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Medial Forebrain Bundle Deep Brain Stimulation Reverses Anhedonic-Like Behavior in a Chronic Model of Depression: Importance of BDNF and Inflammatory Cytokines

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Abstract

Deep brain stimulation (DBS) of the medial forebrain bundle (MFB) displays a promising antidepressant effects in patients with treatment-refractory depression; however, a clear consensus on underlying mechanisms is still enigmatic. Herein, we investigated the effects of MFB-DBS on anhedonic-like behavior using the Froot Loops® consumption in a chronic unpredictable mild stress (CUS) model of depression, biochemical estimation of peripheral and central inflammatory cytokines, stress hormone, and brain-derived neurotrophic factor (BDNF). Seven days of MFB-DBS significantly reversed the 42-day CUS-generated anhedonic-like phenotype ($p < 0.02$) indicated by an increase in Froot Loops® consumption. Gross locomotor activity and body weight remained unaffected across the different groups. A dramatic augmentation of adrenocorticotropic hormone levels was seen in the plasma and cerebrospinal fluid (CSF) samples of CUS rats, which significantly reduced following MFB-DBS treatment. However, C-reactive protein levels were found to be unaffected. Interestingly, decreased levels of BDNF in the CUS animals were augmented in the plasma, CSF, and hippocampus following MFB-DBS, but remained unaltered in the nucleus accumbens (NAc). While multiplex assay revealed no change in the neuronal levels of inflammatory cytokines including IL-1α, IL-4, IL-10, IL-12, IL-13, and IL-17 in the neuroanatomical framework of the hippocampus and NAc, increased levels of IL-1β, IL-2, IL-5, IL-6, IL-7, IL-18, TNF-α, and INF-γ were seen in these brain structures after CUS and were differentially modulated in the presence of MFB stimulation. Here, we show that there is dysregulation of BDNF and neuroimmune mediators in a stress-driven chronic depression model, and that chronic MFB-DBS has the potential to undo these aberrations.

Keywords Deep brain stimulation · MFB · Anhedonia · Chronic unpredictable mild stress · BDNF · Cytokines

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Introduction

Almost 30% of patients with MDD receiving conventional antidepressant therapy fail to achieve remission and show resistance, when administered alone or in combination with psychotherapy and electroconvulsive therapy (ECT)—the medical condition is coined as treatment-resistant depression (TRD) [1–3]. In the last decade, several pharmacological approaches including ketamine [4] and non-pharmacological treatments like electrical stimulation of the brain [5] have been explored for alleviating chronic intractable depressive symptoms. However, the widespread clinical utility of most of these therapeutics is limited due to either lack of efficacy or serious side effects. Recently, deep brain stimulation (DBS) has been emerging as a potential tool for the treatment of severely affected and disabled TRD patients [6, 7].

DBS antidepressant potential has become increasingly demonstrative in reversing the chronic intractable depressive symptoms in patients with TRD [7–11]. Several critical brain regions implicated in the regulation of MDD are studied as potential targets for DBS including the subcallosal cingulate gyrus (SCG), ventral capsule/ventral striatum (VC/VS) or anterior limb of the internal capsule, nucleus accumbens (NAc), medial forebrain bundle (MFB), inferior thalamic peduncle, and lateral habenula (LHb) [6, 7, 12–18]. In preclinical depression models as well, application of DBS has been shown to revert the depressive-like phenotypes [19–28]. However, randomized, sham-controlled clinical trials of DBS for the treatment of TRD have failed to demonstrate a significant antidepressant effect following VC/VS or SCG stimulation [17, 29–31]. Therefore, in-depth characterization of DBS targets is essential. Among the six prominent DBS targets, results of open-labeled clinical trials pertaining to MFB-DBS showed the most rapid and profound antidepressant effects (75–86% response rates) [11, 32]. Moreover, our group has also been invested in studying the capability of MFB stimulation as a tool to understand pathophysiology of MDD and as a potential therapy for TRD [21, 33]. In a recent meta-analysis by Zhou et al. [6], a significant reduction of depressive scores was illustrated following MFB-DBS treatment in patients with TRD. The general description of a mechanism of action of MFB-DBS has been proposed [34–36], while a clear consensus on the rapid effect is yet unclear.

In the present study, we sought to investigate the effect of MFB-DBS on anhedonic-like behavior (via Froot Loops® consumption) employing a chronic unpredictable mild stress (CUS) model of depression in rats. The CUS is a well-studied preclinical model that simulates the clinical depression-like phenotype, confirmed in numerous pharmacological [37–42] and DBS studies [19, 20, 23, 27, 28, 43–45]. While the acute antidepressant effect of MFB-DBS has been reported in our earlier preclinical study [21], herein, we adopted the chronic stimulation paradigm (8 h/day for 7 consecutive days) which has more translational value and which was also employed in other DBS targets [20, 25, 43–46]. Among the several pathophysiological contributors of MDD, aberrations in the immune-inflammatory pathways play a key role [47–49]. Moreover, the importance of inflammatory cytokines like IL-1, IL-6, TNF-α, and IFN-γ in mediating the DBS-induced acute antidepressant effects has been explored in preclinical studies [50, 51]. However, a definite role of these inflammatory mediators is yet to be determined. Owing to the lack of evidence for peripheral and central pro- and anti-inflammatory cytokines in MFB-DBS-generated antidepressant effects, we estimated the levels of IL-1α, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-10, IL-12, IL-13, IL-17, IL-18, TNF-α, and INF-γ in the neuroanatomical framework of the hippocampus and NAc following MFB-DBS using a CUS model of depression, which may be attributed to the regulation of anhedonic-like behaviors. Suicide victims or patients of MDD were shown to have elevated inflammatory markers in plasma, such as C-reactive protein (CRP) [52] and adrenocorticotropic hormone (ACTH), and deficiency of neurotrophic factors like brain-derived neurotrophic factor (BDNF) was altered by DBS [20, 53–57]. On the basis of this knowledge, we estimated the plasma and cerebrospinal fluid (CSF) levels of ACTH, CRP, and BDNF after MFB-DBS in CUS rats.

Methods

Animals

Young adult male Wistar rats ($n = 67$), weighing 225–250 g at the beginning of the experiments, were housed at a temperature of 20 °C and humidity of 30% with 12-h light-dark cycle. The food and water were available ad libitum. All protocols were approved by the Institutional Animal Welfare Committee of the University of Texas Health Science Center at Houston, Texas, USA.

