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Chronic brain stimulation rewarding experience ameliorates depression-induced cognitive deficits and restores aberrant plasticity in the prefrontal cortex

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ABSTRACT

Background: Major depressive disorder (MDD) is a multifactorial disease which often coexists with cognitive deficits. Depression-induced cognitive deficits are known to be associated with aberrant reward processing, neurochemical and structural alterations. Recent studies have shown that chronic electrical stimulation of brain reward areas induces a robust antidepressant effect. However, the effects of repeated electrical self-stimulation of lateral hypothalamus - medial forebrain bundle (LH-MFB) on depression-induced cognitive deficits and associated neurochemical and structural alterations in the prefrontal cortex (PFC) are unknown.

Objectives: We investigated the effect of chronic rewarding self-stimulation of LH-MFB in neonatal clomipramine (CLI) model of depression. During adulthood, neonatal CLI and saline administered rats were implanted with bilateral electrodes stereotaxically in the LH-MFB and trained to receive intracranial self-stimulation (ICSS) for 14 days. The rats were tested for depressive-like behaviors, learning and memory followed by estimation of PFC volumes, levels of monoamines and its metabolites in the PFC.

Results: We found that chronic ICSS of LH-MFB reverses CLI-induced behavioral despair and anhedonia. Interestingly, self-stimulation normalizes the impaired novel object and location recognition memory in CLI rats. The amelioration of learning impairments in CLI rats was associated with the reversal of volume loss and restoration of monoamine metabolism in the PFC.

Conclusion: We demonstrated that repeated intracranial self-stimulation of LH-MFB ameliorates CLI-induced learning deficits, reverses altered monoamine metabolism and the atrophy of PFC. Our results support the hypothesis that chronic brain stimulation rewarding experience might be evolved as a potential treatment strategy for reversal of learning deficits in depression and associated disorders.

Introduction

Major depressive disorder (MDD) is a multifactorial psychiatric illness characterized by affective symptoms and cognitive deficits. Further, dysfunctional reward pathways are being widely reported in both clinical [1,2] and preclinical studies [3–5]. For instance, the imaging studies on MDD patients widely report the aberrant functioning of nucleus accumbens (NAc) [6], ventral tegmental area (VTA) [7] and extended reward circuits such as lateral hypothalamus (LH) and medial forebrain bundle (MFB) [4]. The deficits in the functioning of reward circuitry have also been reported in numerous animal models of depression [8,9]. Interestingly, deep brain stimulation (DBS) of MFB restores depressive symptoms in humans [10,11] as well as in the animal models of depression [12].

Apart from these affective symptoms, cognitive decline in MDD patients is widely reported. A growing body of evidence suggests the prevalence of depression-associated cognitive dysfunctions in various domains such as visuospatial learning, executive function and attention [13–16]. Further, these cognitive impairments are reported in both young adults [16,17] and aged patients [18]. Notably, a recent clinical study demonstrates that depression-induced cognitive deficits are associated with reward dysfunction

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Abbreviations

5-HIAA	5-hydroxyindoleacetic acid
5-HT	5-hydroxytryptamine
ACC	Anterior cingulate cortex
CLI	Clomipramine
DA	Dopamine
DOPAC	3,4-dihydroxyphenylacetic acid
HPLC	High-performance liquid chromatography
HVA	Homovanillic acid
ICSS	Intracranial self-stimulation
LH	Lateral hypothalamus
LTP	Long term potentiation
MDD	Major depressive disorder
MFB	Medial forebrain bundle
MHPG	3-methoxy-4-hydroxyphenylglycol
NAc	Nucleus accumbens
NE	Norepinephrine
PrL	Prelimbic cortex
VTA	Ventral tegmental area

[19] and disrupted signaling of reward prediction error [20]. Our earlier studies and that of others have demonstrated that depressive and anhedonic-like behaviors in various rodent models are often associated with impaired attention, spatial and non-spatial learning deficits [21–25]. In addition, depression-induced cognitive deficits were known to be accompanied with neurochemical alterations and aberrant structural plasticity in discrete brain regions [22,23,26,27]. Indeed, earlier studies have demonstrated that cognitive impairments in various animal models of depression were reversed by chronic treatment with antidepressants [22–26,28,29].

Although pharmacotherapies reverse affective symptoms and cognitive deficits in MDD patients, the relapse rate following the treatment is very high [30,31]. Thus, it is imperative to study the mechanisms of non-pharmacological approaches. A potential candidate for the non-pharmacological approach is chronic electrical stimulation. The stimulation of brain reward areas is known to elicit robust progressive plasticity which are associated with improved cognitive performance [32–39]. Several studies from our laboratory and others have shown that intracranial self-stimulation (ICSS) of either LH-MFB or substantia nigra (SN)-VTA facilitates learning [32,35,40], enhances synaptic plasticity markers [37], increases levels of monoamines [41], enhances dendritic arborization, spinogenesis, synaptogenesis [36,42–45], and augments expression of *c-Fos* and *Nurr-1* in the hippocampus and prefrontal cortex (PFC) [38,39,46]. Seminal studies on ICSS showed that rewarding brain experience reverses the chronic stress or fornix lesion-induced prefrontal and hippocampal plasticity, neurochemical alterations and associated impairments in learning [33,35,36]. Thus, ICSS is a potential non-pharmacological approach which could modulate the dopaminergic reward system involved in anhedonia as well as facilitate robust plasticity and learning.

In the present study, we used neonatal clomipramine (CLI) model of depression which was originally established by Vogel, Neill, Hagler, Kors [47], and we replicated this model in our laboratory with minor modifications [24]. Serotonin (5-HT) and 5-HT transporter (5-HTT) plays a crucial role during early development and shapes the affective and cognitive behaviors in adulthood [48,49]. The blocking of 5-HTT by tricyclic antidepressants during the sensitive period of development (from postnatal days 2–21) causes serotonergic surge and derange the development of PFC, hippocampus, dorsal raphe and many other regions leading to emergence of depressive-like phenotype with impaired cognitive functioning during adulthood [22,23,48,50–53]. These maladaptive behaviors emerge after long-term discontinuation of 5-HTT blockage, suggesting the derangements in developmental trajectories predispose animals to persistent affective and cognitive symptoms later in life. Further, 5-HTT blockage-induced behavioral anomalies resemble transgenic models with increased serotonergic tone [51,52,54]. Interestingly, several human studies demonstrate that 5-HTT gene-linked polymorphic region (5-HTTLPR) variants particularly *s* allele is known to be associated with reduced 5-HTT functioning and increased emergence and severity of MDD [55,56]. Further, there are associations between *s* allele and reduced gray matter volume of PFC and hippocampus in MDD patients [57–59]. Together, reduced 5-HTT functioning and enhanced serotonin surge during the sensitive period provide a cohesive model of depression, which have developmental origins [60]. Hence, this model is often referred as the developmental model of depression [60]. Moreover, these developmental derangements associated with 5-HTT blockage cannot be mirrored in adult-onset stress-based models such as learned helplessness, chronic mild stress etc.

