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ORIGINAL INVESTIGATION

Serotonin 5-HT_{1B} receptors mediate the antidepressant- and anxiolytic-like effects of ventromedial prefrontal cortex deep brain stimulation in a mouse model of social defeat

Esther Silk[1] · Mustansir Diwan[1] · Thallita Rabelo[1] · Hailey Katzman[1] · Ana Carolina P. Campos[1] · Flavia Venetucci Gouveia[1] · Peter Giacobbe[1,2] · Nir Lipsman[1,3] · Clement Hamani[1,3]

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Abstract

Background Deep brain stimulation (DBS) delivered to the ventromedial prefrontal cortex (vmPFC) induces antidepressant- and anxiolytic-like responses in various animal models. Electrophysiology and neurochemical studies suggest that these effects may be dependent, at least in part, on the serotonergic system. In rodents, vmPFC DBS reduces raphe cell firing and increases serotonin (5-HT) release and the expression of serotonergic receptors in different brain regions.

Methods We examined whether the behavioural responses of chronic vmPFC DBS are mediated by 5-HT_{1A} or 5-HT_{1B} receptors through a series of experiments. First, we delivered stimulation to mice undergoing chronic social defeat stress (CSDS), followed by a battery of behavioural tests. Second, we measured the expression of 5-HT_{1A} and 5-HT_{1B} receptors in different brain regions with western blot. Finally, we conducted pharmacological experiments to mitigate the behavioural effects of DBS using the 5-HT_{1A} antagonist, WAY-100635, or the 5-HT_{1B} antagonist, GR-127935.

Results We found that chronic DBS delivered to stressed animals reduced the latency to feed in the novelty suppressed feeding test (NSF) and immobility in the forced swim test (FST). Though no significant changes were observed in receptor expression, 5-HT_{1B} levels in DBS-treated animals were found to be non-significantly increased in the vmPFC, hippocampus, and nucleus accumbens and reduced in the raphe compared to non-stimulated controls. Finally, while animals given vmPFC stimulation along with WAY-100635 still presented significant responses in the NSF and FST, these were mitigated following GR-127935 administration.

Conclusions The antidepressant- and anxiolytic-like effects of DBS in rodents may be partially mediated by 5-$HT1_B$ receptors.

Keywords Deep brain stimulation · Serotonin · Anxiety · Depression · 5-HT_{1B} · 5-HT_{1A}

Introduction

Deep brain stimulation (DBS) involves the delivery of electrical current to specific brain targets via surgically implanted electrodes (Awan et al. 2009; Hamani et al. 2010c; Hamani and Temel 2012). To date, several clinical studies have examined the efficacy of DBS for treatment-resistant depression. While open-label trials have shown promising results when DBS was delivered to the subcallosal cingulate gyrus (SCG) (Mayberg et al. 2005; Riva-Posse et al. 2018), ventral capsule/ventral striatum (VC/VS) (Bergfeld et al. 2016; Malone et al. 2009), medial forebrain bundle (MFB) (Fenoy et al. 2018; Schlaepfer et al. 2013), and nucleus accumbens (NAcc) (Schlaepfer et al. 2008), results of randomized clinical trials comparing active versus sham stimulation were quite disappointing (Dougherty et al. 2015; Holtzheimer et al. 2017). Recent improvements in neuroimaging techniques (Coenen et al. 2019, 2020; Riva-Posse et al. 2014, 2018) and the analysis of patients subdivided into responders and non-responders (Bergfeld et al. 2016; Puigdemont et al. 2015) suggest that improvements in outcome

✉ Clement Hamani
clement.hamani@sunnybrook.ca

[1] Harquail Centre for Neuromodulation, Sunnybrook Health Sciences Centre, Sunnybrook Research Institute, 2075 Bayview Av, S126, Toronto, ON M4N3M5, Canada

[2] Department of Psychiatry, Sunnybrook Health Sciences Centre, Toronto, ON M4N 3M5, Canada

[3] Division of Neurosurgery, Department of Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON M4N 3M5, Canada

are possible and that specific populations of patients may be more suitable candidates for DBS. This urges the investigation of predictors of response and mechanisms for the antidepressant effects of DBS (Brown et al. 2020; Davidson et al. 2020; Frank et al. 2021; Sankar et al. 2020).

Preclinical research has been important for studying potential mechanisms and the development of novel treatments for debilitating psychiatric disorders, including DBS for major depression (Dandekar et al. 2019; Edemann-Callesen et al. 2015; Furlanetti et al. 2015; Hamani and Nobrega 2012; Hamani et al. 2010c; Hamani and Temel 2012; Jimenez-Sanchez et al. 2016a, b; Krishnan and Nestler 2011; Lim et al. 2015a, b; Papp et al. 2019; Rummel et al. 2016; Thiele et al. 2018; Torres-Sanchez et al. 2017, 2018). Despite the complex nature of this disorder, valuable animal models have emerged over the years, including the exposure of animals to chronic social defeat stress (CSDS) (Bartolomucci et al. 2001; Berton et al. 1999, 2006; Hammels et al. 2015; Kudryavtseva et al. 1991; Raab et al. 1986). In a commonly used paradigm, a male "intruder" rodent is placed in the home cage of an unfamiliar male "resident" (Golden et al. 2011). The intruder is often dominated by the resident and, after several exposures, develops anxiety- and depressive-like responses (Berton et al. 2006; Golden et al. 2011; Iniguez et al. 2014; Krishnan et al. 2007; Warren et al. 2014). In addition to a valid behavioural phenotype, susceptible intruders demonstrate physiological changes associated with a depressive-like state, including changes in the hypothalamic–pituitary–adrenal axis (Dallman et al. 2000; Gomez-Lazaro et al. 2011; Kronfeld-Schor and Einat 2012), increases in pro-inflammatory cytokines (Gomez-Lazaro et al. 2011), reduced synaptic plasticity, and neurogenesis (Christoffel et al. 2011; Gomez-Lazaro et al. 2011; Krishnan et al. 2007; Lagace et al. 2010; Warren et al. 2013, 2014).

Chronic stimulation delivered to the ventromedial prefrontal cortex (vmPFC), a region considered to be the rodent homologue of the human SCG (Hamani et al. 2011; Hamani and Nobrega 2012; Hamani and Temel 2012), reverses depressive- and anxiety-like behaviours in various animal models and rat lines (Bambico et al. 2015; Bregman et al. 2018; Bruchim-Samuel et al. 2016; Edemann-Callesen et al. 2015; Furlanetti et al. 2015; Gersner et al. 2010; Hamani et al. 2010a, b, 2012a, b,2014; Jimenez-Sanchez et al. 2016a, b; Lim et al. 2015b; Moshe et al. 2016; Papp et al. 2018; Thiele et al. 2018; Veerakumar et al. 2014). In rodent models, vmPFC DBS has been shown to modulate several neurotransmitters closely related to depression, including the serotonergic system (Bregman et al. 2018; Hamani et al. 2010b; Volle et al. 2018). Serotonin (5-HT)-depleting raphe lesions block the effects of vmPFC stimulation (Hamani et al. 2010b). Likewise, DBS in this target reduces the firing of raphe cells (Lim et al. 2015b; Srejic et al. 2015) and increases serotonin release in the hippocampus (Hamani et al. 2010b; Volle et al. 2018). Despite the fact that vmPFC DBS increases 5-HT$_{1B}$, but not 5-HT$_{1A}$ receptor expression (Volle et al. 2018), the functional role of specific serotonin receptors in the behavioural effects of DBS remains poorly understood.

We delivered chronic vmPFC stimulation to intruders in a modified CSDS paradigm to test whether the anxiolytic and antidepressant-type effects of DBS were mediated by 5-HT$_{1B}$ receptors.

Materials and methods

All procedures were approved by the Sunnybrook Research Institute Animal Care Committee.

Modified chronic social defeat stress model

C57BL/6 male resident mice (Charles River, Quebec) were pair-housed with tube-ligated females. Three weeks later, residents were screened for aggressive behaviour with training Balb/c males (Charles River, Quebec). During screening, the female was removed, and the training mouse was transferred into the resident's home cage in a perforated metal barrier for 2 min. The training mouse was then removed from the barrier and placed in the resident's home cage for a 5-min unprotected encounter. For each resident, two screening sessions were performed daily with different training mice used in consecutive sessions. Daily screening was repeated until residents demonstrated a latency to aggression of 30 s or less and a consistent number of aggressive bouts in consecutive sessions. Once these aggression endpoints were met, screening was terminated.

The modified social defeat stress included 6 days of interactions between C57BL/6 male aggressive residents and Balb/c male intruders. After the female was removed, the intruder mouse was transferred into the resident's home cage in a perforated metal barrier for 2 min. The intruder was then removed from the barrier and placed in the resident's home cage for a 5-min contact encounter. Following the interaction, the intruder mouse was returned to its home cage. Each intruder was submitted to one defeat session per day over 3 consecutive days, followed by a 4-day break and another 3 consecutive days of defeat sessions (a total of 6 social defeat sessions per intruder). To avoid individual differences in defeat intensity, intruders were confronted with alternating residents on subsequent days. Non-stressed controls did not undergo social defeat, remaining in their home cage during an equivalent interval.