CUS

Application of CUS to rats is a well-validated animal paradigm of depression, simulates the human chronic depression-like phenotype, and produces anhedonic-like behaviors as reported in our earlier studies as well as described by others [20, 39–41, 58–60]. Moreover, DBS of the vmPFC, NAc, and LHb have shown to reverse the depressive phenotype induced by CUS [19, 20, 23, 25, 56, 57, 61, 62]. In our study, we modified the CUS procedure to some extent for effective application. Briefly, 1-week post-acclimatization animals were divided into two experimental groups, rats that were not subjected to stress (Non-CUS control group, $n = 24$) and rats that were subject to 42-day stress (CUS group, $n = 19$). The different types of stressors were randomly scheduled over 42 days in

the following manner: (i) food deprivation for 16 h and 30 h on days 2 and 7; (ii) partial food deprivation for 16 h each on days 15 and 21; (iii) water deprivation for 16 h, 19 h, 20 h, and 30 h on days 1, 10, 20, and 33; (iv) empty bottle for 1 h each on days 9 and 39; (v) restraint at room temperature for 3 h each on days 9, 23, and 31; (vi) restraint at 4 °C for 2 h each on days 13, 26, and 34; (vii) forced swimming in normal and ice cold water for 5 min each on days 8, 16, 27, 35, and 40; (viii) stroboscopic illumination exposure in dark room for 4 h each time on days 6 and 14; (ix) continuous 85 dB white noise for two 5-h and one 4-h periods on days 22, 28, and 32; (x) social isolation for 12 h each on days 3, 4, 5, 17, 18, 19, 24, 25, 36, and 37; (xi) wet cage for two periods of 17 h and 18 h on days 6 and 41; (xii) cage tilt 45 and 60 degrees for 21 h and 41 h on days 11 and 29; (xiii) housing with intruder for 6 h each on days 8, 16, 27, 35, and 40; and (xiv) reversing the day and night schedule (one period of continuous illumination in the dark phase (12 h), two periods of darkness in the light phase) on days 12, 30, and 42. The stress type and execution time were pseudo-randomly organized and changed to minimize the predictability of stimuli by animals. Control animals (Non-CUS) were kept undisturbed in their home cages during application of stress to CUS group, except during body weight measurements and routine cage changing.

Surgical Procedures and Study Design

After concluding the 5 weeks of CUS, all the animals (CUS and Non-CUS) were subjected to electrode implantation surgery in the right MFB. The stereotactic surgical procedure for electrode placement has already been standardized in our laboratory [21]. Briefly, rats were anesthetized with inhaled 3% isoflurane, and a stainless steel concentric bipolar electrode was implanted in the MFB using the coordinates relative to bregma: − 2.52-mm anteroposterior, + 1.7-mm mediolateral, and − 8-mm dorsoventral [63]. Unilateral stimulation of MFB displayed an acute antidepressant effect in human trials and preclinical study [21, 33, 64–67]. For the placement verification, at the end of study, brains were stained with cresyl violet for light microscopic observation of electrode tip placements (Fig. 1).

After a hiatus of 7 days for surgical recovery, CUS animals were again subjected to the remaining sessions of stress (see "CUS" section). At the completion of 42 days of CUS, each experimental group of animals (i.e., Non-CUS and CUS) were further subdivided into two groups as following, those given active MFB-DBS (Non-CUS DBS-On and CUS DBS-On), and inactive MFB-DBS groups (Non-CUS DBS-Off and CUS DBS-Off). The electrical stimulation was applied using a computer-interfaced current generator (World Precision Instruments, Isostim A320) to the MFB with the parameters of 130 Hz, 200-μA amplitude, and 90-μs pulse width [20, 21, 26, 45, 68]. The DBS-On groups (both Non-CUS and CUS) were stimulated for 8 h per day for 7 days before testing for the Froot Loops® consumption and locomotor activity assays. The time frame of DBS was selected based on previous reports [20, 25, 44, 46]. While this preclinical electrical stimulation on/off paradigm does not simulate the clinical scenario, we were unable to leave animals connected to the equipment at night due to an external DBS set-up. Moreover, animals were disconnected from the electrical stimulation during behavioral screening due to the nature of test. Thus, under these circumstances it is possible that behavioral responses may be ascribed to rebound effects associated with the immediate cessation of current delivery. The DBS-Off groups (both Non-CUS and CUS) were connected to stimulation cables for the same period of time but did not receive stimulation.

Behavioral Measurements

Froot Loops® Consumption Assay (Anhedonia Test)

Anhedonia, a common symptom of clinical depression, is commonly assessed in animal models via a sweet food preference assay [58, 69]. To verify the anhedonic-like phenotypes (i.e., lack of interest in the ingestion of sweet food) in CUS animals, we employed a Froot Loops® consumption assay. The Froot Loops® consumption assay has already been developed and standardized in our laboratory [70–72]. Briefly, this assay runs through 7 days (5 days of trial sessions followed by 2 days of the actual test), and we conducted it at the end of each day of MFB-DBS (i.e., daily 8 h after electric stimulation in DBS-On group or without stimulation in DBS-Off group). The day before (22 h) commencement of 7 days of DBS, rats were deprived of food to motivate eating of Froot Loops® (Kellogg's® pellets of wheat and sucrose) on the following day [39] and the same procedure was implemented through the 5-day trial session. During the five-day trial sessions, ten Froot Loops® were served to rats in open-field cages (Ugo Basile 47420) for maximum 3 min each day, to familiarize themselves with the taste of Froot Loops® and the novel environment [70–73]. Then, on the sixth and seventh day of the test session of 5 min each, the number of Froot Loops® consumed by each rat was manually recorded. Consumption of partial Froot Loops® (i.e., 1, 1/2, 1/3, 1/3, or 1/4) was also recorded. The amount of Froot Loops® consumed was expressed as the average of those two testing sessions. The gross locomotor activity was also monitored throughout this study. At the end of behavioral screening, the rats were deeply anesthetized for obtaining blood and CSF samples, and then brain tissues were harvested for ELISA, multiplex, and histological analyses.

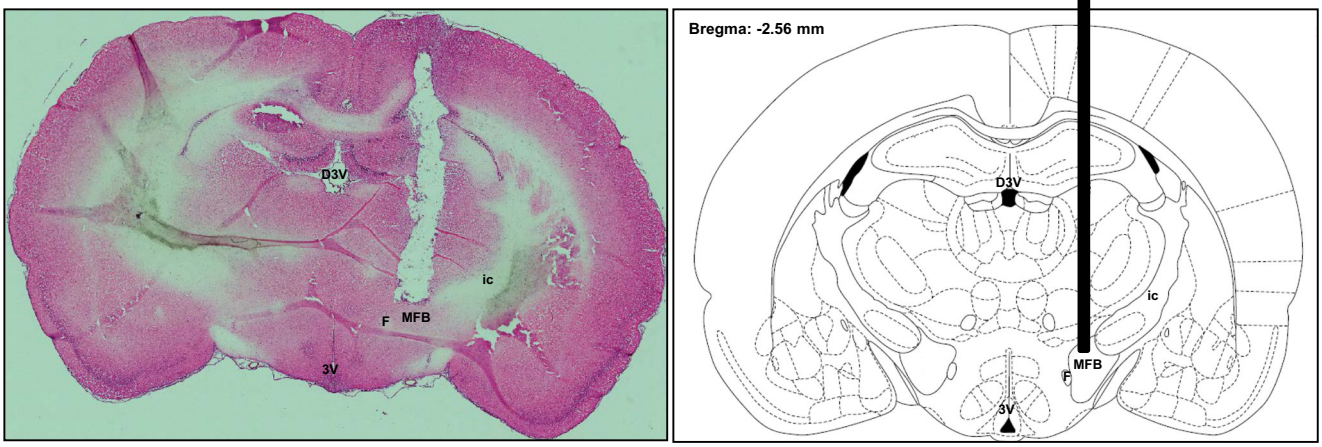


Fig. 1 Schematic representation of coronal brain sections adapted from the rat brain atlas of Paxinos and Watson [63] showing the region in which electrode was targeted for DBS. Rats were perfused transcardially and brains were dissected out and stained with cresyl violet for light microscopic examination of electrode tip placements. The terminal end of electrodes was found at the level of bregma − 2.56 mm as depicted in the right hemisphere of the rat brain. D3V, dorsal third ventricle; F, fornix; mfb, medial forebrain bundle; ic, internal capsule; 3V, third ventricle

Spontaneous Locomotor Activity

As described in the "Froot Loops® consumption assay (Anhedonia test)" section, the spontaneous locomotor activity of rats was simultaneously recorded at the time of the Froot Loops® consumption assay. The set-up consists of an electronic recorder and an infrared beam cage (clear perspex, 40 × 40 cm) with two sets of emitter/sensor arrays. Crossing of the beams provided counts of motor activity in terms of horizontal and vertical activity, and total counts using CUB2015 software (Ugo Basile). On the sixth and seventh day of the Froot Loops® consumption assay, individual rats were assessed for 10 min in an activity cage.