Although in this model reduced 5-HTT functioning is induced by exogenous neonatal administration of CLI, the early developmental derangement associated with blockage of 5-HTT precipitates affective and cognitive dysfunctions later in life. Further, the symptoms observed by Vogel and others mimic some components of human endogenous depression such as reduced sexual drive [61], anhedonia [22,23], decreased aggression [62], altered REM sleep [63,64] etc. Thus, it was initially proposed as the model of endogenous depression by Vogel et al. [47]. Notably, neonatal CLI-induced depressive-like behaviors were associated with enhanced anxiety [23,51], impaired spatial learning in radial arm maze [23,24], reduced levels of monoamines in the PFC and hippocampus [22,25], altered acetylcholinesterase activity [22], volumetric atrophy in hippocampus [23], hypertrophy of basolateral amygdala [23], reduction of serotonergic cells and 5-HT_{1A} receptor expression in dorsal raphe [50,65], and decreased long-term potentiation (LTP) at CA3-CA1 hippocampal synapses [22,23,25]. We hypothesized that ICSS could be a novel therapy with potential for amelioration of neonatal CLI-induced cognitive deficits and associated changes in the neurochemical and structural alterations in the PFC. Further, bilateral DBS of MFB is known to produce antidepressant and anti-anhedonic effects in animal models of depression [12,66,67]. However, to the best of our knowledge, it is not known whether ICSS of LH-MFB would restore depression-induced impairments in recognition memory, and associated structural and neurochemical alterations in the PFC, which is addressed in the current study.

Material and methods

Animals

Wistar dams were obtained from the Central Animal Research Facility (CARF), National Institute of Mental Health and Neuro Sciences (NIMHANS). 3 days following delivery, the male pups were cross-fostered and the litters were equally distributed ($n = 6$ pups/dam). Male pups with dams were housed in a climate-controlled vivarium with a 12:12 h dark/light cycle. Animals were maintained on *ad libitum* food and water except during experimental and surgical procedure. All the experimental procedures, behavioral analysis except sucrose preference test, and sample collection were performed during the light phase between 10:00 h to 14:00 h. All experimental protocols were approved by the Institutional Animal Ethics Committee and experiments were performed according to the guidelines of the Committee for the Purpose of

Control and Supervision of Experiments on Animals, Government of India. The experiments were started with 128 male Wistar rats. A total of 32 animals were excluded from the study owing to the removal of stereotaxic implants ($n = 9$) and failure to acquire stable ICSS behavior due to misplacement of electrodes ($n = 9$ from CLI group; $n = 8$ from ICSS alone group). Further, neonatal CLI-administered rats failed to exhibit anhedonia ($n = 6$) during baseline sucrose preference test was also excluded from the study.

Experimental design

The experimental timelines are illustrated in Fig. 1. In the present study, we followed a 2 × 2 design, thus yielding 4 groups. (1) Sham Control (SC): Neonatal vehicle (saline) administered rats from postnatal days (PND) 64–66 were subjected to stereotaxic implantation of bipolar electrodes at the level of LH-MFB, bilaterally; (2) CLI: Neonatal clomipramine (CLI) administered rats exhibited depressive-like behaviors at PND 60 and were implanted with bipolar electrodes at the level of LH-MFB, bilaterally and not subjected to stimulation; (3) ICSS alone: Neonatal vehicle administered rats from PND 64–66 were subjected to stereotaxic implantation of bipolar electrodes at the level of LH-MFB, bilaterally and received 15 min of ICSS per site/day for 14 days and (4) CLI + ICSS: CLI rats subjected to ICSS of LH-MFB from PND 77–90.

Induction of depressive-like behavior by neonatal administration of clomipramine

Clomipramine hydrochloride (Sigma-Aldrich, St. Louis, MO, USA) was dissolved in 0.9% saline and administered through subcutaneous route at a dose of 15 mg kg^{-1} body weight twice daily from PND 8–21 and these animals exhibited depressive-like behavior at adulthood (PND 60). The neonatal vehicle control group received the same volume of 0.9% saline twice daily.

Surgery and chronic ICSS treatment

Under ketamine (90 mg kg^{-1}) and xylazine (10 mg kg^{-1}) anesthesia, insulated nichrome bipolar electrode (28 gauge) was implanted bilaterally into LH-MFB with following stereotaxic co-ordinates: anteroposterior: 1.5 to −2.8 mm from bregma, mediolateral: 1.6–1.8 mm and dorsoventral: 8.4–8.5 mm from dura, adopted from Paxinos and Watson rat atlas [69]. The electrodes were secured using stainless steel anchoring screws and dental cement. Following post-surgical recovery, each rat was trained to self-stimulate by pressing a lever, mounted on the wall of modified Skinner's box, connected to a pulse generator. Each pedal press delivered a 0.3 s trains of 100 Hz square waves of current intensity ranging from 100 to 400 μA with a pulse duration of 0.1 ms [35,36,42,43]. Each rat was subjected to screening and shaping for ICSS behavior. The optimum current intensity was determined for each rat and defined as an intensity at which maximum response was elicited without any aversive indications such as vocalization, head nodding, circling, etc. The positive animals were trained to receive a self-stimulation bilaterally for 15 min/site/day on a continuous reinforcement schedule of 1:1 for 14 days. The SC and CLI rats were connected to cables and introduced to Skinner's chamber but no stimulation was delivered. The chamber was cleaned with 70% alcohol following each session. The number of pedal press responses (mean ± SEM, $n = 24$ per group) in ICSS alone and CLI + ICSS rats were 1187 ± 107 and 1173 ± 115, respectively.

Assessment of depressive behaviors

Behavioral despair and anhedonia were evaluated using sucrose preference test (SPT) and forced swim test (FST) as described previously [23,24] (for detailed procedure please see supplementary methods). The locomotor activity was assessed 2 h following FST in an open field apparatus for 20 min to eliminate any false positives.

Assessment of novel object and novel location recognition memory

The novel object recognition (NOR) task was standardized and adopted from our previous study [27]. The novel location recognition (NLR) task was modified and adopted from Ennaceur, Neave, Aggleton [68] (for detailed procedure please see supplementary methods).