Behavioural testing

The sequence of tests was chosen so that animals were subjected to the more stressful paradigms as the testing progressed.

Open field test (OFT)

Mice were placed in a 20 cm × 20 cm square plexiglass container and recorded for 5 min. The duration of locomotion and the distance travelled were quantified with a tracking software (Any-Maze; Wood Dale, IL).

Defensive burying test (DBT)

One hour after the OFT, mice were placed in a standard cage containing 5 cm of clean flattened bedding and 8 identical marbles evenly arranged in two columns. The number of marbles buried in a 30-min session was quantified. A marble was considered buried when 50% or less of its surface was visible.

Novel location recognition tests (NLRT) and novel object recognition (NORT)

One day after a 5-min habituation session, mice were allowed to explore a 20 cm × 20 cm square plexiglass arena containing two identical objects for 5 min (familiarization). During the location testing, one of the identical objects was repositioned into a novel quadrant. During object recognition testing, the object in the original location was replaced with a different object. NORT and NLRT sessions lasted 5 min each. Videotaped sessions were analysed with a tracking software (Any-Maze; Wood Dale, IL). The location recognition index was calculated according to the formula: time of novel location exploration divided by the total exploration time × 100. The object recognition index was calculated as follows: duration of novel object exploration divided by total exploration time × 100 (Lueptow 2017).

Novelty suppressed feeding test (NSF)

Two days prior to the test, animals were trained to consume food treats (fruit loops) in their home cage. After a 16-h food deprivation, mice were placed in a plexiglass arena (50 cm × 10 × 60) containing a white platform with the habituated treat. The latency to eat the treat was recorded. Animals that did not eat were excluded from the analysis ($n = 1$ DBS stress animal in the first experiment; $n = 2$ stress vehicle, $n = 1$ DBS stress vehicle; $n = 2$ DBS stress GR-127935 animals in pharmacological experiments).

Forced swim test (FST)

Mice were placed in an inescapable cylindrical tank (30 cm height × 20 cm diameter) filled 15 cm from the top with 26 °C water for 5 min. The last 3 min of the session were scored, and the total immobility time was quantified. We chose to measure immobility during the last 3 min of testing because this is the timeline in which differences between stimulated and non-stimulated animals are more prominent (Hamani and Nobrega 2012).

DBS surgery and stimulation

A timeline with the behavioural DBS experiments is provided in Fig. 1. Male Balb/c mice (Charles River, Quebec, Canada; 20–25 g) were anesthetized with isoflurane and received bilateral vmPFC stainless-steel implants to be used as cathodes (0.5 mm lead exposure, AP: + 1.9 mm: ML: ± 0.3 mm; DV: − 2.9 mm; Plastics One model 333/3) (Paxinos and Franklin 2012). Screws implanted into the skull over the parietal cortex served as anodes. Sham DBS animals had electrodes implanted but received no stimulation. Control surgeries omitted electrode implants. Exposure to resident mice commenced 5–7 days after the procedure.

vmPFC DBS was delivered with a handheld stimulator (ANS model 3510, Plano, TX), connected to the animals through extension cables (Plastics One, model 335–340/3). Stimulation was delivered at 130 Hz, 90 µs, 100 µA (Bregman et al. 2018; Hamani et al. 2012b; Hamani and Nobrega 2012) for 3 h/day prior to behavioural testing/encounters and 5 h/day on non-testing days. No stimulation was delivered during the first 3 days of social encounters. Following the experiments, animals were sacrificed, and the brains of eight animals per group were randomly selected for neurochemical analyses.

Drug administration

WAY-100635 maleate (2.5 mg/kg s.c.; Tocris) and GR-127935 hydrochloride (5 mg/kg i.p.; Tocris) were diluted in saline and administered to the animals 30 min before DBS on behavioural testing days. Selected doses were based on safety profile or previous work suggesting that these drugs antagonized the effects of antidepressant medications (Castro et al. 2008; Cryan et al. 2005b; de Almeida et al. 2001; Hogg and Dalvi 2004; Kaster et al. 2005; Lopez-Mendoza et al. 1998; Mayorga et al. 2001; O'Neill and Conway 2001; Rogoz et al. 2012; Takahashi et al. 2020; Tatarczynska et al. 2002; Zanelati et al. 2010). In pharmacologic

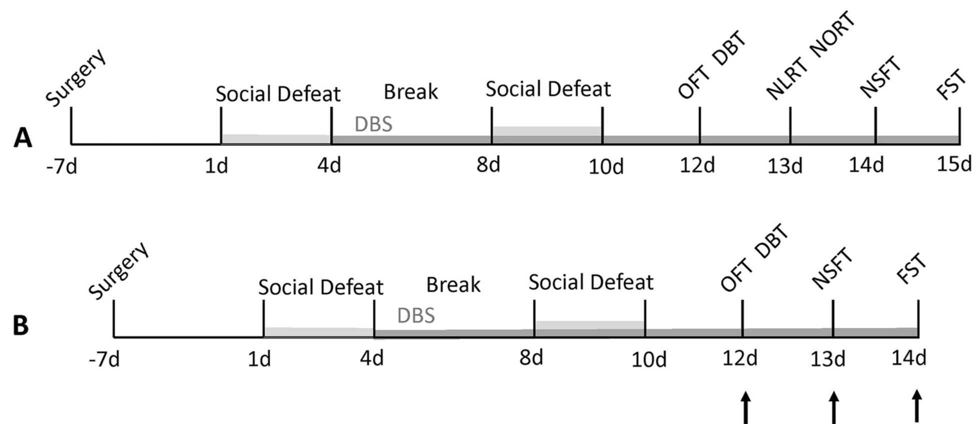

Fig. 1 Timeline of behavioural experiments. **A** After 3 days of social defeat, animals went on a break for 4 days, followed by another 3 days of social defeat and then behavioural testing. DBS was started 1 day after the first round of social defeat sessions and continued to the end of the experiment. **B** Social defeat and behavioural testing conducted during pharmacological experiments. DBS was started 1 day after the first round of social defeat sessions and continued to the end of the experiment. Arrows represent the timepoints of drug administration. D, day; DBS, deep brain stimulation; DBT, defensive burying test; FST, forced swim test; NLRT, novel location recognition test; NORT, novel object recognition test; NSF, novelty suppressed feeding test; OFT, open field test

experiments, stress animals underwent surgical procedures but were not implanted with electrodes.

Western blot and histology

After removal from the skull, brains were stored at − 80 C°. In animals that did not undergo neurochemical analyses, vmPFC electrode placement was confirmed in cresyl violet stained sections (Fig. 2) (Gidyk et al. 2021; Hamani et al. 2010a, b, 2014). In brains processed for western blot, electrode tracks were visually inspected in thick coronal sections prior to tissue processing. After this step, the following regions were dissected using a biopsy punch tool for analysis: ventromedial prefrontal cortex, nucleus accumbens (NAcc), dorsal hippocampus (HPC), and raphe (all raphe nuclei). Tissue from both hemispheres was collected for analysis. Protein extracts were separated by sodium dodecyl sulphate–polyacrylamide gel electrophoresis followed by transfer onto polyvinylidene fluoride membranes. These were then exposed to blocking buffer at 4 °C overnight. Primary antibodies were added at the following dilutions: anti-5-HT_{1B} rabbit pAb [Abcam: ab13896] 1:1000 and anti-5-HT_{1A} rabbit pAb [abcam # ab227165] 1:1000. For loading control, the membranes were incubated with