Body Weight Measurements

Application of CUS may produce a deleterious effect on the animal body weight. Rats were weighed prior to the initiation of food control and then weekly once to monitor the any change in the animals' weight.

Estimation of CRP Levels in Plasma and CSF Using ELISA

CRP levels in the plasma and CSF were determined using a sandwich-ELISA assay with monoclonal antibodies specific for CRP (Millipore, USA and Canada). The microtitre plates (96-well flat-bottom) were coated for 30 min with the samples and a standard curve (ranging from 4.2 to 133.3 ng/mL of CRP). The plates were then washed four times with the sample diluent. Next, an anti-CRP antibody (diluted 1:100) was added to each well and incubated for 30 min at room temperature. Following this, a peroxidase-conjugated anti-rabbit antibody was added to each well and incubated at room temperature for 10 min. After the addition of the streptavidin enzyme, substrate, and stop solution, the amount of CRP was determined by measuring the absorbance at 450 nm.

Estimation of BDNF Levels in NAc and Hippocampus Using ELISA

The BDNF levels in brain tissues (prepared according to the instructions provided by Bio-Plex Cell Lysis kit (#171304011) with a protease inhibitor cocktail (Sigma-Aldrich, St. Louis, MO, USA), followed by centrifugation at 4 °C for 10 min at 10,000 × *g*) were determined using a sandwich-ELISA assay with monoclonal antibodies specific for BDNF (Millipore, USA and Canada). The microtitre plates (96-well flat-bottom) were coated for 24 h with the samples and a standard curve was used (ranging from 7.8 to 500 pg/mL of BDNF). The plates were then washed four times with the sample diluent. Next, a monoclonal anti-BDNF rabbit antibody (diluted 1:1000) was added to each well and incubated for 3 h at room temperature. Following, a peroxidase-conjugated anti-rabbit antibody (diluted 1:1000) was added to each well and incubated at room temperature for 1 h. After the addition of the streptavidin enzyme, substrate, and stop solution, the amount of BDNF was determined by measuring the absorbance at 450 nm. The concentration of each sample was determined in reference to standard curves from 7.8 to 500 pg/ml BDNF ($R2 \geq 0.94$). Total protein concentration was determined using a BCA assay (Thermo Scientific Pierce).

Quantification of ACTH, BDNF, and Inflammatory Cytokines Using Multiplex Assay

The cytokines levels were assayed using multiplex fluorescent immunoassay kits (Bio-Plex Pro™ Rat Cytokine 14-Plex Assay), and BDNF and ACTH levels in plasma and CSF were assayed using multiplex fluorescent immunoassay kits (Millipore, Rat Pituitary Magnetic Bead Panel, RPTMAG-86K). The xMAP platform used here was based on the Rules-Based Medicine (RBM) fluorescent beads and antibody pairs. These are sensitive, specific, and widely used reagents, sourced by numerous manufacturers, and data collected using xMAP multiplex beads are widely reported in the literature in studies in which multiple proteins are assayed simultaneously. Tissue lysates were prepared according to the instructions provided by Bio-Plex Cell Lysis kits (#171304011) with a protease inhibitor cocktail (Sigma-Aldrich, St. Louis, MO, USA), followed by centrifugation at 4 °C for 10 min at 10,000 × *g*. The multiplex assays were conducted according to the manufacturer's recommendations. Samples were run in duplicate using a Bio-Plex system (Bio-Plex 200 Systems, BioRad, Hercules, CA) and data analysis was conducted in Bio-Plex Manager 4.0 using a five-parameter logistic regression model.

Statistical Analyses

The data is expressed as mean ± standard error of the mean (S.E.M.) and the statistical analyses were performed using GraphPad Prism 6.0. The data from the Froot Loops® consumption, locomotor activity, ELISA, and multiplex assay were analyzed using two-way analysis of variance (ANOVA) followed by post-hoc Tukey's multiple comparison test. Moreover, Froot Loops® consumption and locomotor activity data were analyzed by two-tailed unpaired *t* test. All *p* values less than 0.05 were considered significant.

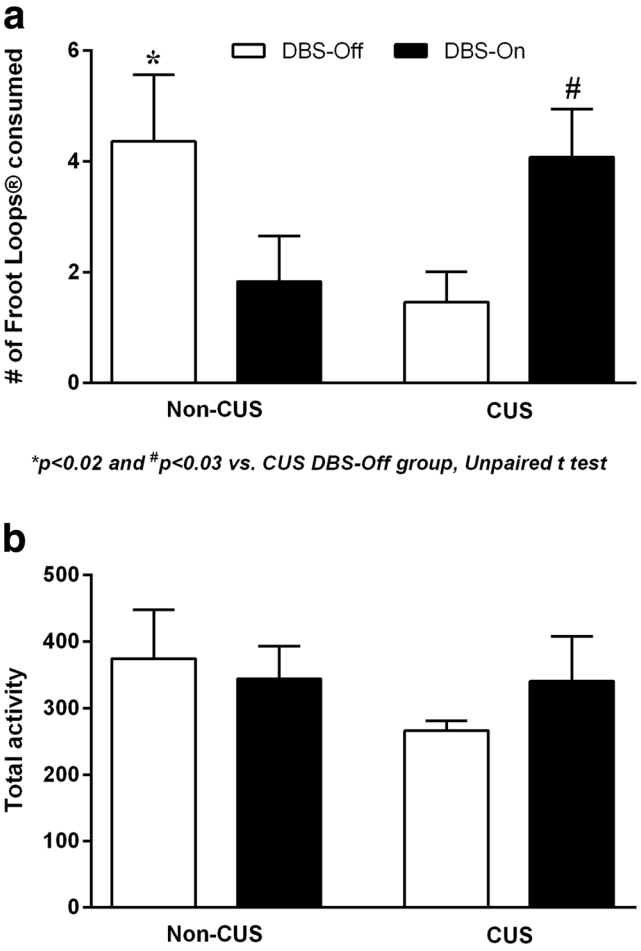


Fig. 2 Effect of 7 days of MFB-DBS on the number of Froot Loops® consumed (**a**) and locomotor activity (**b**) in rats. Both groups of animals, Non-CUS and CUS, were divided into either active DBS group (DBS-On) or DBS-Off group (not exposed to DBS). The DBS parameters were chosen as frequency 130 Hz, amplitude, 200-μA current, and 90-μs pulse width. The MFB-DBS was delivered daily for 8 h for 7 consecutive days. The data are analyzed using two-tailed unpaired *t* test and two-way analysis of variance (ANOVA) followed by post-hoc Tukey's multiple comparison test. **a** Each bar is the mean ± S.E.M. for 9–14 rats, $^{*}p < 0.02$, and $^{\#}p < 0.03$ vs CUS DBS-Off group. **b** Each bar is the mean ± S.E.M. for six rats. No significant differences, unpaired *t* test

Results

Effect of MFB-DBS on Froot Loops® Consumption

A significant decrease in Froot Loops® consumption was observed in the non-stimulated rats subjected to CUS for 42 days (CUS DBS-Off) as compared to those in the control group (Non-CUS DBS-Off), indicating an anhedonic-like phenotype in animals [unpaired *t* test $t = 2.277$, df = 17, $p < 0.036$; Fig. 2a]. Application of MFB-DBS for 7 days significantly reversed the decrease of Froot Loops® intake ($p < 0.02$) seen in CUS DBS-Off animals [unpaired *t* test $t = 2.531$, df = 18, $p < 0.0209$]. However, Froot Loops® consumption of Non-CUS animals did not change by MFB-DBS, compared to that in Non-CUS DBS-Off group. Two-way ANOVA followed by post-hoc Tukey's multiple comparison test revealed a statistically significant interaction between groups [CUS × DBS; $F(1,39) = 8.382$, $p < 0.0062$].