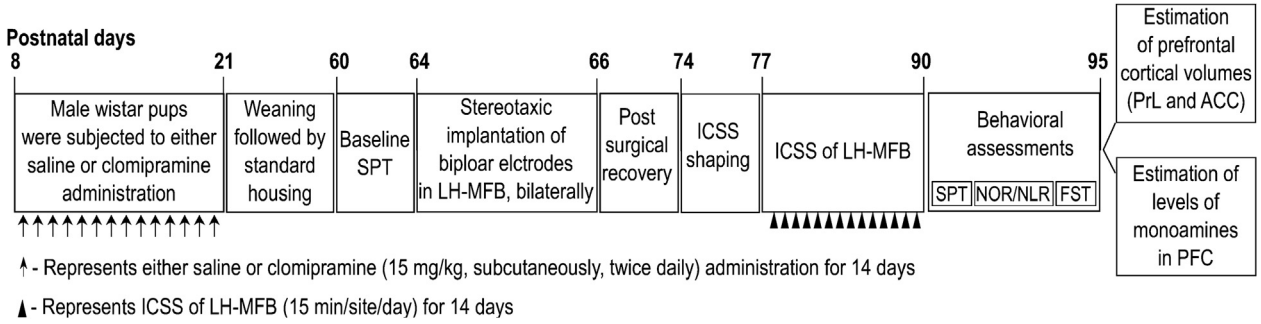

Fig. 1. Schematic representation of experimental design and timelines. Male Wistar pups received either saline or clomipramine (CLI; 15 mg kg^{-1} body weight, subcutaneously, twice daily) injections from postnatal days (PND) 8–21. Following weaning, rats were group housed and reared in standard housing conditions. On postnatal day 60, a baseline sucrose preference test was performed to evaluate the depressive-like behavior. Thereafter, neonatal saline and CLI-administered rats were subjected to stereotaxic surgeries, followed by post-surgical recovery. On PND 74, the neonatal saline administered and CLI rats were subjected to either intracranial self-stimulation (ICSS) shaping or no stimulation. ICSS shaping was completed within three days. Following shaping, rats obtained electrical self-stimulation for 15 min/site/day on a continuous reinforcement schedule of 1:1for 14 days from lateral hypothalamus - medial forebrain bundle (LH-MFB), bilaterally. On postnatal day 91, the animals were subjected to sucrose preference test (SPT, $n = 24$ *per group*) followed by either novel object recognition (NOR, $n = 12$ *per group*) or novel location recognition (NLR; $n = 12$ *per group*) task. Then the animals were subjected to forced swim test (FST, $n = 24$ *per group*). One day following FST, one set of rats ($n = 12$ *per group*) were sacrificed and the volumes of prelimbic (PrL) and anterior cingulate (ACC) subregions of the prefrontal cortex (PFC) were estimated. Another set of rats ($n = 12$ *per group*) were sacrificed, PFC was microdissected and snap frozen in liquid nitrogen and stored in −80 °C for neurochemical analysis using HPLC. The NOR and NLR task were performed in different groups of animals and the data for SPT, FST, volume and HPLC were combined and presented. For correlations, respective data from the cohort of NOR and NLR task were utilized.

Histology

24 h following FST, rats were euthanized and perfused with cold 0.1 M phosphate buffered saline followed by 4% paraformaldehyde in 0.1 M phosphate buffer. The brains were harvested and post-fixed in the same fixative. Every sixth 40 μm thick coronal vibratome sections was obtained through rostrocaudal extent of the prelimbic (PrL, +5.16 mm to +2.52 mm) and anterior cingulate cortex (ACC, +4.20 mm to +2.16 mm) with reference to rat brain atlas [69]. For verification of electrode placements, 50 μm thick coronal sections spanning LH-MFB from Bregma −1.30 to −3.60 mm [69,70] were collected. The sections were stained with cresyl violet as described in our earlier studies [23,71] (for details see supplementary methods). Schematic representation of bilateral electrode placement into the LH-MFB for CLI + ICSS and ICSS alone groups are shown in Fig. 2. Schematic representation of electrode placement for SC and CLI groups are shown in Supplementary Fig. 2.

Stereological procedure

All the slides were coded and analyzed in a blinded manner. The volumes of the PrL and ACC were quantified by unbiased stereology using Cavalieri's principle as described previously [23,27,71,72] (for detailed procedure please see supplementary methods).

Estimation of levels of monoamines and its metabolites in the PFC and hippocampus using high-performance liquid chromatography (HPLC)

The method for estimation of norepinephrine (NE), dopamine (DA) and 5-hydroxytryptamine (5-HT) and its metabolites levels was modified and standardized from Reinhoud, Brouwer, van Heerwaarden, Korte-Bouws [73] (for details see supplementary methods).

Statistical analysis

A two-way ANOVA or paired *t*-test was performed for analyzing the effects of ICSS on CLI-induced alterations. The sources of significance were detected using Tukey's post-hoc test (for details see supplementary methods).

Results

Chronic ICSS of LH-MFB reverses CLI-induced depressive and anhedonic-like behavior

The assessment of baseline anhedonic-like behavior prior to ICSS is shown in Supplementary Table 1. The percentage sucrose preference in CLI rats was significantly lesser as compared to non-depressed control rats ($F_{(1, 92)} = 172.4$, $p < 0.0001$, Supplementary Table 1). A two-way ANOVA of sucrose preference test showed a significant effect of CLI administration ($F_{(1, 92)} = 23.27$, $p < 0.0001$), ICSS ($F_{(1, 92)} = 18.00$, $p < 0.0001$) and interaction ($F_{(1, 92)} = 36.58$, $p < 0.0001$). CLI rats showed a significantly lesser sucrose preference as compared to SC ($p < 0.001$, $d = 2.37$), suggesting anhedonic-like behavior. CLI rats subjected to self-stimulation showed a reversal of anhedonic-like behavior ($p < 0.001$ vs. CLI, $d = 2.01$; Fig. 3A). ICSS alone had no effect on sucrose preference ($p > 0.05$ vs. SC). Further, the baseline water intake remained unaltered among the groups ($p > 0.05$ vs. SC, data not shown).

Similar to SPT, a two-way ANOVA of immobility time following chronic ICSS revealed a significant effect of CLI administration ($F_{(1, 92)} = 25.798$, $p < 0.0001$), ICSS treatment ($F_{(1, 92)} = 23.353$, $p < 0.0001$) and interaction ($F_{(1, 92)} = 19.22$, $p < 0.0001$). Post hoc