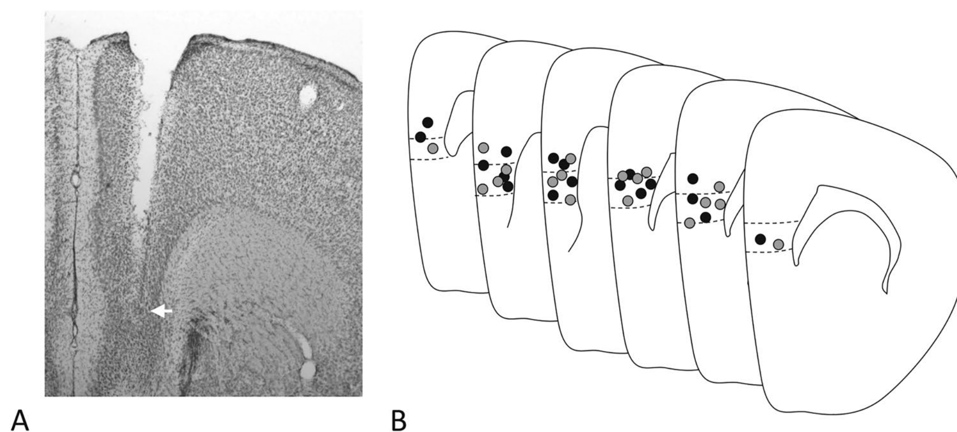

Fig. 2 Electrode location. **A** Photomicrograph of a coronal brain section illustrating the trajectory of an electrode placed in the vmPFC (arrow). **B** Schematic representation of coronal brain sections showing the location of the tip of the electrodes implanted in animals receiving deep brain stimulation (black circles; $n=9$) or sham stimulation (light grey circles; $n=9$). Electrodes implanted bilaterally are depicted in a single hemisphere. In this representation, only electrodes associated with the initial set of behavioural experiments were plotted. Electrodes in the remainder experiments were placed in a similar location

anti-tubulin-β3 mouse mAb [BioLegend #801202] 1:2000. After washing, they were incubated with secondary antibodies: 1:2000 HRP-linked, anti-rabbit IgG [CST #7074] and HRP-linked, anti-mouse IgG [CST #7076]. Thereafter, the membranes were washed, incubated in SignalFire™ ECL Reagent substrate solution, and imaged with a MicroChemi 4.2 unit (DNR Bio-Imaging Systems) using GelCapture Chemi software. Representative blots of the groups included in our study may be found in Supplementary Figs. 1 and 2. 5-HT1_A and 5-HT1_B values in the manuscript refer to protein expression.

Statistical analyses

One-way ANOVA (Tukey post hoc) was used to compare data across groups. Two-way ANOVA (Tukey post hoc) was used to analyse pharmacological data with DBS and drug administration as factors. A Student's *t* test was used to compare behavioural data between stressed and non-stressed mice. Results in the text and figures are expressed as means ± standard errors. Statistical significance was set at $p \leq 0.05$.

Results

Stress effects

Prior to DBS experiments, we tested the effects of stress in our modified paradigm. In the open field test, stressed animals without any surgical manipulation ($n = 16$) had a lower locomotion (189.4 ± 6.8 s vs 218.5 ± 6.3 s; $p = 0.004$; Fig. 3A) and travelled smaller distances (8.2 ± 0.5 s vs 10.9 ± 0.8 s; $p = 0.005$; Fig. 3B) compared to non-stressed controls ($n = 20$). In contrast, no group differences were found in the defensive burying test ($p = 0.1$; Fig. 3C), novel location recognition test ($p = 0.4$; Fig. 3D), and novel object recognition test ($p = 0.4$; Fig. 3E). In the NSF, stressed mice

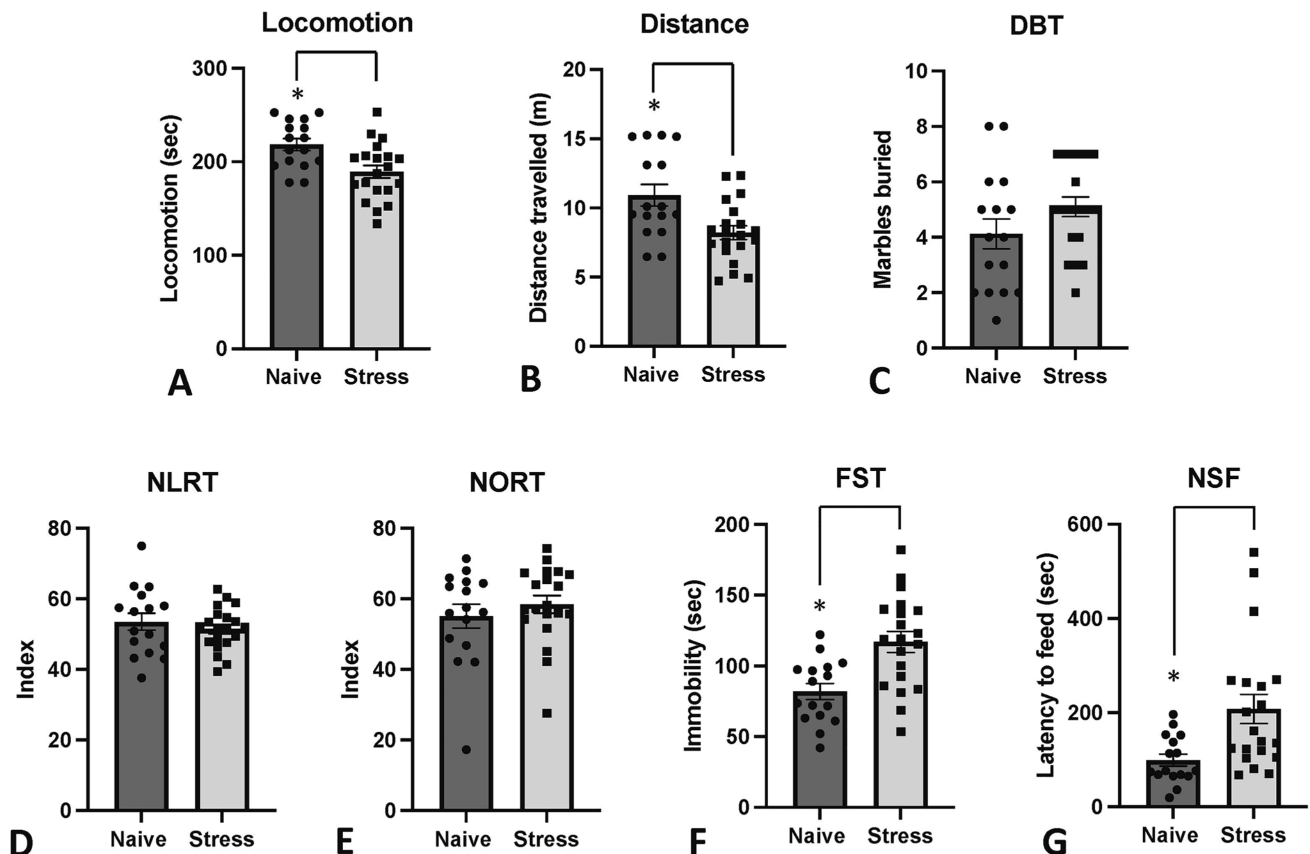

Fig. 3 Stress-induced effects in a modified chronic social defeat stress paradigm. **A** In the open field, **A** locomotion and the **B** distance travelled were significantly lower in stress-exposed mice ($n = 16$) compared to non-stressed controls ($n = 20$). **C** In the defensive burying test (DBT), no difference was found in the number of marbles buried by stressed and non-stressed animals. Similarly, no differences between groups were found in the **D** the novel location recognition test (NLRT) or **E** the novel object recognition test (NORT). **F** In the novelty suppressed feeding test (NSF), the latency to feed in stressed animals was significantly higher than in non-stressed controls. **G** In the forced swim test (FST), stressed mice had significantly more immobility than non-stressed controls. Values represent mean and standard error. *Statistically significant

had a significantly longer latency to feed (207.7 ± 30.8 s) compared to non-stressed controls (99.2 ± 12.8 s; $p = 0.005$; Fig. 3F). In the FST, animals exposed to stress spent a higher time in immobility (117.0 ± 7.4 s) compared to non-stressed controls (82.0 ± 5.7 s; $p = 0.001$; Fig. 3G).

Chronic vmPFC DBS

Open field test

One-way ANOVA revealed a significant treatment effect on locomotion (F [2,25] = 3.96, $p = 0.03$), due to the higher value recorded in Sham DBS stress mice (216.0 ± 8.4 s; $n = 9$;) compared to Sham controls (183.4 ± 6.9 s; $p = 0.03$; $n = 10$), but not to the DBS stress group (189.6 ± 10.6 s; $n = 9$; Fig. 4A). In contrast, no significant treatment effect was found for the distance travelled (F [2,25] = 2.90, $p = 0.07$), with similar values recorded in Stress controls (6.9 ± 0.5 m), Sham stress (8.7 ± 0.5 m), and DBS stress mice (7.8 ± 0.6 m; Fig. 4B).

Defensive burying

No significant effect of stimulation was found in the DBT (F [2,25] = 2.34, $p = 0.12$), despite the lower number of marbles buried by DBS stress animals (4 ± 0.9) compared to Stress controls (5.9 ± 0.5) and the Sham DBS stress group (5.3 ± 0.5; Fig. 4C).