Effect of MFB-DBS on Locomotor Activity and Body Weight

The locomotor activity of rats subjected to the spontaneous locomotor test is presented in Fig. 2b. MFB-DBS treatment (DBS-On) did not influence the total activity (horizontal +

vertical) in both CUS and Non-CUS animals as compared to that in the non-stimulated animals (DBS-Off).

No significant change was seen in body weight of animals subjected to CUS procedure and after application of MFB-DBS compared to their respective control groups (Table 1).

Effect of MFB-DBS on ACTH and CRP Concentrations in Plasma and CSF Samples

A significant increase in the plasma and CSF levels of ACTH was observed following 42 days of CUS in rats (Fig. 3a, b). MFB-DBS for 7 days significantly reversed the increased levels of ACTH in both plasma and CSF samples ($p < 0.01$ each). Two-way ANOVA revealed a statistically significant interaction between groups [CUS × DBS; $F(1,19) = 8.53$, $p < 0.01$ and $F(1,20) = 14.55$, $p < 0.01$] in plasma and CSF samples, respectively. However, in the Non-CUS groups, ACTH levels were remained in a similar range in both plasma and CSF samples, irrespective of DBS-Off or DBS-On condition (Fig. 3a, b).

We did not observe any change in the plasma and CSF levels of CRP either following 42 days of CUS or application of MFB-DBS for 7 days (Fig.3c, d).

Effect of MFB-DBS on BDNF in Plasma, CSF, Hippocampus, and NAc

BDNF levels were significantly decreased in the plasma [$F(1,20) = 9.43$, $p < 0.006$] and CSF samples $F(1,20) = 15.92$, $p < 0.0008$] of CUS animals as compared to that in Non-CUS control subjects (Fig. 4a, b). Interestingly, application of 7 days of MFB-DBS significantly reversed the decreased plasma ($p < 0.0001$) and CSF ($p < 0.03$) levels of BDNF.

Similarly, a significant decrease in the levels of BDNF was seen in the hippocampus of stressed animals as compared to that in Non-CUS control subjects [$F(1,20) = 23.6$, $p < 0.0001$, Fig. 4c]. Application of MFB-DBS partially reversed these deficits and showed a trend toward an increase of BDNF levels. Two-way ANOVA revealed a significant interaction between CUS and DBS in the MFB [$F(1,20) = 11.93$, $p < 0.002$]. On the other hand, in the NAc samples, while there was a statistically significant interaction between these two interventions [$F(1,20) = 5.08$, $p < 0.05$], the stress exposure and DBS did not have an independent effect on the BDNF levels in NAc (each $p > 0.05$, Fig. 4d).

Effect of MFB-DBS on TNF-α, INF-γ, and IL-1β in Hippocampus and NAc

A significant augmentation was observed in the levels of TNF-α [$F(1,20) = 19.68$, $p < 0.01$] and INF-γ [$F(1,20) = 32.55$, $p < 0.01$] in the hippocampus after 42 days of CUS in

Table 1 Effect of 42 days of CUS and 7 days of MFB-DBS on change in the animal body weights. The animal body weights were recorded weekly once throughout the study duration

Animal groups	Treatment condition	Body weight (g)							
		Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8
		Mean ± S.E.M.	Mean ± S.E.M.	Mean ± S.E.M.	Mean ± S.E.M.	Mean ± S.E.M.	Mean ± S.E.M.	Mean ± S.E.M.	Mean ± S.E.M.
Non-CUS ($n = 24$)	DBS-Off	256.5 ± 5.58	293 ± 8.08	304.69 ± 10.56	343.69 ± 11.85	366.56 ± 13.95	384.05 ± 15.85	407.33 ± 17.77	398.33 ± 20.23
	DBS-On							408.00 ± 17.93	397.00 ± 22.09
CUS ($n = 19$)	DBS-Off	260.38 ± 4.78	277.93 ± 6.20	306.06 ± 7.69	330.43 ± 8.78	356.43 ± 8.70	363.75 ± 12.49	398.17 ± 9.72	395.17 ± 8.36
	DBS-On							393.50 ± 8.33	385.67 ± 4.46

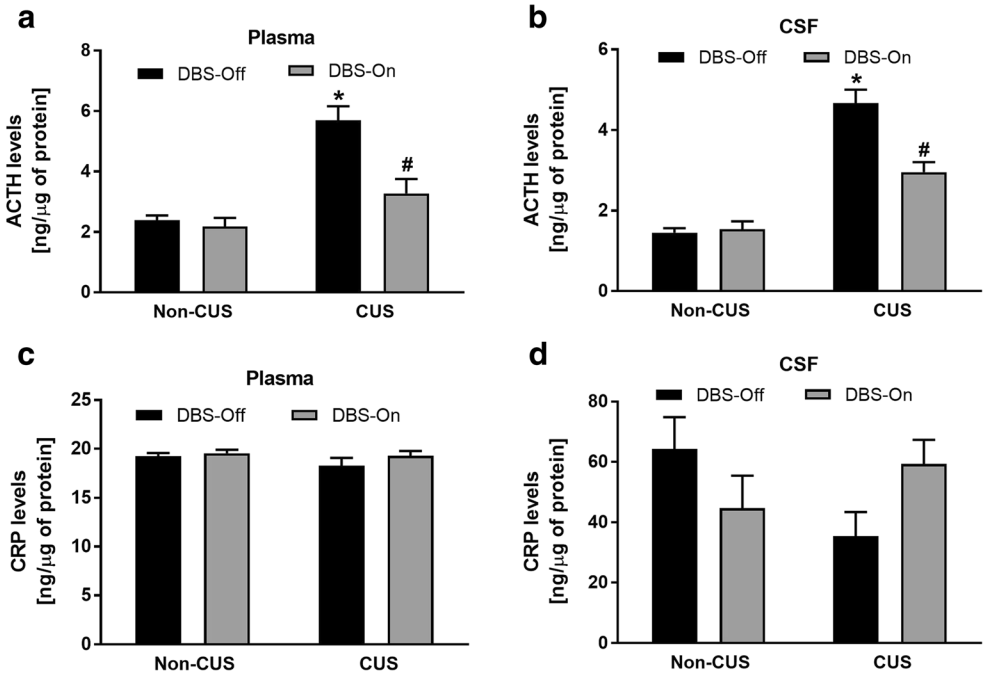


Fig. 3 Effect of 7 days of MFB-DBS on the ACTH (**a**, **b**) and CRP levels (**c**, **d**) measured in the blood plasma and CSF samples (ng/μg of protein) of rat. The Non-CUS and CUS animals were divided into either active DBS group (DBS-On) or DBS-Off group (not exposed to DBS). The DBS parameters were chosen as frequency 130 Hz, amplitude, 200-μA current, and 90-μs pulse width. The MFB-DBS was delivered daily for 8 h for 7 consecutive days. The data are analyzed by two-way analysis of variance (ANOVA) followed by post-hoc Tukey's multiple comparison test. Each bar is the mean ± S.E.M. for six rats. **a** $^{*}p < 0.0001$ vs Non-CUS DBS-Off and $^{\#}p < 0.0009$ vs CUS DBS-Off group, and **b** $^{*}p < 0.0001$ vs Non-CUS DBS-Off and $^{\#}p < 0.0003$ vs CUS DBS-Off group