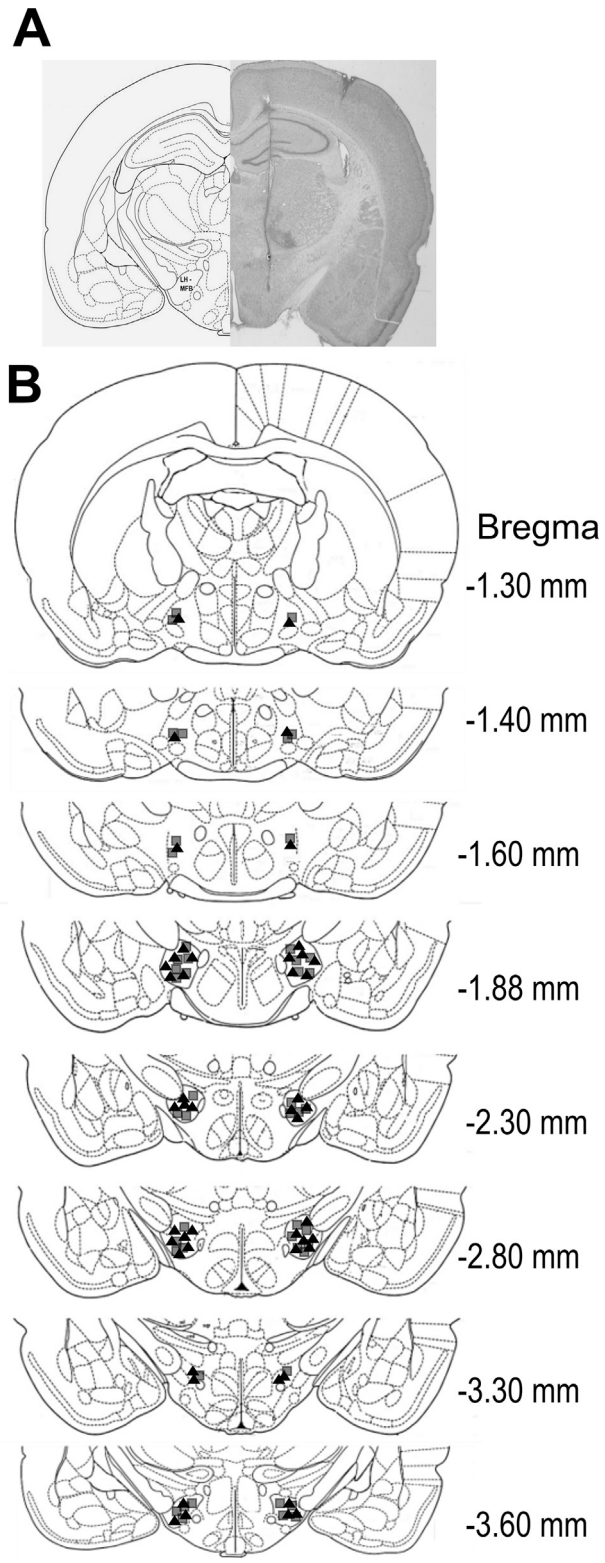

Fig. 2. Schematic diagram showing the placement of bipolar electrodes in the LH-MFB, bilaterally. Representative cresyl-violet stained coronal section showing the electrode in the MFB at the level of LH-MFB (A). Bilateral mapping of electrode placement within LH-MFB for CLI + ICSS and ICSS alone groups ($n = 24$ *per group*, B). Each filled triangle or square represents the location of the bipolar electrode for CLI + ICSS and ICSS alone group, respectively. The placement of electrode tips range between bregma −1.30 to −3.60 mm corresponding to Paxinos and Watson rat atlas [69]. CLI + ICSS: CLI administered rats were subjected to ICSS of LH-MFB for 15 min per site/day for 14 days from PND 77–90; ICSS alone: Neonatal vehicle administered rats from PND 64–66 were subjected to stereotaxic implantation of bipolar electrodes at the level of LH-MFB, bilaterally and received 15 min of ICSS per site/day for 14 days.

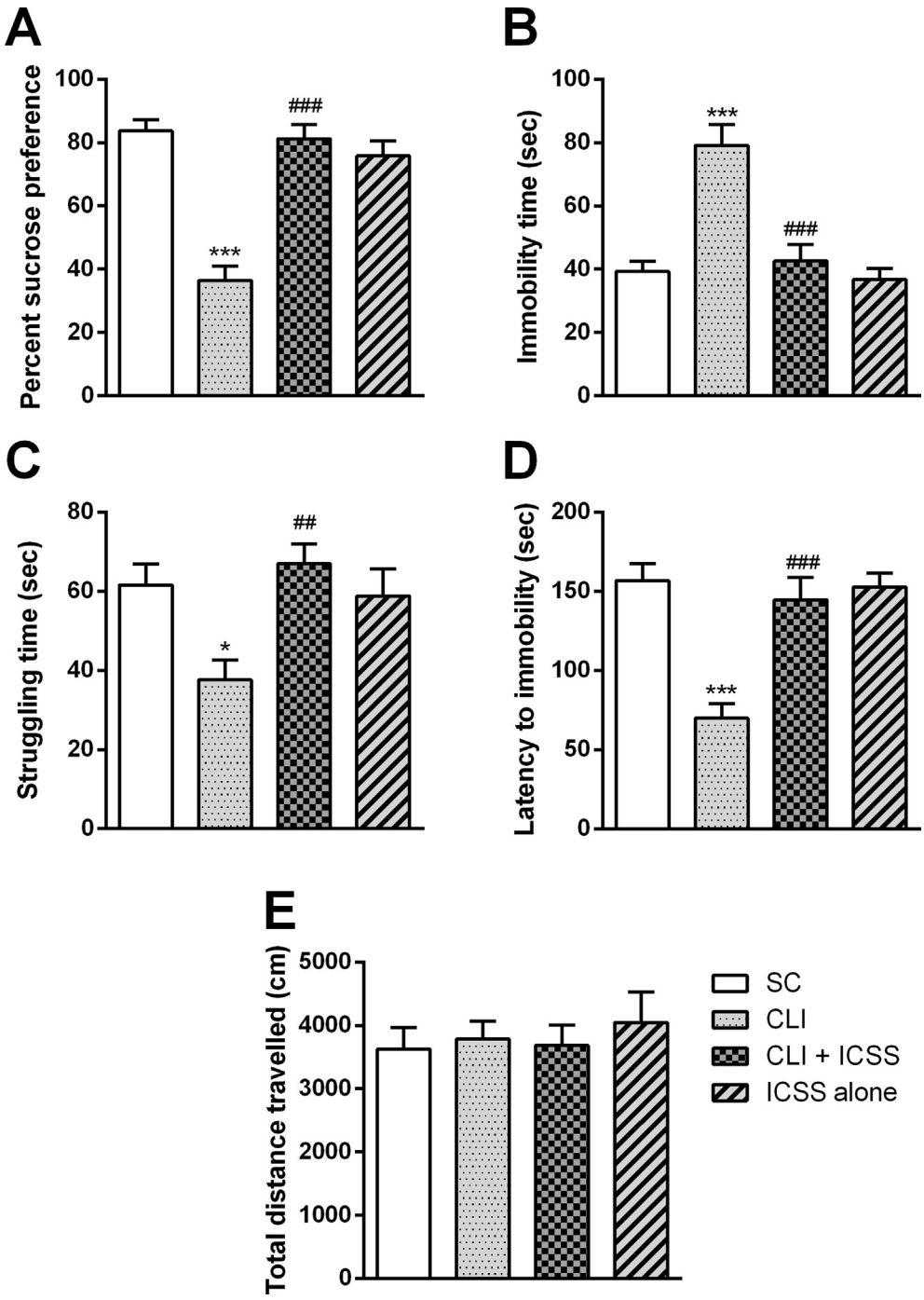

Fig. 3. Chronic self-stimulation of LH-MFB reverses CLI-induced depressive-like behaviors. ICSS reverses the anhedonic-like behavior (A), enhanced immobility time (B), reduced struggling time (C) and decreased latency to immobility (D) in CLI administered rats. Locomotor activity (E) remains unaffected. Data are expressed as Mean ± SEM. SC: Sham Control (Neonatal vehicle (saline) administered rats from PND 64–66 were subjected to stereotaxic implantation of bipolar electrodes at the level of LH-MFB, bilaterally); CLI: Neonatal clomipramine administered rats exhibited depressive-like behaviors at PND 60 and were implanted with bipolar electrodes at the level of LH-MFB, bilaterally and not subjected to stimulation); CLI + ICSS: CLI administered rats were subjected to ICSS of LH-MFB for 15 min per site/day for 14 days from PND 77–90; ICSS alone: Neonatal vehicle administered rats from PND 64–66 were subjected to stereotaxic implantation of bipolar electrodes at the level of LH-MFB, bilaterally and received 15 min of ICSS per site/day for 14 days. $^{***}p < 0.001$, $^{*}p < 0.05$ vs. SC, $^{###}p < 0.001$, $^{##}p < 0.01$ vs. CLI, two-way ANOVA followed by Tukey's post hoc test ($n = 24$ *per group*).

comparisons suggested that CLI rats had significantly higher immobility time as compared to SC ($p < 0.001$, $d = 2.16$; Fig. 3B). Interestingly, CLI rats subjected to ICSS showed a comparable immobility time as that of SC, indicating reversal of behavioral despair ($p < 0.001$ vs. CLI, $d = 2.01$). Repeated ICSS alone for 14 days had no effect on immobility time ($p > 0.05$ vs. SC). Further, analysis of struggling time revealed a significant effect of ICSS treatment ($F_{(1, 92)} = 5.74$, $p < 0.05$) and interaction ($F_{(1, 92)} = 8.41$, $p < 0.01$). Post hoc analysis revealed that CLI rats had significantly lower struggling time as compared to SC ($p < 0.05$, $d = 1.09$; Fig. 3C). CLI rats subjected to ICSS treatment showed an increase in struggling time ($p < 0.01$ vs. CLI, $d = 1.22$). A two-way ANOVA of latency to immobility revealed a significant effect of CLI administration ($F_{(1, 92)} = 21.35$, $p < 0.001$), ICSS treatment ($F_{(1, 92)} = 9.57$, $p < 0.001$) and

interaction $F_{(1, 92)} = 12.01$, $p < 0.001$). Post hoc analysis revealed that CLI rats had significantly lesser latency to immobility as compared to SC ($p < 0.001$, $d = 2.27$; Fig. 3D). CLI rats following ICSS treatment showed an increase in latency ($p < 0.001$ vs. CLI, $d = 1.93$). ICSS alone had no effect on struggling time and latency to immobility ($p > 0.05$ vs. SC). Further, there was no significant effect of ICSS or CLI administration on the swimming time ($p > 0.05$ vs. SC, data not shown). Additionally, we did not observe change in locomotor activity in any of the experimental groups ($p > 0.05$ vs. SC, Fig. 3E), suggesting the antidepressant-like effects of ICSS on FST was free from confounding factors.