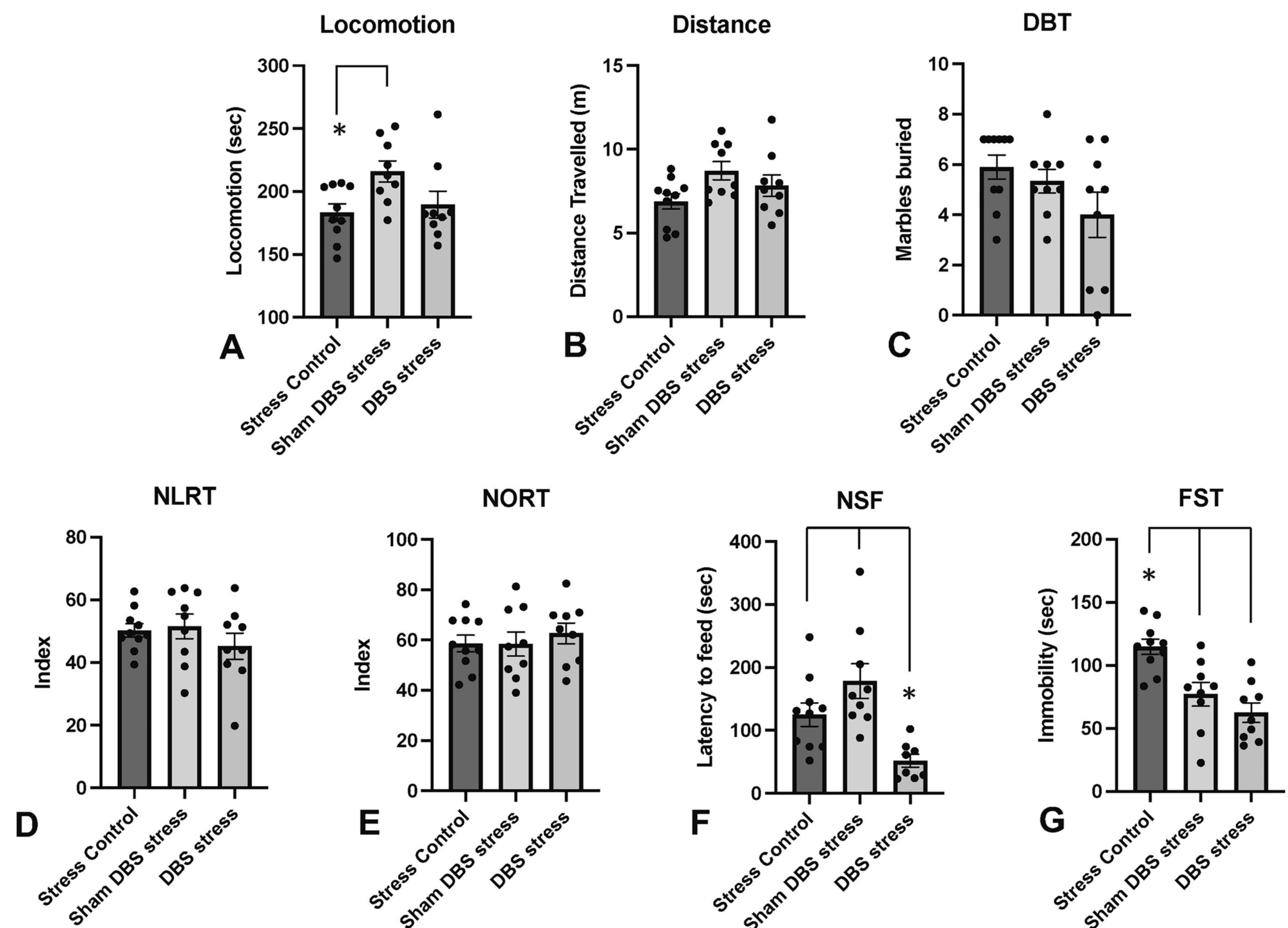

Fig. 4 Antidepressant- and anxiolytic-like effects of deep brain stimulation (DBS) in a modified chronic social defeat stress paradigm. **A** In the open field, locomotion was significantly higher in Sham DBS stress mice ($n = 9$) than in animals exposed to stress without implanted electrodes (Stress controls; $n = 10$), but not to the DBS stress group ($n = 9$). **B** In contrast, the distance travelled in the apparatus was similar across groups. **C** In the defensive burying test (DBT), no difference was found in the number of marbles buried by animals in different groups. Similarly, no differences across groups were found when the indexes calculated for **D** the novel location recognition test (NLRT) or **E** the novel object recognition test (NORT) were considered. **F** In the novelty suppressed feeding test (NSF), the latency to feed in DBS stress animals ($n = 8$) was significantly lower than in the Sham DBS stress group ($n = 9$) or in Stress controls ($n = 10$). **G** In the forced swim test (FST), both DBS stress and Sham DBS stress animals had significantly less immobility than Stress-exposed controls. Values represent mean and standard error. *Statistically significant

Novel location and novel object recognition tests

One-way ANOVA revealed no significant stimulation effects in the novel location (F [2,25] = 0.91, p = 0.42; Fig. 4D) and novel object recognition tests (F [2,25] = 0.34, p = 0.71; Fig. 4E). Similar NLRT and NORT indices were respectively observed in DBS stress mice (45.3 ± 4.2; 62.7 ± 4.2), Sham DBS stress animals (51.6 ± 3.9; 58.4 ± 4.8) and Stress controls (50.3 ± 2.1; 58.6 ± 3.4).

Novel suppressed feeding

A significant treatment effect (F [2,24] = 9.0, p = 0.001) was observed in the NSF, with DBS stress animals presenting a lower latency to feed (51.6 ± 10.1 s; n = 8) compared to Sham DBS stress animals (178.7 ± 27.3 s; p = 0.0008; n = 9) and Stress controls (125.3 ± 18.7 s; p = 0.048; n = 10; Fig. 4F).

Forced swim test

One-way ANOVA revealed a significant treatment effect (F [2,26] = 12.4, p = 0.0002). Both DBS stress (62.5 ± 7.7 s; p = 0.0002) and Sham DBS stress animals (77.2 ± 9.4 s; p = 0.005) had significantly less immobility than Stress-exposed controls (114.9 ± 6.1 s; p = 0.0002; Fig. 4G).

5-HT$_{1A}$ and 5-HT$_{1B}$ expression

Overall, no significant vmPFC stimulation effects were observed in the expression of 5-HT$_{1A}$ or 5-HT$_{1B}$ (Table 1). In most studied regions, 5-HT$_{1A}$ levels were non-significantly lower, whereas 5-HT$_{1B}$ expression was non-significantly higher in DBS-treated animals compared to controls (Fig. 5).

Pharmacological experiments

In our initial experiment, we showed that vmPFC DBS improved anxiety- and depressive-like responses in mice exposed to social defeat stress. To test whether the DBS effects are mediated by 5-HT$_{1A}$ or 5-HT$_{1B}$ receptors, we treated different groups of animals with WAY-100635 (WAY) or GR-127935 (GR). Since DBS did not induce memory changes in our initial experiment, we did not conduct novel location or novel object recognition testing in pharmacological preparations. As Sham DBS stress animals did not differ substantially from non-implanted Stress controls, only the latter group was injected with drugs.

Table 1 Statistical results of 5-HT1$_A$ and 5-HT1$_B$ comparisons in stressed mice given DBS, Sham stimulation or with no implanted electrodes according to region

Brain region	5-HT1$_A$	5-HT1$_B$
vmPFC	$F_{(2,21)}$ = 0.35; p = 0.71	$F_{(2,21)}$ = 0.31; p = 0.74
Hippocampus	$F_{(2,21)}$ = 2.36; p = 0.12	$F_{(2,21)}$ = 1.94; p = 0.17
NAcc	$F_{(2,21)}$ = 0.11; p = 0.90	$F_{(2,18)}$ = 2.58; p = 0.22
Raphe	$F_{(2,21)}$ = 0.15; p = 0.86	$F_{(2,19)}$ = 0.36; p = 0.70

NAcc nucleus accumbens, *vmPFC* ventromedial prefrontal cortex

5-HT$_{1A}$ antagonism—WAY-100635

Open field test

Two-way ANOVA revealed a significant effect of DBS (F [1,27] = 6.40, p = 0.02) but no effect of drug (F [1,27] = 0.26, p = 0.61), or a DBS × drug interaction (F [1,27] = 1.52, p = 0.23) on locomotion (Fig. 6A). No effects of DBS (F [1,27] = 3.1, p = 0.09), drug (F [1,27] = 0.01, p = 0.99), or a DBS × drug interaction (F [1,27] = 0.87, p = 0.36) were observed on the distance travelled (Fig. 6B). No significant differences were found when either variable was compared among animals receiving DBS stress WAY (159.2 ± 11.5 s; 6.5 ± 0.7 m.; n = 8), DBS stress vehicle (180.6 ± 13.1 s; 7.3 ± 0.8 m.; n = 10), Stress WAY (205.4 ± 4.6 s; 8.7 ± 0.8 m.; n = 7), and Stress vehicle (196.6 ± 15.1 s; 8.0 ± 1.0 m.; n = 6).