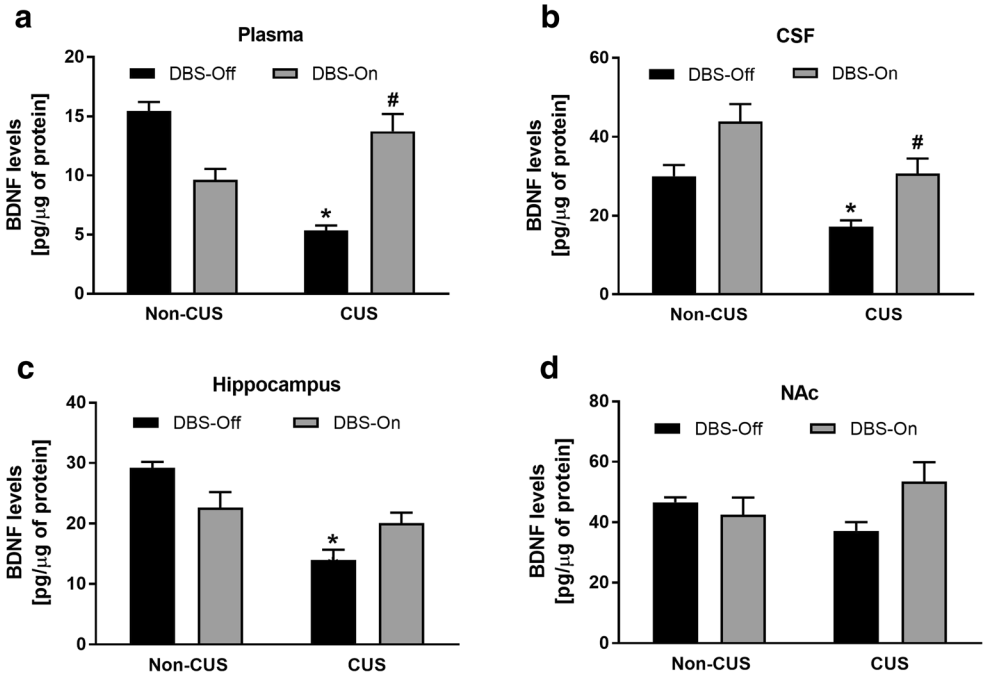


Fig. 4 Effect of 7 days of MFB-DBS on the BDNF levels (pg/μg of protein) measured in the blood plasma (**a**), CSF samples (**b**), hippocampus (**c**), and NAc (**d**) regions of rat. The Non-CUS and CUS animals were divided into either active DBS group (DBS-On) or DBS-Off group (not exposed to DBS). The DBS parameters were chosen as frequency 130 Hz, amplitude, 200-μA current, and 90-μs pulse width. The MFB-DBS was delivered daily for 8 h for 7 consecutive days. The data are analyzed by two-way analysis of variance (ANOVA) followed by post-hoc Tukey's multiple comparison test. Each bar is the mean ± S.E.M. for six rats. **a**, **c** $^{*}p < 0.0001$ vs Non-CUS DBS-Off and $^{\#}p < 0.0001$ vs CUS DBS-Off group, and **b** $^{*}p < 0.04$ vs Non-CUS DBS-Off and $^{\#}p < 0.03$ vs CUS DBS-Off group

rats. Treatment with MFB-DBS did not alter the increased levels of these inflammatory cytokines (Fig. 5a, c). Two-way ANOVA revealed no interaction between stress exposure and DBS on the levels of TNF-α [$F(1,20) = 0.03$, $p > 0.05$] and INF-γ [$F(1,20) = 0.25$, $p > 0.05$] in the hippocampal samples.

In the NAc samples, 42 days of CUS significantly elevated the TNF-α level ($p < 0.01$), and application of MFB-DBS significantly lowered the augmented levels of TNF-α [$F(1,20) = 4.84$, $p < 0.05$; Fig. 5b]. However, two-way ANOVA revealed no interaction between CUS and DBS in the NAc ($p > 0.05$). All the four experimental groups displayed similar levels of INF-γ in the NAc (Fig. 5d).

Compared to Non-CUS animals, rats that underwent 42 days of CUS showed significantly higher levels of IL-1β in the hippocampus ($p < 0.01$, Fig. 5e) and NAc ($p < 0.01$, Fig. 5f). While MFB-DBS for 7 days showed a significant decrease in IL-1β in the hippocampus as compared to those in CUS DBS-Off animals [$F(1,20) = 40.86$, $p < 0.01$], no effect of DBS was seen on IL-1β levels in the NAc [$F(1,20) = 1.13$, $p > 0.05$]. Two-way ANOVA revealed a significant interaction between stress exposure and DBS in the hippocampus [$F(1,20) = 15.22$, $p < 0.01$], and in NAc [$F(1,20) = 6.34$, $p < 0.05$].

Effect of MFB-DBS on IL-2, IL-5, IL-6, IL-7, and IL-18 in Hippocampus and NAc

Forty-two days of CUS dramatically augmented the levels of IL-2 ($p < 0.01$), IL-5 ($p < 0.01$), IL-6 ($p < 0.01$), IL-7 ($p < 0.01$), and IL-18 ($p < 0.05$) in the hippocampus (Fig. 6a, c, e, g, i). While application of MFB-DBS for 7 days did not alter the increased cytokine levels of IL-2, IL-6, and IL-7, a significant decrease was seen in the IL-5 ($p < 0.01$) and IL-18 ($p < 0.05$) cytokines.

In the NAc, a significant augmentation was observed in the levels of IL-6 ($p < 0.05$) and IL-7 ($p < 0.05$) of CUS groups as compared to all Non-CUS animals (Fig. 6f, h). While application of MFB stimulation for 7 days reversed the increased levels of IL-6 [$F(1,20) = 4.95$, $p < 0.05$], no changes were noticed in the levels of IL-7 cytokine [$F(1,20) = 0.58$, $p > 0.05$]. However, levels of IL-2, IL-5, and IL-18 remained similar in range in the NAc across all the studied groups (Fig. 6b, d, j).