Chronic ICSS ameliorates CLI-induced deficits in novel object recognition memory

Following SPT, we performed NOR task to evaluate the effect of chronic ICSS on CLI-induced alterations in non-spatial memory. Fig. 4 shows the representative spatial maps (A), time spent with novel and familiar objects (B) and discrimination indices (C) during the test phase. A paired Student's *t*-test revealed that SC rats explored the novel object for a significantly longer time as compared to the familiar object ($t_{(11)} = 5.57$, $p < 0.001$ vs. familiar object). CLI administered rats showed an impaired ability to discriminate between the novel and familiar object ($t_{(11)} = 1.89$, $p > 0.05$ vs. familiar object), indicating diminished recognition memory. Interestingly, CLI rats subjected to chronic ICSS performed significantly better by spending more time in exploring novel object ($t_{(11)} = 10.89$, $p < 0.001$ vs. familiar object). Rats subjected to ICSS showed an enhanced recognition memory as compared to SC. Rats subjected to ICSS spent significantly more time with novel object as compared to familiar ($t_{(11)} = 8.16$, $p < 0.001$ vs. familiar object; Fig. 4B). In addition, we have compared the intergroup difference between time spent with novel and familiar object during test phase using two-way ANOVA. We found that ICSS rats spent significantly more time with novel and familiar objects as compared to CLI rats ($p < 0.001$). The total exploration time during test phase remains unaltered among groups (Table 1). The rats subjected to ICSS and their respective sham controls spent almost equal time exploring identical copy of the objects during familiarization phase (for all groups, $p > 0.05$ vs. object 2; data not shown).

A two-way ANOVA of discrimination index revealed a significant effect of CLI administration ($F_{(1, 44)} = 76.76$, $p < 0.0001$), ICSS ($F_{(1, 44)} = 80.64$, $p < 0.0001$) and interaction ($F_{(1, 44)} = 6.12$, $p < 0.05$). Tukey's post-hoc comparisons indicated that CLI rats had a

Table 1
Total exploration time during the test session of novel object recognition task.

Total object exploration time (sec)			
SC	CLI	CLI + ICSS	ICSS alone
110.06 ± 12.73	115.11 ± 12.95	104.50 ± 7.79	122.80 ± 12.16

Data are expressed as Mean ± SEM. SC: Sham Control (Neonatal vehicle (saline) administered rats from PND 64–66 were subjected to stereotaxic implantation of bipolar electrodes at the level of LH-MFB, bilaterally); CLI: Neonatal clomipramine administered rats exhibited depressive-like behaviors at PND 60 and were implanted with bipolar electrodes at the level of LH-MFB, bilaterally and not subjected to stimulation); CLI + ICSS: CLI administered rats were subjected to ICSS of LH-MFB for 15 min per site/day for 14 days from PND 77–90; ICSS alone: Neonatal vehicle administered rats from PND 64–66 were subjected to stereotaxic implantation of bipolar electrodes at the level of LH-MFB, bilaterally and received 15 min of ICSS per site/day for 14 days (*n = 12 per group*).

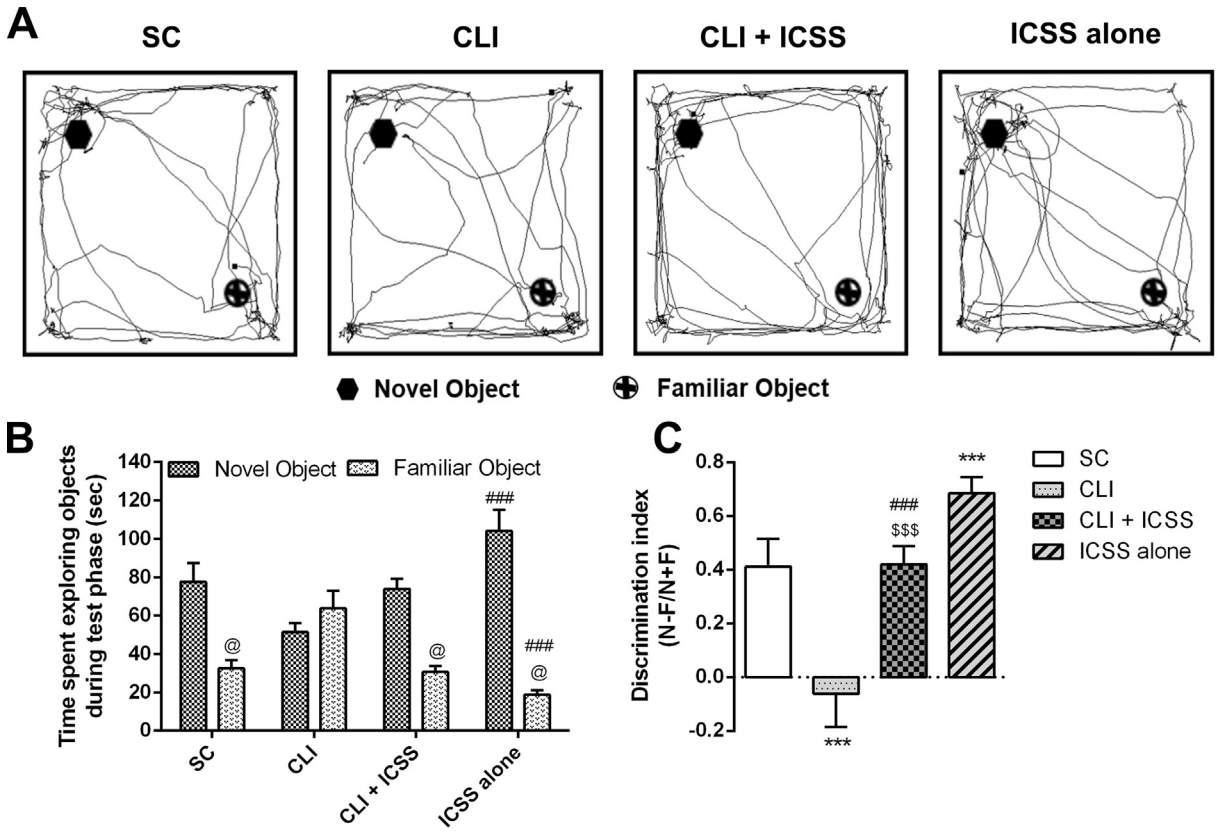

Fig. 4. Chronic ICSS of LH-MFB ameliorates CLI-induced impairment in novel object recognition memory. Representative spatial maps (A), time spent with novel and familiar objects during test phase (B) and discrimination index (C). Data are expressed as Mean ± SEM. Groups as described in Fig. 3. $^{@}p < 0.001$ vs. familiar object, Paired *t*-test; $^{***}p < 0.001$ vs. SC, $^{###}p < 0.001$ vs. CLI, $^{$$$}p < 0.001$ vs. ICSS alone, two-way ANOVA followed by Tukey's post hoc test (*n = 12 per group*).

significant decline in discrimination index ($p < 0.001$ vs. SC, $d = 2.63$; Fig. 4C). Chronic ICSS treatment significantly reversed the CLI-induced impairment in discrimination index, suggesting restoration of recognition memory ($p < 0.001$ vs. CLI, $d = 3.08$). Rats subjected to ICSS showed an increase in discrimination index, signifying a procognitive effect ($p < 0.001$ vs. SC).