Defensive burying

No effects of DBS (F [1,27] = 0.50, p = 0.49), drug (F [1,27] = 0.57, p = 0.46), or a DBS × drug interaction (F [1,27] = 0.53, p = 0.47) were noted in the DBT. The number of marbles buried was similar in groups receiving DBS stress WAY (4.9 ± 0.9), DBS stress vehicle (3.6 ± 0.9), Stress WAY (4.9 ± 0.5), or Stress vehicle (4.8 ± 0.9; Fig. 6C).

Novel suppressed feeding

In the NSF, two-way ANOVA revealed a significant DBS effect (F [1,25] = 76.5, p < 0.0001), but no drug effect (F [1,25] = 0.90, p = 0.35), or a DBS × drug interaction (F [1,25] = 0.66, p = 0.42). A significant reduction in the latency to feed was observed between DBS stress vehicle animals (49.8 ± 9.2 s; n = 9) and both Stress vehicle (261.2 ± 49.3 s; n = 5; p < 0.0001) and Stress WAY groups (222.1 ± 25.1 s; n = 7; p < 0.0001). Similarly, a reduction in the latency to feed was found between DBS stress WAY mice (46.8 ± 7.8 s; n = 8) and both the Stress vehicle (p < 0.0001) and Stress WAY groups (p < 0.0001; Fig. 6D).

Forced swim test

Two-way ANOVA revealed a significant effect of DBS (F [1,27] = 37.5, p < 0.0001), but no drug effect (F [1,27] = 0.78, p = 0.39), or a DBS × drug interaction (F

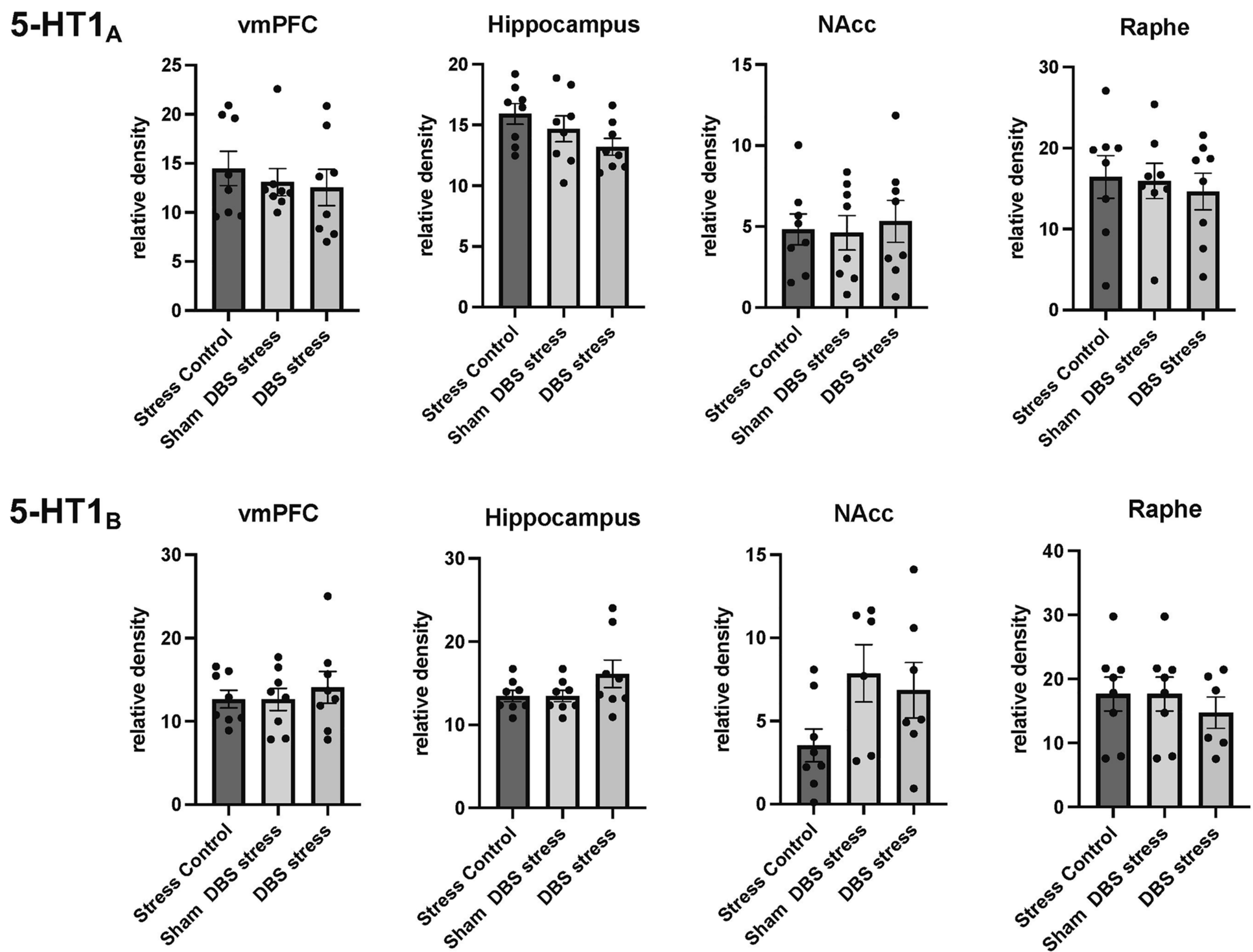

Fig. 5 5-HT_{1A} (upper panel) and 5-HT_{1B} (lower panel) receptor protein expression measured with western blot in the Stress control, Sham DBS stress, and DBS stress groups. **A** 5-HT_{1A} expression was non-significantly reduced by 11–17% in the vmPFC, hippocampus, and raphe, and increased by 10% in the NAcc of DBS-treated animals, compared to controls. **B** 5-HT_{1B} expression in the stimulated group was non-significantly increased by 11% in the vmPFC, 19% in the hippocampus, 94% in the NAcc, and reduced by 16% in the raphe, compared to Stress controls. Values represent mean and standard error. $n=8$ animals/group

[1,27] = 1.0, $p=0.33$). A significant reduction in immobility time was observed between the animals receiving DBS stress vehicle (63.0 ± 6.9 s) and both Stress vehicle (100.5 ± 11.3 s; $p=0.006$) and Stress WAY groups (114.2 ± 6.6 s; $p=0.001$). Similarly, a reduction in the latency to feed was found between DBS stress WAY mice (62.1 ± 3.8 s) and both Stress vehicle ($p=0.007$) and Stress WAY groups ($p=0.002$; Fig. 6E).

5-HT_{1B} antagonism—GR-127935

Open field test

Two-way ANOVA revealed no effects of DBS (F [1,28] = 1.08, $p=0.31$), drug (F [1,28] = 0.01, $p=0.92$), or a DBS × drug interaction (F [1,28] = 0.61, $p=0.44$) on locomotion (Fig. 7A). Similarly, no effects of DBS (F [1,28] = 0.13, $p=0.14$), drug (F [1,28] = 0.30, $p=0.59$), or a DBS × drug interaction (F [1,28] = 2.30, $p=0.14$) were observed on the distance travelled (Fig. 7B). No significant differences were found for either variable when DBS stress GR (172.2 ± 13.7 s; 6.6 ± 0.7 m.; $n=8$), DBS stress vehicle (180.6 ± 13.1 s; 7.3 ± 0.8 m.; $n=10$), Stress GR (194.4 ± 7.4 s; 7.9 ± 0.3 m.; $n=7$) and Stress vehicle groups were compared (183.8 ± 10.2 s; 6.5 ± 0.6 m.; $n=7$).

Defensive burying

No effects of DBS (F [1,28] = 0.14, $p=0.72$), drug (F [1,28] = 0.01, $p=0.95$), or a DBS × drug interaction (F [1,28] = 0.14, $p=0.72$) were found in the DBT. The number of marbles buried was similar in groups receiving DBS