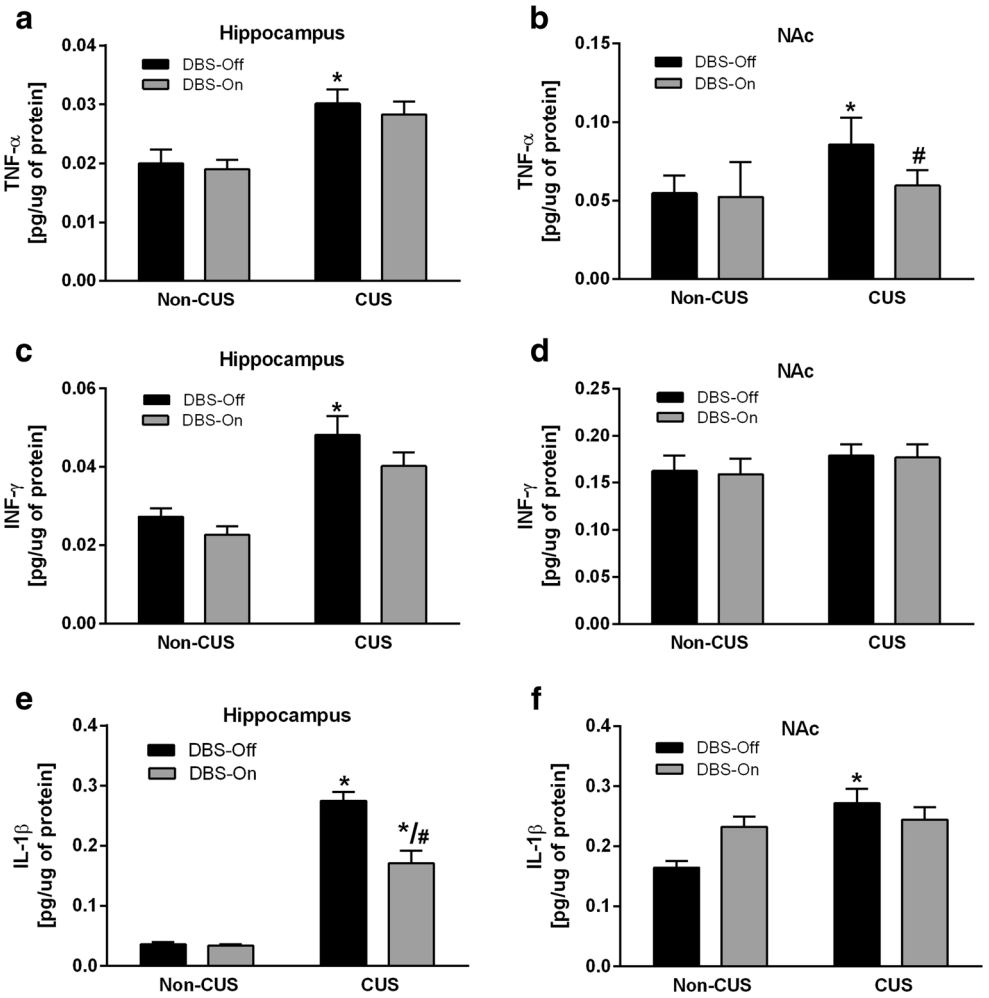


Fig. 5 Effect of 7 days of MFB-DBS on the TNF-α (**a**, **b**), INF-γ (**c**, **d**), and IL-1β (**e**, **f**) levels (pg/μg of protein) in the hippocampus and NAc regions of rat. The Non-CUS and CUS animals were divided into either active DBS group (DBS-On) or DBS-Off group (not exposed to DBS). The DBS parameters were chosen as frequency 130 Hz, amplitude, 200-μA current, and 90-μs pulse width. The MFB-DBS was delivered daily for 8 h for 7 consecutive days. The data are analyzed by two-way analysis of variance (ANOVA) followed by post-hoc Tukey's multiple comparison test. Each bar is the mean ± S.E.M. for six rats. **a** $^{*}p < 0.02$ vs Non-CUS DBS-Off, **b** $^{*}p < 0.01$ vs Non-CUS DBS-Off and $^{\#}p < 0.04$ vs CUS DBS-Off group, **c** $^{*}p < 0.011$ vs Non-CUS DBS-Off, **e** $^{*}p < 0.0001$ vs Non-CUS DBS-Off and $^{\#}p < 0.0001$ vs CUS DBS-Off group, and **f** $^{*}p < 0.003$ vs Non-CUS DBS-Off

Effect of MFB-DBS on IL-1α, IL-4, IL-10, IL-12, IL-13, and IL-17 in Hippocampus and NAc

There was no apparent interaction between stress exposure and DBS or differences between groups (Non-CUS vs CUS) in levels of IL-1α, IL-4, IL-10, IL-12, IL-13, and IL-17 ($p > 0.05$ for each) for both the hippocampus and NAc brain samples (Table 2).