Chronic ICSS ameliorates CLI-induced deficits in object location memory

In a separate cohort of rats, we assessed anhedonia and then subjected the rats to NLR task, to evaluate the effect of chronic ICSS on CLI-induced alterations in spatial memory. Fig. 5 shows the representative spatial maps (A), time spent with objects at novel and familiar locations (B) and discrimination indices (C) during the test phase. A paired Student's *t*-test revealed that SC rats explored object at novel location for a significantly longer time as compared to object at familiar location ($t_{(11)} = 5.01$, $p < 0.001$). CLI rats showed an impaired ability to discriminate between objects at novel and familiar location ($t_{(11)} = 1.28$, $p > 0.05$ vs. familiar location), indicating diminished novel location memory. Interestingly, CLI rats subjected to chronic ICSS performed significantly better by spending more time in exploring object at novel location ($t_{(11)} = 6.56$, $p < 0.001$ vs. familiar location). Rats subjected to ICSS spent significantly more time with object at novel location ($t_{(11)} = 5.80$, $p < 0.001$ vs. familiar location; Fig. 5B), suggesting procognitive effects of ICSS on location memory. The total exploration time during test phase remains unaltered among groups (Table 2). The rats subjected to ICSS and their respective sham controls spent almost equal time exploring identical copy of the objects placed in location 1 and 2 during familiarization phase (for all groups, $p > 0.05$ vs. location 2; data not shown).

A two-way ANOVA of discrimination index revealed a significant effect of CLI administration ($F_{(1, 44)} = 81.95$, $p < 0.0001$), ICSS ($F_{(1, 44)} = 141.7$, $p < 0.0001$) and interaction ($F_{(1, 44)} = 24.46$, $p < 0.0001$). Tukey's post-hoc comparisons indicated that CLI rats had a significant decline in discrimination index ($p < 0.001$ vs. SC, $d = 4.22$; Fig. 5C). Chronic ICSS treatment significantly reversed the CLI-induced impairment in discrimination index, suggesting restoration of location memory ($p < 0.001$ vs. CLI, $d = 5.41$). Rats subjected

Table 2
Total exploration time during the test session of novel location recognition task.

Total object exploration time (sec)			
SC	CLI	CLI + ICSS	ICSS alone
104.60 ± 16.68	96.86 ± 7.83	95.31 ± 12.28	106.25 ± 15.65

Data are expressed as Mean ± SEM. SC: Sham Control (Neonatal vehicle (saline) administered rats from PND 64–66 were subjected to stereotaxic implantation of bipolar electrodes at the level of LH-MFB, bilaterally); CLI: Neonatal clomipramine administered rats exhibited depressive-like behaviors at PND 60 and were implanted with bipolar electrodes at the level of LH-MFB, bilaterally and not subjected to stimulation); CLI + ICSS: CLI administered rats were subjected to ICSS of LH-MFB for 15 min per site/day for 14 days from PND 77–90; ICSS alone: Neonatal vehicle administered rats from PND 64–66 were subjected to stereotaxic implantation of bipolar electrodes at the level of LH-MFB, bilaterally and received 15 min of ICSS per site/day for 14 days (*n = 12 per group*).

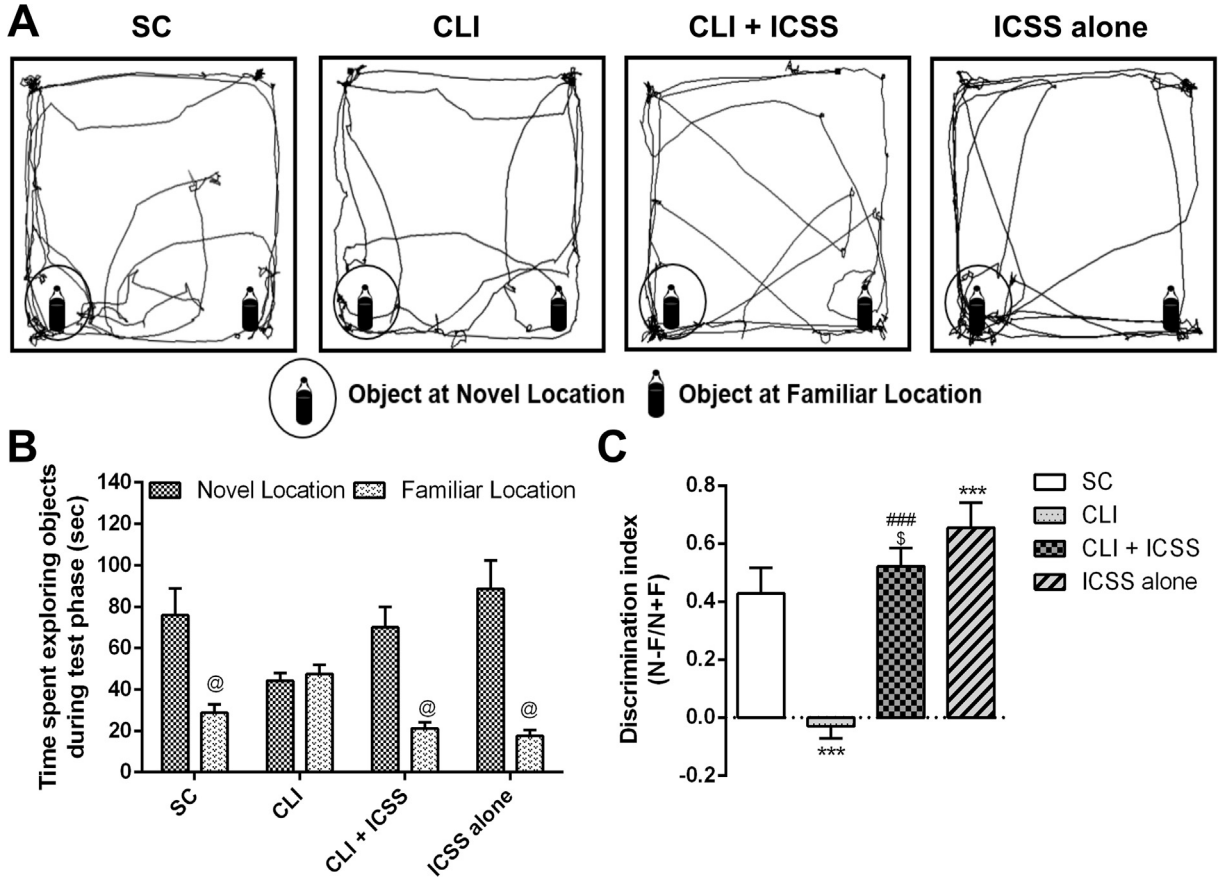

Fig. 5. Chronic ICSS of LH-MFB reverses CLI-induced impairment in object location memory. Representative spatial maps (A), time spent with objects at the novel and familiar location during test phase (B) and discrimination index (C). Data are expressed as Mean ± SEM. Groups as described in Fig. 3. $^{@}p < 0.001$ vs. familiar location, Paired *t*-test; $^{***}p < 0.001$ vs. SC, $^{###}p < 0.001$ vs. CLI, $^{\$}p < 0.05$ vs. ICSS alone, two-way ANOVA followed by Tukey's post hoc test (*n = 12 per group*).

to ICSS showed an increase in discrimination index, signifying enhanced spatial memory ($p < 0.001$ vs. SC).