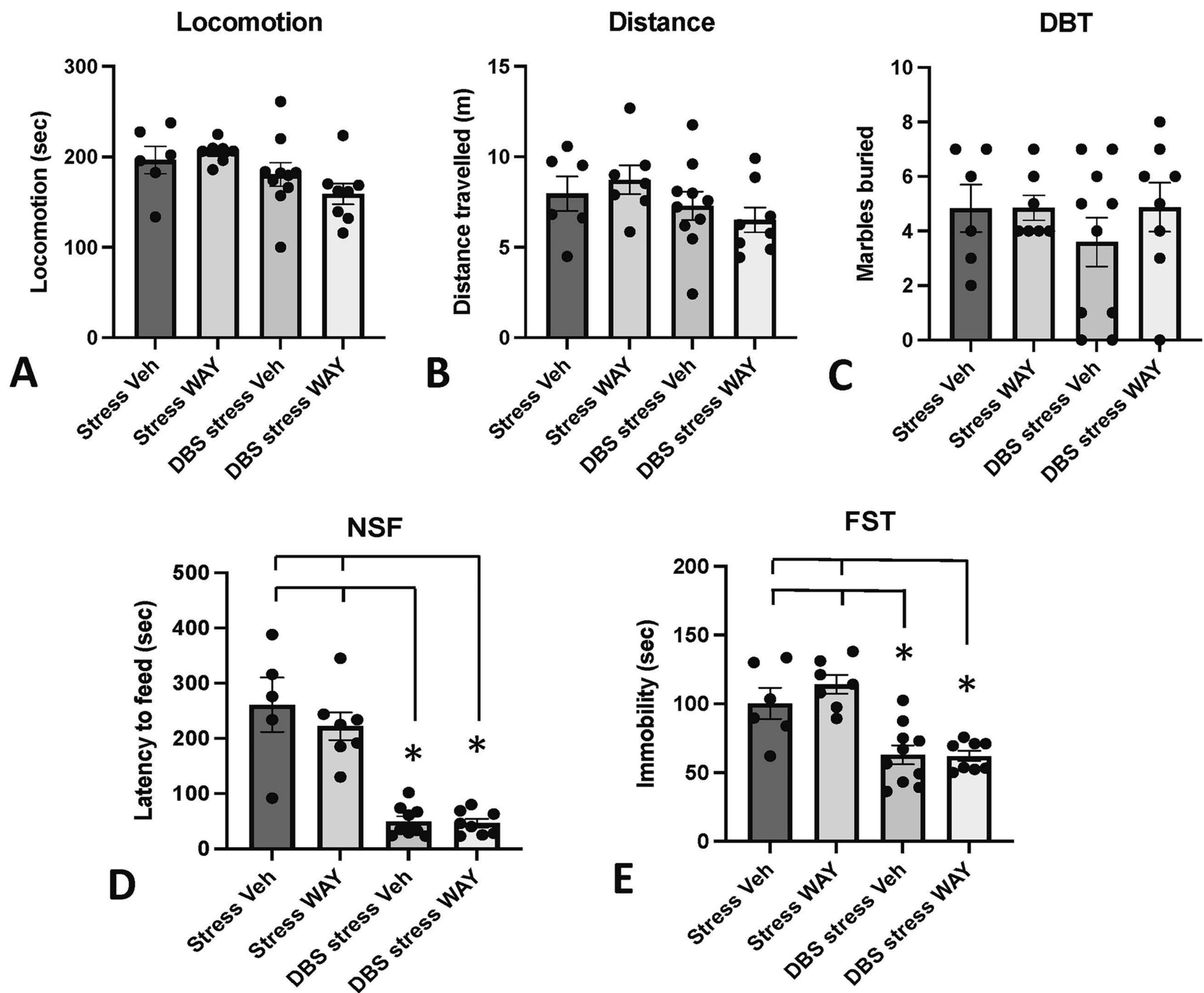

Fig. 6 Antidepressant- and anxiolytic-like effects of deep brain stimulation (DBS) are unaffected by the 5-HT$_{1A}$ antagonist WAY-100635 (WAY). **A** Locomotion in the open field, **B** the distance travelled, and **C** the number of buried marbles in the defensive burying test (DBT) were similar in animals receiving Stress vehicle (Veh; $n=6$), Stress WAY ($n=7$), DBS stress vehicle ($n=10$), or DBS stress WAY ($n=8$). **D**) In the novelty suppressed feeding test (NSF), a significant reduction in the latency to feed was observed when DBS stress animals treated with either vehicle ($n=9$) or WAY ($n=8$) were compared to groups receiving Stress vehicle ($n=5$) or Stress WAY ($n=7$). **E** In the forced swim test (FST), a significant decrease in immobility was observed when either DBS stress vehicle animals or DBS stress WAY mice were compared to groups receiving Stress vehicle or Stress WAY. Values represent mean and standard error. *Statistically significant

stress GR (4.0 ± 0.8), DBS stress vehicle (3.6 ± 0.9), Stress GR (4.00 ± 1.0), or Stress vehicle (4.3 ± 0.9; Fig. 7C).

Novel suppressed feeding

Two-way ANOVA revealed a significant DBS effect (F [1,25] = 8.0, $p=0.009$), but no drug effect (F [1,25] = 0.08, $p=0.78$), or a DBS × drug interaction (F [1,25] = 2.2, $p=0.16$). A significant reduction in the latency to feed was observed between groups receiving DBS stress vehicle (49.8 ± 9.2 s; $n=9$) and Stress vehicle (213.0 ± 49.3 s; $n=7$; $p=0.02$). Values recorded in DBS stress GR animals (115.7 ± 38.6 s; $n=6$) and Stress GR mice (168.1 ± 49.9 s; $n=7$) were similar to stress vehicle controls (Fig. 7D).

Forced swim test

Two-way ANOVA revealed significant effects of DBS (F [1,28] = 4.4, $p=0.05$) and drug (F [1,28] = 7.8, $p=0.01$), but no DBS × drug interaction (F [1,28] = 1.4, $p=0.24$). Significant differences in immobility were found between groups receiving DBS stress vehicle (63.0 ± 6.9 s), and

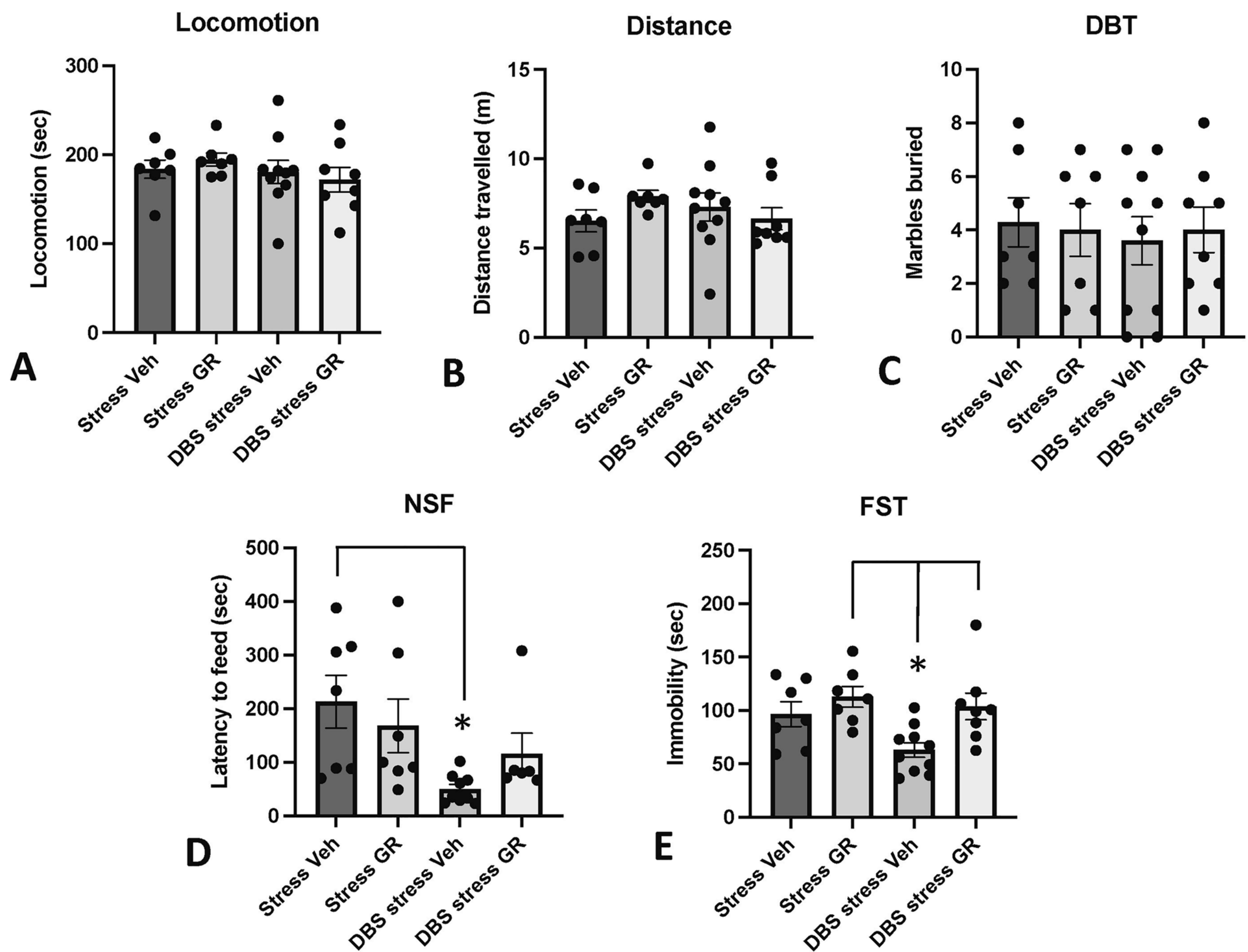

Fig. 7 The antidepressant- and anxiolytic-like effects of deep brain stimulation (DBS) are diminished by the 5-HT_{1B} antagonist GR-127935 (GR). No significant differences were found when groups receiving Stress vehicle (Veh; $n=7$), Stress GR ($n=7$), DBS stress vehicle ($n=10$), or DBS stress GR ($n=8$) were compared in **A**, **B** the open field or **C** the defensive burying test (DBT). **D** In the novelty suppressed feeding test (NSF), a significant reduction in the latency to feed was observed between groups receiving DBS stress vehicle ($n=9$) and Stress vehicle ($n=7$). Values recorded in DBS stress GR animals ($n=6$) and Stress GR mice ($n=7$) were similar to those observed in Stress vehicle controls. **E** In the forced swim test (FST), significant differences in immobility were found between groups receiving DBS stress vehicle and either Stress GR or DBS stress GR. None of the groups differed significantly from Stress vehicle controls. Values represent mean and standard error. *Statistically significant

either Stress GR (112.9 ± 9.8 s; $p=0.01$), or DBS stress GR (103.8 ± 12.5 s; $p=0.03$). None of the groups differed significantly from Stress vehicle controls (96.6 ± 11.7 s; Fig. 7E).