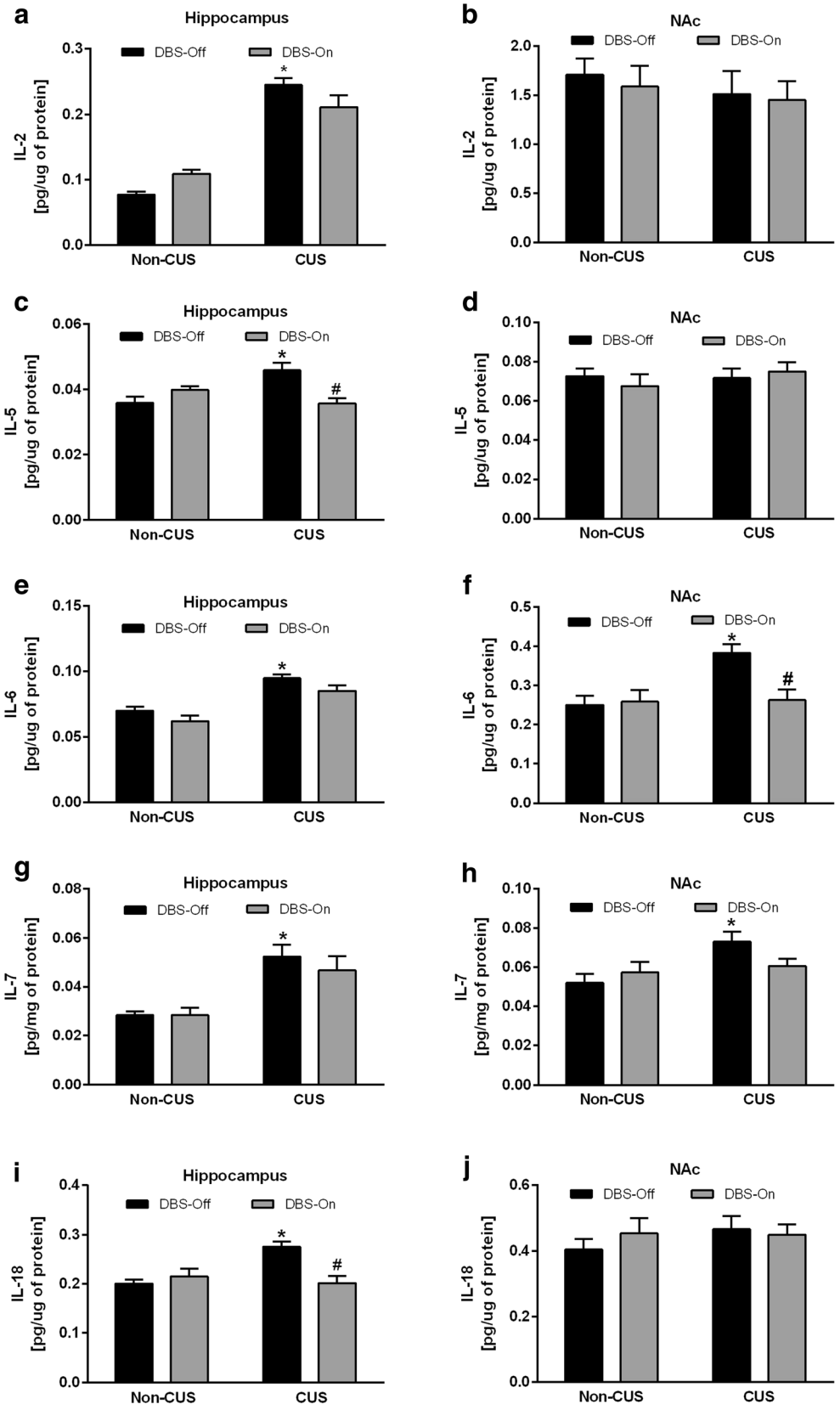
Discussion

Anhedonia is one of the crucial clinical symptoms of depression that represents the decreased ability to experience pleasurable activity. In this study, we observed a significant anhedonic-like behavior in rats subjected to the 42-day CUS protocol, and 7-day treatment with MFB-DBS abrogated these phenotypic changes. Gross locomotor activity and body weight remained in a similar range across the different groups, which negate the possibility of stimulation-induced nonspecific increases in food consumption or preference. The acute antidepressant-like response of MFB-DBS has already been reported in our previous study [21], and also supported by others [26, 74, 75]. Recent open-labeled clinical studies also demonstrated a rapid and long-term antidepressant response after activation of MFB in TRD patients [11, 32, 33]. Our preclinical results ratify this clinical observation and suggest that, at clinically relevant stimulation parameters, MFB-DBS has the potential to undo anhedonic- and depressive-like behaviors.

The most accepted underlying neural mechanisms of antidepressant therapies are linked to monoaminergic systems and neurotrophins [7, 16, 76]. Although the application of MFB-DBS also modulates the dopaminergic system at remote nodes for rescuing depressive-like phenotypes [21, 32, 36, 68], the biological effects of DBS might not exclusively belong to dopaminergic transmission [59, 68, 77]. Moreover, the relatively rapid and robust behavioral response of DBS in the CUS model may preclude the possibility of neurogenesis or neuroplasticity, and therefore the role of other early expressed biomarkers like stress hormones, BDNF, and inflammatory mediators have been anticipated to play a role in the antidepressant effects [20, 54, 78]. In this study, we observed a significant decrease of BDNF levels in both plasma and CSF samples of rats undergoing CUS. Similarly, reduced levels of BDNF were reported in patients with clinical depression [79–81], and stressed rodents [54, 57]. Application of MFB-DBS for 7 days significantly reverted the decreased BDNF profile to normal levels in peripheral and CSF samples. Additionally, we observed an overall decrease level of BDNF in the hippocampus and NAc of CUS rats; the application of MFB-DBS profoundly reversed this neurotrophin to normal level in the former brain structure compared to the latter region. That being said, it is possible that an increase in peripheral and central levels of BDNF might contribute to the effects of DBS on reversal of anhedonic-like phenotype, as evident in our behavioral study. The current literature also supports these findings. Low BDNF expression was reported in hippocampus samples of depressed suicide victims and patients with TRD [76, 82, 83]. Moreover, direct infusion of BDNF into the hippocampus produced an antidepressant response [84], and increased BDNF expression was seen in postmortem tissue of depressed patients who were receiving antidepressant medications [53, 85]. Even in preclinical findings, increased BDNF concentration has been reported in the hippocampus of rats receiving DBS in the vmPFC [20, 54, 57] or in the VTA, NAc, and vPL [19, 55, 64]. Additionally, modulation of BDNF activity following MFB-DBS may be linked to the augmented mitochondrial function [86], as evidenced earlier by Kim et al. [87] after 7 days of NAc-DBS. Also, similar to our observations, the effects of BDNF in the NAc were reported inconsistent [88]. Since application of CUS or intervention with antidepressant agents reported the regional differences in the expression of BDNF [89–91], the region-specific analyses of this neurotrophin in hippocampus (ventral and dorsal sub-regions) and NAc (core and shell parts) would have been helpful. Thus, further investigation on the effects of DBS on BDNF levels at different locations of the brain would be valuable. Based on our results, we speculate that BDNF may be one of the important players in producing anti-anhedonic effects in humans receiving MFB-DBS, as suggested in earlier DBS studies for SCG and vPL targets [19, 20].

As anticipated, increased levels of ACTH were seen in the plasma and CSF samples of rats that underwent CUS as opposed to the control Non-CUS animals. This endorses a successful implementation of our chronic stress-induced depression-like phenotype. Drugs that suppress HPA activation or inhibit the synthesis of glucocorticoids have shown antidepressant effects [92]. Along a similar argument, we have obtained lowered levels of ACTH in the plasma and CSF of animals that received MFB-DBS for 7 days within the CUS group. This biological effect may be linked to increased BDNF concentrations in this group of animals, as these two endogenous substances produced antagonistic effects on hippocampal functions [93–95]. We suggest that there may be a causal relationship between the functional effects of MFB-DBS and a reduction of the stress hormone ACTH and increase of BDNF, but it is too early yet to comment on one precise underlying mechanism for DBS-generated antidepressant effects. However, in contrast to Valkanova et al. [52] analysis in depressed patients, we did not observe any effects of either 42-day CUS or MFB-DBS on the peripheral and CSF concentrations of CRP in rats.

Inflammation may be centrally involved in the pathogenesis of MDD by compromising BDNF, serotonin and



dopaminergic signaling, and impairing synaptic plasticity [96, 97]. The elevated levels of several inflammatory markers and cytokines have been reported in patients with MDD; moreover, depressive symptoms were also abrogated in the

Fig. 6 Effect of 7 days of MFB-DBS on the IL-2 (**a**, **b**), IL-5 (**c**, **d**), IL-6 (**e**, **f**), IL-7 (**g**, **h**), and IL-18 (**i**, **j**) levels (pg/μg of protein) in the hippocampus and NAc regions of rat. The Non-CUS and CUS animals were divided into either active DBS group (DBS-On) or DBS-Off group (not exposed to DBS). The DBS parameters were chosen as frequency 130 Hz, amplitude, 200-μA current, and 90-μs pulse width. The MFB-DBS was delivered daily for 8 h for 7 consecutive days. The data are analyzed by two-way analysis of variance (ANOVA) followed by post-hoc Tukey's multiple comparison test. Each bar is the mean ± S.E.M. for six rats. **a** $*p < 0.0001$ vs Non-CUS DBS-Off, **c** $*p < 0.003$ vs Non-CUS DBS-Off and $^{\#}p < 0.003$ vs CUS DBS-Off group, **e** $*p < 0.0008$ vs Non-CUS DBS-Off, **f** $*p < 0.006$ vs Non-CUS DBS-Off and $^{\#}p < 0.01$ vs CUS DBS-Off group, **g** $*p < 0.003$ vs Non-CUS DBS-Off, **h** $*p < 0.02$ vs Non-CUS DBS-Off, and **i** $*p < 0.002$ vs Non-CUS DBS-Off and $^{\#}p < 0.002$ vs CUS DBS-Off group

presence of anti-inflammatory drugs [98–100]. Similarly, pre-clinical DBS studies demonstrated altered immunity caused by the increased levels of pro-inflammatory IL-1, IL-6, TNF-α, and IFN-γ cytokines following electrical stimulation of the ventromedial hypothalamic nucleus in rats [50]. In the present study, we found dramatic increased levels of cytokines including TNF-α, INF-γ, and IL-1β in the hippocampus and NAc of rats that underwent CUS. Following 7-day treatment with MFB-DBS, increased levels of all these cytokines remained unaltered in both regions except for IL-1β and TNF-α levels, which were significantly reversed in the hippocampus and NAc. Interestingly, the role of inflammatory mediators in the DBS-induced antidepressant effect has also been speculated by Perez-Caballero et al. [51]. Similar to our observations, high baseline levels of TNF-α were found in the blood of treatment-resistance cases and depressed patients [48, 101–105]. Additionally, the functional antagonism of TNF-α resulted in a reduced depressive-like behavior in rats by improving hippocampal levels of BDNF [106, 107], as well as mitigating depression severity in patients with TRD [108, 109]. Similarly, in our study, levels of TNF-α may be associated with the BDNF expression in the hippocampus after MFB-DBS. A recent meta-analysis found the increased levels of IL-1β in the blood and brain samples of patients with suicidal depression compared to healthy subjects [110], which may be linked to impaired hippocampal functions in depressed patients [111]. Similar to ketamine's effects [112], we have noticed decreased expressions of IL-1β within the hippocampus following chronic treatment with MFB-DBS. The enhanced levels of another pro-inflammatory cytokine,

