day 1 and day 5. The data represent the mean + SEM. *p<0.05, ***p<0.001 vs. Pre-SS; #p<0.05 vs. control animals; two-way RM ANOVA, Bonferroni's post hoc test.

engagement of opioid afferents or other inhibitory LC afferents by stressors. Alpha2-adrenoceptors may also play a pivotal role in this phenomenon as they are a primary negative regulator of LC electrical activity, alongside μ-opioid receptors. There is documented reciprocal influence between these receptors within the LC: the blockade of alpha2-adrenoceptors was reported to intensify opioid-mediated inhibition in the LC (Illes and Nörenberg, 1990), and the activation of alpha2-adrenoceptors resulted in a reduction in opioid inhibition in the

LC (Schoffelmeer et al., 1986). Thus, the desensitization of alpha2-adrenoceptors induced by vmPFC DBS, as previously demonstrated in our laboratory (Torres-Sanchez et al., 2018), would support the potential involvement of opioid mediation in the inhibitory effect of DBS on LC activity after stress.

Acute stressors, including social defeat stress, typically decrease LC sensory-evoked discharge while increasing spontaneous activity (Curtis et al., 2012; Valentino and Wehby, 1988; Zitnik et al., 2016). Following acute social stress, there was a reduction in the number of auditory-evoked spikes and duration of the auditory-evoked response (Curtis et al., 2012; Zitnik et al., 2016). This stress-induced effect on the LC sensory-evoked response implies that the cells are less responsive to discrete stimuli and this has been proposed to be associated with a shift from focused to scanning attention (Aston-Jones and Cohen, 2005). This transient attentional state could enhance behavioral flexibility, proving adaptive in dealing with immediate environmental challenges (Aston-Jones and Cohen, 2005; Valentino and Van Bockstaele, 2008). Notably, the duration of the evoked response was preserved in DBS animals after acute stress. The present study confirmed that social stress reshaped LC auditory-evoked responses by decreasing the number of spikes and the duration of the response. Although DBS did not affect the stress-induced decrease in the number of auditory-evoked LC spikes, it prevented the stress-induced decrease in the response duration. By changing how stress reshapes the pattern of LC sensory-evoked responses DBS may promote a more focused or selective attentional state. Additional studies beyond the scope of this investigation are necessary to determine how these neuronal effects translate to changes in attention and/or cognitive flexibility and whether they would facilitate an adaptive stress response strategy. It is intriguing to note that, much like DBS, atomoxetine, a NE reuptake inhibitor used in attention deficit/-hyperactivity disorder (ADHD), preserves the evoked response to sensory stimulation while reducing spontaneous activity in LC neurons simultaneously with attention-enhancing effects in ADHD patients (Bari and Aston-Jones, 2013; Chamberlain et al., 2007).

In the present study, stress-induced LC activation was attenuated with repeated stress in the control group. This suggests that with repeated stress there is an adaptation to the mechanisms through which a single resident-intruder exposure activates LC neurons, making subsequent exposures less effective compared to the acute stress experienced on day 1. However, this contrasts with our previous finding that LC neurons were still robustly activated by the 5 presentation of social stress (Zitnik et al., 2016). The basis for this discrepancy between the studies is not yet resolved. Importantly, vmPFC DBS induced a comparable inhibitory effect on spontaneous LC activity with the fifth repeated stress as observed with acute stress (62 % inhibition), potentially mediated by the inhibitory action of endogenous opioids. Previous studies have demonstrated that distinct coping strategies are associated with the predominant activation of specific circuitries following repeated stress, with the activation of inhibitory opioid enkephalin afferents to the LC primarily linked to a more active coping strategy (Reyes et al., 2015). Moreover, although auditory-evoked responses in the absence of stress on day 5 were similar to those observed on day 1 in both control and DBS groups, the number of evoked spikes was higher in DBS animals than in controls prior to the fifth stress session. These findings may indicate that DBS promotes a partial recovery of sensory-evoked LC responses following prolonged stress exposure. Therefore, although further behavioral studies are necessary to directly correlate DBS-induced modulation of LC activity with coping behaviors—an important limitation of the present study—our results suggest that DBS may enhance stress resilience by promoting a shift toward an active coping strategy.

5. Conclusions

The LC-NE system, implicated in stress-related disorders such as depression, plays a crucial role in the emotional and cognitive dimensions of the stress response. Our findings indicate that vmPFC DBS effectively modulates the response of the LC-NE system to stress, creating a condition whereby social stress presented either acutely or repeatedly produced a profound inhibition of LC discharge rate. One limitation of this study is the absence of behavioral assessments, which are essential to directly correlate the observed electrophysiological changes with stress-related coping strategies. Future research that includes comprehensive behavioral evaluations will test the causality of this link. Additionally, further investigations are required to elucidate the specific neurobiological mechanisms triggered by vmPFC DBS in response to stress, DBS clearly counteracted the documented stress-related LC activation which has been associated with sleep disturbances, concentration difficulties, and emotional-related disorders (Berridge and Waterhouse, 2003; Naegeli et al., 2018; Osorio-Forero et al., 2022).

Notably, the DBS also generally preserved LC sensory-evoked responses in stress conditions, suggesting potential benefits for sensory processing and performance in attention-related tasks. It is noteworthy that long-term SCC DBS improves cognitive and executive functioning in MDD patients, and this improvement appears to be a useful predictor of DBS response (McInerney et al., 2017; Moreines et al., 2014; Serra--Blasco et al., 2015). In essence, this study elucidates the impact of vmPFC DBS on LC activity under conditions of social stress, potentially orchestrating a more effective coping strategy.

CRediT authorship contribution statement

Sonia Torres-Sanchez: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis. **Andre L. Curtis:** Methodology, Investigation, Formal analysis. **Rita J. Valentino:** Writing – review & editing, Supervision, Resources, Methodology. **Esther Berrocoso:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Funding acquisition, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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Data availability

Data will be made available on request.

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