Discussion

Our study shows that chronic vmPFC stimulation induces anxiolytic and antidepressant-like effects in a chronic social defeat stress paradigm. Most importantly, the behavioural response of DBS was mitigated by the administration of the 5-HT_{1B} but not 5-HT_{1A} antagonists. This finding suggests that, in contrast to antidepressant medications (Lesch 1991; Lucki 1996; Lucki et al. 1994), the anxiolytic- and antidepressant-like effects of vmPFC stimulation may be mediated by 5-HT_{1B} serotonin receptors.

Based on anatomical connections and cytoarchitectural features, the ventral aspect of the medial prefrontal cortex (vmPFC) has been suggested to be the anatomical correlate of the subgenual cingulum (Gabbott et al. 2003; Hamani et al. 2010b, 2011; Takagishi and Chiba 1991). Since the SCG is a commonly stimulated target in clinical trials for major depression (Holtzheimer et al. 2012, 2017; Lozano et al. 2012; Mayberg et al. 2005; Riva-Posse et al. 2018), we opted to stimulate the vmPFC in the current study.

The behavioural effects of chronic vmPFC stimulation have been previously demonstrated in rodent models induced by stress, neurobiological preparations, and in

specific animal lines (Bambico et al. 2015; Gersner et al. 2010; Hamani et al. 2012b; Lim et al. 2015b; Moshe et al. 2016; Veerakumar et al. 2014). A commonly used rodent paradigm involves exposure to chronic unpredictable mild stress (Muscat et al. 1988; Willner et al. 1992, 1987). This model, however, is notoriously complex and difficult to replicate (Antoniuk et al. 2019; Willner 2017). Moreover, it is particularly cumbersome in mice, often requiring long timeframes and complex readouts to detect anxiety- and depressive-like behaviours (Maluach et al. 2017; Prevot et al. 2019). An alternative model is chronic social defeat stress, which has been shown to induce depressive- and anxiety-type behaviours in rodents (Bartolomucci et al. 2001; Berton et al. 1999, 2006; Hammels et al. 2015; Kudryavtseva et al. 1991; Raab et al. 1986). In the current study, we used a modified version of this paradigm. In contrast to a continuous interaction (Golden et al. 2011), intruders were exposed to residents in two 3-day sessions separated by a 4-day break. By inserting an interval between two runs of social defeat, we were able to deliver 1 week of DBS to stress-exposed animals before behavioural testing began. This timeline corresponds to a scenario in which patients would receive DBS after the development of the disease. In addition, in this modified version of the model, DBS could be administered for 1–2 weeks, a timeframe that would allow several neuroplastic phenomena to develop. In general, the expression of anxiety and depression-type responses following stress tends to decrease over time following stress exposure. By dividing the 6 days of social encounters into two segments of 3 days, we theoretically maximized the chances of detecting depressive- and anxiety-like behaviours. While our modified preparation was adequate for our purposes, we do not know if changes in the interval between exposure trials or the timeframe between stress and testing would yield different results.

In the clinical scenario, DBS has been shown to improve several symptoms associated with depression (Holtzheimer et al. 2012, 2017; Lozano et al. 2012; Mayberg et al. 2005; Riva-Posse et al. 2018). In the current study, we have selected a battery of behavioural tests to study the effects of DBS in multiple dimensions, including depressive-like behaviour (e.g. FST), anxiety (e.g. defensive burying, novelty supressed feeding), and memory function (e.g. novel object and location recognition). We found that vmPFC stimulation was most effective in improving depressive- and anxiety-like behaviour, exerting no effect on memory performance. Though anhedonic-like behaviour following vmPFC stimulation has been previously demonstrated by our group and others (Bambico et al. 2015; Hamani et al. 2012b; Lim et al. 2015b), this was not formally assessed in the current study. Whether DBS-induced improvements in sucrose preference, sucrose consumption, or the splash test are dependent on 5-HT_{1B} receptors remains to be demonstrated.

The main findings of our initial behavioural experiments were that vmPFC DBS reduced the latency to feed in the NSF and immobility in the FST. In the latter, the effects of DBS could not exclusively be attributed to the electrical current delivered to the parenchyma but instead to a combination of stimulation plus electrode insertion since sham implanted animals also presented an antidepressant-like effect. In contrast, stimulation did not affect defensive burying in the DBT or memory performance in the NORT and NLRT. The former is an innate rodent behaviour that has routinely been used as a measure of anxiety (Reznikov et al. 2016). In our memory paradigm, no substantial interval was given between the initial item presentation and changes in either object or location. We investigated short-term memory because we were directly stimulating the vmPFC, a region largely involved in mechanisms of novel object recognition, novel location recognition, and working memory (Aggleton and Nelson 2020; Chao et al. 2020). Previous studies have shown that DBS delivered to stressed rats rescued CUMS-induced memory deficits (Papp et al. 2018, 2019). Future work in CSDS paradigms is still required to test whether vmPFC stimulation mitigates deficits in hippocampus- or amygdala-dependent memory tasks.

Similar to our previous work, one of the main tests used to measure depression-like behaviour in the current study was the FST (Hamani et al. 2010a, b, 2014). In addition to immobility, different types of behaviours may be assessed in this test, including swimming and climbing. Previous work has shown that the former is more sensitive to serotonergic compounds while the latter is more responsive to drugs that modulate catecholamine transmission (Cryan et al. 2002, 2005a, b; Detke et al. 1995). Our choice to predominantly focus on immobility time was based on three factors observed in our previous work. DBS had no significant effect on climbing (Hamani et al. 2010a, b, 2014). Reductions in immobility time were almost always the inverse representation of swimming (Hamani et al. 2010a, b, 2014). Immobility has been a reliable measure for the study of the antidepressant-like effects of DBS in mice (Bregman et al. 2018; Hamani and Nobrega 2012).

As described above, some DBS effects may be partially attributed to electrode implantation. This so-called insertional effect has been previously reported in rodents. In those studies, animals demonstrated behavioural or neurochemical changes following electrode insertion that resembled those recorded after DBS, albeit of smaller magnitude (Casquero-Veiga et al. 2018; Hamani and Nobrega 2012; Perez-Caballero et al. 2018). The mechanisms responsible for such an effect are still disputed. Perez-Caballero et al. have shown that an increase in astrocytic immunoreactivity temporally correlates with behavoural responses (Perez-Caballero et al. 2018). Of note, however, the consequences of electrode insertion may still be observed long after surgery in brain

regions distant from the stimulated target (Chakravarty et al. 2016; Hamani et al. 2012b; Hamani and Nobrega 2012). Similar to rodent studies, the presence of an insertional effect has been documented in patients with tremor, pain, epilepsy, and even depression (Fenoy et al. 2018; Hamani et al. 2006, 2021; Lim et al. 2007; Tasker 1998). Clinically, this is characterized by symptomatic amelioration following electrode implantation, prior to the administration of current.

In our view, the consequences of DBS, at least in preclinical models, are a composite of electrode insertion and current delivery. As the effects of DBS often tend to be more robust than those of electrode insertion alone (Hamani et al. 2012b; Hamani and Nobrega 2012; Hammels et al. 2015), we opted to only include DBS-treated animals and not a separate sham implanted group during our pharmacological experiments. Previous studies have shown that the administration of anti-inflammatory drugs, but not analgesics mitigated the antidepressant-like effects of DBS in rodents (Perez-Caballero et al. 2014, 2018). This was particularly evident when the interval between surgery and testing was relatively short (Perez-Caballero et al. 2014). Though evidence for a focal inflammatory effect of electrode insertion is compelling, it is possible that additional mechanisms may play a role. For example, the behavioural effects of DBS have been mitigated by blocking serotonergic transmission (Hamani et al. 2010b; Perez-Caballero et al. 2014). In our current study, GR-127935 countered antidepressant- and anxiolytic-type responses.