Table 2 Effect of 7 days of MFB-DBS on the IL-1α, IL-4, IL-10, IL-12, IL-13, and IL-17 levels (pg/μg of protein) in the hippocampus and NAc regions of rat. The Non-CUS and CUS animals were divided into either active DBS group (DBS-On) or DBS-Off group (not exposed to DBS). The DBS parameters were chosen as frequency 130 Hz, amplitude, 200-μA current, and 90-μs pulse width. The MFB-DBS was delivered daily for 8 h for 7 consecutive days. The data are analyzed by two-way analysis of variance (ANOVA) followed by post-hoc Tukey's multiple comparison test. Each bar is the mean ± S.E.M. for six rats

Cytokines (pg/μg of protein)	Treatments	Brain regions, $n = 6$	
		Hippocampus (mean ± S.E.M.)	Nucleus accumbens (mean ± S.E.M.)
IL-1α	Non-CUS DBS-Off	0.017 ± 0.0018	0.027 ± 0.0040
	Non-CUS DBS-On	0.018 ± 0.0017	0.025 ± 0.0034
	CUS DBS-Off	0.020 ± 0.0015	0.029 ± 0.0037
	CUS DBS-On	0.017 ± 0.0011	0.024 ± 0.0031
IL-4	Non-CUS DBS-Off	0.007 ± 0.0080	0.013 ± 0.0012
	Non-CUS DBS-On	0.007 ± 0.0003	0.012 ± 0.0010
	CUS DBS-Off	0.008 ± 0.0005	0.014 ± 0.0014
	CUS DBS-On	0.008 ± 0.0004	0.015 ± 0.0018
IL-10	Non-CUS DBS-Off	0.020 ± 0.0011	0.056 ± 0.0037
	Non-CUS DBS-On	0.018 ± 0.0018	0.047 ± 0.0062
	CUS DBS-Off	0.022 ± 0.0019	0.060 ± 0.0046
	CUS DBS-On	0.026 ± 0.0018	0.060 ± 0.0062
IL-12	Non-CUS DBS-Off	0.009 ± 0.0007	0.027 ± 0.0049
	Non-CUS DBS-On	0.009 ± 0.0008	0.025 ± 0.0051
	CUS DBS-Off	0.012 ± 0.0009	0.031 ± 0.0056
	CUS DBS-On	0.123 ± 0.0016	0.027 ± 0.0022
IL-13	Non-CUS DBS-Off	0.016 ± 0.0010	0.037 ± 0.0036
	Non-CUS DBS-On	0.017 ± 0.0013	0.030 ± 0.0070
	CUS DBS-Off	0.017 ± 0.0011	0.039 ± 0.0059
	CUS DBS-On	0.020 ± 0.0020	0.032 ± 0.0047
IL-17	Non-CUS DBS-Off	0.009 ± 0.0008	0.024 ± 0.0020
	Non-CUS DBS-On	0.010 ± 0.0006	0.023 ± 0.0021
	CUS DBS-Off	0.011 ± 0.0003	0.028 ± 0.0033
	CUS DBS-On	0.011 ± 0.0011	0.025 ± 0.0033

IFN-γ, were reverted in patients with depression after ECT and fluoxetine treatment [97, 113, 114]. In our study, the increased levels of IFN-γ in the hippocampus were also partially reversed in the presence of MFB-DBS. Taken together, we suggest a seemingly subtle association between TNF-α, IFN-γ, and IL-1β cytokines and the pathophysiology of MDD as proposed earlier by Haapakoski et al. [115], and treatment of TRD patients with MFB-DBS might help to regulate the levels of these cytokines in the brain.

In addition, elevated levels of other inflammatory cytokines like IL-2, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, and IL-18 have been reported in patients with MDD [47, 116–118]. In multiplex assay, we also noticed increased levels of most of these cytokines including the IL-2, IL-5, IL-6, IL-7, and IL-18 in the hippocampus and/or NAc of rats subjected to 42 days of CUS. Application of MFB-DBS showed a reversal of effect on the increased levels of IL-6, IL-7, and IL-18 cytokines in both these brain structures. Increased levels of IL-6 in the blood and postmortem brain samples of patients with suicidality [110] and TRD [101–103, 105, 119] were associated with decreased psychomotor speed [100]. Increased status of this cytokine was found to be reverted after antidepressant therapy including ketamine in the human [120], and rat hippocampus [112]. Therefore, we speculate an important role of IL-6 cytokine in the underlying mechanism of MFB-DBS-generated antidepressant effect. In contrast, we did not observe any substantial changes in the levels of anti-inflammatory (IL-4, IL-10, IL-12, and IL-13) and pro-inflammatory (IL-1α and IL-17) cytokines either with application of 42 days of CUS or MFB-DBS treatment. In previous reports, IL-4 and IL-10 were correlated with depression severity [121, 122], and differentially expressed in the presence antidepressant treatments [97, 114, 123]. Moreover, it is worthy to note that several neuroinflammatory studies reported a divergent relationship between cytokines and the severity of depression in humans [117, 118, 124–126]. In summary, while most of the pro-inflammatory cytokines were found to be profoundly elevated in the hippocampus and/or NAc regions after 42 days of CUS in rats, MFB-DBS was found to reverse only some of these elevated cytokines levels.

Conclusion

In summary, we employed a CUS animal model to simulate the clinical depression-like endophenotype, which displayed an activated HPA axis, decreased BDNF expression, and augmented cytokines levels in the brain. We then corroborated the therapeutic evidence for DBS of the MFB as a potential target for ameliorating cardinal symptoms of depression using this preclinical paradigm. We also highlighted potential key components underlying the mechanism of action of MFB-DBS. We found a dramatic effect of CUS on the peripheral and central concentrations of ACTH and BDNF, as well as levels of TNF-α, IFN-γ, IL-1β, IL-2, IL-5, IL-6, IL-7, and IL-18 cytokines measured within the hippocampus and NAc regions of rats. Seven-day treatment with MFB-DBS showed an overall reversal on levels of these inflammatory mediators and neurotrophic factor. However, since the importance of cytokines in the regulation of clinical depression is still debatable [97, 126], they may not be necessarily causative "mechanisms of action" per se. Further, clinical investigations are needed to strengthen the precise effects of chronic MFB-DBS treatment on peripheral and central inflammatory mediators.

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Compliance with Ethical Standards

All protocols were approved by the Institutional Animal Welfare Committee of the University of Texas Health Science Center at Houston, Texas, USA.

Conflict of Interest Drs. Albert J. Fenoy and Joao Quevedo reported no biomedical financial interests.

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