ICSS restores CLI-induced volume loss in the PFC

To evaluate the morphological correlates of impaired novel object and location recognition memory, we estimated the volumes of PrL (Fig. 6A) and ACC (Fig. 6B) using Cavalieri's principle. A two-way ANOVA of volumes indicated a significant effect of CLI administration (PrL: $F_{(1, 44)} = 111.4$, $p < 0.0001$; ACC: $F_{(1, 44)} = 149.7$, $p < 0.0001$) and ICSS (PrL: $F_{(1, 44)} = 185.1$, $p < 0.0001$; ACC: $F_{(1, 44)} = 79.00$, $p < 0.001$). The post hoc analysis revealed that CLI rats had a significant reduction in the volume of PrL ($p < 0.001$, $d = 3.72$) and ACC ($p < 0.001$, $d = 6.17$) as compared to SC. Interestingly, repeated ICSS of MFB ameliorated CLI-induced volume loss in PrL and ACC (both, $p < 0.001$ vs. CLI, $d = 4.55$, 2.88 respectively; Fig. 6A and B). Further, we observed a significant increase in the volumes of PrL and ACC in rats subjected to ICSS (both, $p < 0.01$ vs. SC). Remarkably, we found a significant correlation between novel object recognition memory and volumetric alterations in the PrL ($r = 0.92$, $r^2 = 0.84$, $p < 0.001$, Fig. 8A) and ACC ($r = 0.84$, $r^2 = 0.72$, $p < 0.001$, Fig. 8B) subregions of PFC. Furthermore, deficits in novel location memory were also correlated with volume loss in the PrL ($r = 0.89$, $r^2 = 0.80$, $p < 0.001$, Fig. 9A) and ACC ($r = 0.85$, $r^2 = 0.73$, $p < 0.001$, Fig. 9B).

ICSS restores CLI-induced alterations in the levels of monoamines and its metabolites in the PFC

24 h following FST, we estimated the levels of monoamines and its metabolites in the PFC (Fig. 7). A two-way ANOVA of levels of monoamines and its metabolites in the PFC indicated a significant effect of CLI administration (NE: $F_{(1, 44)} = 48.94$, $p < 0.0001$; MHPG/NE ratio: $F_{(1, 44)} = 22.08$, $p < 0.01$; DA: $F_{(1, 44)} = 29.39$, $p < 0.0001$; DOPAC + HVA/DA ratio: $F_{(1, 44)} = 63.30$, $p < 0.0001$; 5-HT: $F_{(1, 44)} = 25.01$, $p < 0.001$; 5-HIAA/5-HT ratio: $F_{(1, 44)} = 4.61$, $p < 0.05$) and ICSS treatment (NE: $F_{(1, 44)} = 54.59$, $p < 0.0001$; MHPG/NE ratio: $F_{(1, 44)} = 11.38$, $p < 0.001$; DA: $F_{(1, 44)} = 59.50$, $p < 0.0001$; DOPAC + HVA/DA ratio: $F_{(1, 44)} = 44.60$, $p < 0.0001$; 5-HT: $F_{(1, 44)} = 51.65$, $p < 0.0001$; 5-HIAA/5-HT ratio: $F_{(1, 44)} = 2.18$, $p = 0.14$).

Post-hoc analysis indicated that CLI rats had a significant decrease in NE ($p < 0.01$, $d = 3.86$, Fig. 7A), DA ($p < 0.01$, $d = 3.29$, Fig. 7C) and 5-HT ($p < 0.001$, $d = 2.67$, Fig. 7E) levels in the PFC as compared to SC. ICSS treatment significantly reversed CLI-induced decline in levels of NE ($p < 0.01$, $d = 2.52$), DA ($p < 0.01$, $d = 1.81$) and 5-HT ($p < 0.001$, $d = 2.93$) as compared to CLI rats. Further, NE ($p < 0.01$), DA ($p < 0.001$) and 5-HT ($p < 0.05$) levels were higher in the rats subjected to ICSS as compared to SC. In addition to monoamine levels, we found that CLI rats had a significant increase in MHPG/NE ratio ($p < 0.001$, $d = 3.02$, Fig. 7B), DOPAC + HVA/DA ratio ($p < 0.001$, $d = 4.35$, Fig. 7D) and 5−HIAA/5-HT ratio ($p < 0.01$, $d = 1.47$, Fig. 7F), suggesting enhanced catabolism of the monoamines in the PFC. The ICSS treatment completely restored the CLI-induced changes in the metabolism of the monoamines in the PFC (all, $p < 0.01$ vs. CLI). Interestingly, we found a significant correlation between novel object recognition memory and neurochemical changes in the PFC (MHPG/NE ratio: $r = -0.29$, $r^2 = 0.22$, $p < 0.05$, Fig. 8C; DOPAC + HVA/DA ratio: $r = -0.64$, $r^2 = 0.42$, $p < 0.001$, Fig. 8D; 5-HIAA/5-HT: $r = -0.32$, $r^2 = 0.25$, $p < 0.05$, Fig. 8E). Similarly, the performance of rats in novel location test were correlated with neurochemical changes in the PFC (MHPG/NE ratio: $r = -0.77$, $r^2 = 0.60$, $p < 0.001$, Fig. 9C; DOPAC + HVA/DA ratio: $r = -0.85$, $r^2 = 0.73$, $p < 0.001$, Fig. 9D; 5-HIAA/5-HT: $r = -0.56$, $r^2 = 0.31$, $p < 0.01$, Fig. 9E). Furthermore, the increase in behavioral despair or anhedonia were correlated to the performance in novel object ($r = -0.71$, $r^2 = 0.51$, $p < 0.001$, Fig. 8F) and novel location recognition ($r = 0.45$, $r^2 = 0.15$, $p < 0.01$, Fig. 9F) task, respectively.

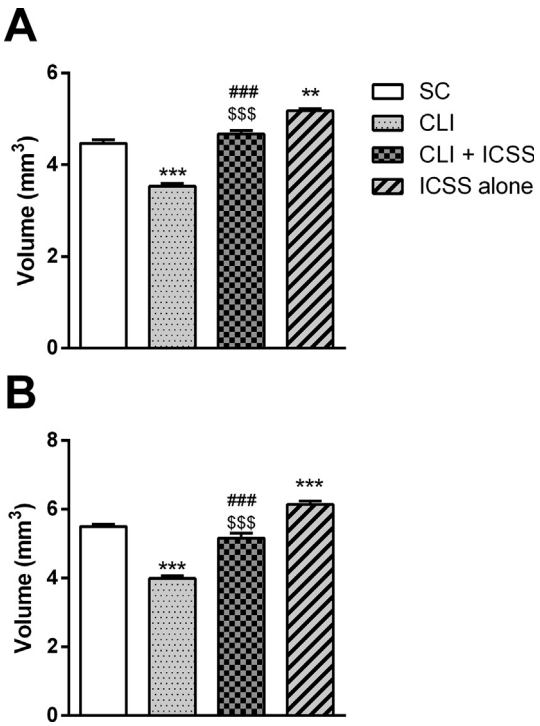

Fig. 6. CLI-induced volume loss in the PFC was reversed by ICSS of LH-MFB. Volumes of the PrL (A) and ACC (B). Data are expressed as Mean ± SEM. Groups as described in Fig. 3. $^{***}p < 0.001$, $^{**}p < 0.01$ vs. SC, $^{###}p < 0.001$ vs. CLI, $^{$$$}p < 0.001$ vs. ICSS alone, two-way ANOVA followed by Tukey's post hoc test ($n = 12$ *per group*).