At present, the mechanisms through which DBS exerts its antidepressant effects remain elusive (Dandekar et al. 2018; Hamani and Nobrega 2012; Hamani and Temel 2012). One possibility is the modulation of the serotonergic system (Dandekar et al. 2018; Hamani and Nobrega 2012; Hamani and Temel 2012). vmPFC stimulation increases serotonin levels in several brain regions and induces neuroplasticity of raphe nuclei and serotonin receptors (Bregman et al. 2018; Hamani et al. 2010b; Lim et al. 2015b; Srejic et al. 2015; Veerakumar et al. 2014; Volle et al. 2018). In addition, the antidepressant-like effects of DBS were not observed in rats bearing serotonin-depleting raphe lesions (Hamani et al. 2010b). We have recently measured 5-HT_{1A} and 5-HT_{1B} receptor binding in several areas receiving serotonergic projections, as well as their mRNA expression in the raphe following acute and chronic treatment with vmPFC DBS or fluoxetine (Volle et al. 2018). In general, chronic DBS increased 5-HT_{1B} receptor binding in the dorsal raphe, prelimbic cortex, substantia nigra, and lateral globus pallidum, but did not alter the binding of the 5-HT_{1A} receptor in any region (Volle et al. 2018). In contrast, chronic fluoxetine administration decreased 5-HT_{1A} binding in the PFC and hippocampus but did not affect 5-HT_{1B} binding (Volle et al. 2018). In the current study, we investigated whether chronic vmPFC DBS altered 5-HT_{1A} or 5-HT_{1B} protein expression in the vmPFC, hippocampus, nucleus accumbens, and raphe. As some of the structures showing significant binding in our previous report were too small to be dissected, they were not analysed in the current study. While no significant differences were found when DBS, sham stimulation, or non-implanted Stress controls were compared, DBS-treated mice had a non-significant increase in 5-HT_{1B} expression in all investigated structures, but the raphe.

5-HT_{1B} receptors can be categorized as autoreceptors or heteroreceptors (Sari 2004). In general, 5-HT_{1B} autoreceptors inhibit the release of 5-HT into the synapse, whereas heteroreceptors modulate the transmission of glutamate, GABA, ACh, and DA (Maura and Raiteri 1986; Moore et al. 2000; Sari 2004; Tiger et al. 2018). In the raphe, 5-HT_{1B} receptors are expressed in interneurons and principal cells, including collateral axonal projections (Bagdy et al. 2000; Davidson and Stamford 1995; Tao et al. 1996). The activation of raphe 5-HT_{1B} autoreceptors reduces neuronal firing and serotonin release (Lim et al. 2015b; Srejic et al. 2015). From a behavioural perspective, mice with selective knockdown of raphe 5-HT_{1B} autoreceptors present reduced depressive-like behaviours, while the overexpression of raphe 5-HT_{1B} receptors is anxiogenic (Anthony et al. 2000; Nautiyal et al. 2016; Neumaier et al. 1996). In our study, vmPFC DBS induced antidepressant- and anxiolytic-like effects, while non-significantly reducing raphe 5-HT_{1B} protein expression. Though these findings may help to explain the reduced firing of raphe cells following DBS, they are difficult to reconcile with the increase in serotonin release observed after vmPFC stimulation (Volle et al. 2018). Also difficult to reconcile are the disparities observed in the current study and the increased 5-HT_{1B} binding observed in DBS-treated rats from our previous report. Potential explanations for these discrepancies include the use of different species, techniques to detect 5-HT_{1B} expression, and the use of naïve versus stressed animals. Future studies need to be conducted to clarify the neurochemical effects of vmPFC stimulation in raphe serotonin receptors.

In contrast to the raphe, our current and previous findings suggest that 5-HT_{1B} expression increased, albeit non-significantly, in regions expressing heteroreceptors (e.g. PFC). 5-HT_{1B} heteroreceptors have been associated with the antidepressant-like effect of SSRIs in the FST (Chenu et al. 2008; Medrihan et al. 2017). Moreover, the pharmacological activation of these receptors induces antidepressant- and anxiolytic-like effects in different rodent models (Tatarczynska et al. 2004). To examine whether 5-HT_{1B} and 5-HT_{1A} receptors are involved in the antidepressant-like effects of vmPFC stimulation, we conducted pharmacological experiments antagonizing these receptors in animals receiving DBS. Based on our current and previous work, we predicted that blocking 5-HT_{1B} but not 5-HT_{1A} receptors would mitigate behavioural DBS responses. Confirming our

hypothesis, the antidepressant- and anxiolytic-like effects of DBS were countered in animals given the 5-HT$_{1B}$ antagonist GR-127935, but not in those given the 5-HT$_{1A}$ antagonist WAY-100635. These effects could not be attributed to the simple administration of the drugs, as no differences were found between animals given GR-127935 or WAY-100635 alone and vehicle-treated controls.

In our study, 5-HT$_{1B}$ and 5-HT$_{1A}$ antagonists were administered 30 min prior to stimulation for the last 4 days of the study (i.e. 3.5 h before behavioural testing began). This timing was chosen to ensure that the drugs would peak during the onset of DBS. The dose of WAY was selected based on previous work showing that it could mitigate the neurochemical effects of several antidepressants, including SSRI-induced improvements in the FST (Castro et al. 2008; Cryan et al. 2005b; Kaster et al. 2005; O'Neill and Conway 2001; Takahashi et al. 2020; Zanelati et al. 2010). Moreover, at this dose range, WAY was observed to counter gepirone-mediated changes in aggressive behaviour (Lopez-Mendoza et al. 1998; Rogoz et al. 2012; Tatarczynska et al. 2002). Finally, 2.5 mg/kg of WAY administered to residents receiving DBS in our paradigm successfully decreased the anti-aggressive-like effects of this therapy (data not shown). Considering that vmPFC did not change 5-HT$_{1A}$ receptor binding or protein levels in our studies (Volle et al. 2018), it was not surprising that WAY administration did not block the anxiolytic- and antidepressant-like effects of DBS in the CSDS model. Despite not mitigating the antidepressant- or anxiolytic-like effects of vmPFC stimulation, we note that it is still possible that 5-HT$_{1A}$ might play a role in the behavioural effects of DBS. Different and sometimes antagonistic effects have been recorded with the focal administration of drugs that modulate 5-HT$_{1A}$ autoreceptors and heteroreceptors in different parts of the brain (Bambico et al. 2018; Blier et al. 1998; Gardier et al. 1996; Popova and Naumenko 2013). Future work taking these variables into account is still required.

To determine whether 5-HT$_{1B}$ receptors were involved in the DBS response, we administered GR-127935 at a 5.0-mg/kg dose 30 min prior to DBS onset. Corroborating our initial hypothesis, antagonism of the 5-HT$_{1B}$ receptor countered the effects of DBS in the NSF and FST. Previous studies suggest that this drug blocks 5-HT$_{1B}$ receptors at a wide dose range (0.056–10 mg/kg) (de Almeida et al. 2001; Hogg and Dalvi 2004; Mayorga et al. 2001). Though GR-127935 has primarily been studied in the context of aggressive behaviour (Bannai et al. 2007), it has also been shown to block the effects of antidepressants. At 10 mg/kg, GR-127935 diminished immobility induced by the agonist RU 24,969, imipramine, and paroxetine in the tail suspension test (O'Neill et al. 1996). Likewise, 4 mg/kg of GR-127935 reduced the antidepressant-like effects of paroxetine and citalopram in the FST (Chenu et al. 2008). Though GR-127935 was found to block the effects of some antidepressant treatments, the administration of this drug even at high doses (e.g. 10 mg/kg in mice and 20 mg/kg in rats) was not found to induce depressive-like behaviour (O'Neill and Conway 2001; Tatarczynska et al. 2002). In a pilot study, we have injected animals with 10 mg/kg and found this dose to be toxic, with the animals presenting a substantial decrease in locomotion, grooming, and shivering. Therefore, we have decided to lower the dose to 5 mg/kg, a threshold recommended in this compound's safety sheet (Tocris Safety Data Sheet).

Conclusion

Our study shows that chronic vmPFC stimulation induces antidepressant- and anxiolytic-like responses in a modified CSDS paradigm. More importantly, we demonstrate that the behavioural effects of DBS were mitigated in animals given the 5-HT$_{1B}$ antagonist GR-127935. Future studies are still necessary to further dissect the molecular and neurochemical mechanisms through which DBS interacts with 5-HT$_{1B}$ receptors and modulates the serotonergic system.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00213-022-06259-6.

Author contribution ES, MD, TR, HK, ACPC, and FVG conducted behavioural and neurochemical experiments. ES and CH analysed the results and wrote the manuscript. PG and NL critically revised the manuscript. All authors approved the final version.

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Declarations

Competing interests The authors declare no competing interests.

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