Discussion

Numerous clinical reports demonstrate that chronic stimulation of MFB ameliorates depression and anhedonia [1,74]. Extending the clinical observations, we provide mechanistic evidences for beneficial effects of chronic ICSS of LH-MFB on CLI-induced spatial and non-spatial learning impairments. In addition, several clinical [20,75] and preclinical [3,76] studies on depression have demonstrated a profound decline in reward processing leading to anhedonia. Notably, these reward dysfunctions were associated with cognitive decline in MDD patients [19] as well as in several preclinical models of depression [22,23,26]. Here, we show that repeated electrical self-stimulation of LH-MFB ameliorates behavioral despair and anhedonia in neonatal CLI model of depression. Further, we demonstrate for the first time that impairments in novel object and location recognition memory were completely restored by ICSS in a neonatal CLI model of depression. The improved learning in CLI rats following ICSS was associated with restoration of PFC volumes and neurochemical deficits in the PFC.

Although several clinical studies demonstrate the therapeutic potential and efficacy of chronic electrical stimulation of MFB for depressive disorders, few emphasize on the mechanisms associated with it. Thus, preclinical studies elucidating the structural and neurochemical correlates of improved mood and cognition following repeated self-stimulation of LH-MFB are imperative. In concordance with earlier preclinical studies [12,66,67], we found that self-stimulation of LH-MFB improves affective symptoms in neonatal CLI model of depression. Indeed, stimulation of MFB improves affective symptoms including anhedonia in MDD patients [1,11,74]. We selected LH-MFB as a target for stimulation as it has

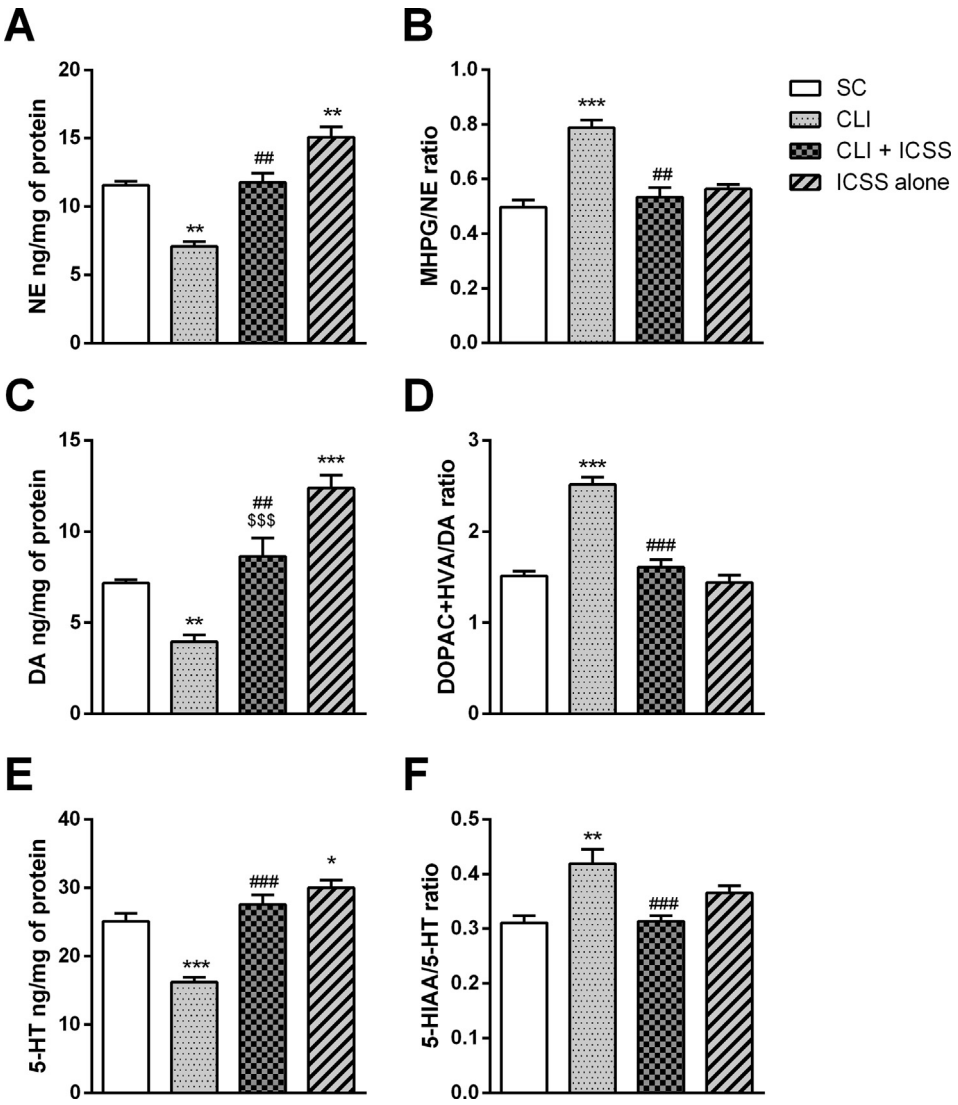

Fig. 7. Repeated ICSS of LH-MFB restores CLI-induced alterations in the levels of monoamines and its metabolites in the PFC. The effect of ICSS on depression-induced changes in the norepinephrine (NE, A), MHPG/NE ratio (B), dopamine (DA, C), DOPAC + HVA/DA ratio (D), 5-hydroxytryptamine (5-HT, E) and 5HIAA/5-HT ratio (F) in the PFC. Data are expressed as Mean ± SEM. Groups as described in Fig. 3. $^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$ vs. SC, $^{\#\#\#}p < 0.001$, $^{\#\#}p < 0.01$ vs. CLI, $^{\$\$\$}p < 0.001$ vs. ICSS alone, two-way ANOVA followed by Tukey's post hoc test ($n = 12$ *per group*).

intense connections with PFC [77,78] and other limbic areas including the hippocampus and VTA [79]. Further, depressive disorders are multifactorial in nature and we believe that the therapeutic approach to combat depression should also be multitargeted. Remarkably, MFB can interact with multiple neurotransmitter systems, regulatory peptides, receptors and thus, can produce robust progressive plasticity [79,80].

MDD is known to be associated with cognitive decline. The NOR task was utilized for assessment of non-spatial working memory [68]. Whereas, NLR task was used to assess spatial working memory [68]. Thus, in the present study, we evaluated two components of learning. These tasks were selected as they are relatively low-stress paradigm. Further, both are free from external motivation, reward or punishment and thus comparable to human cognitive test [81]. Moreover, these tasks robustly evaluate non-spatial and spatial learning [81,82]. Presently, the effect of neonatal CLI administration on recognition memory in adulthood is unknown. Therefore, in the present study, we attempted to evaluate recognition memory in neonatal CLI model of depression. We found that CLI rats had a significant decline in novel object recognition memory, indicating impaired non-spatial learning. Further, CLI rats showed an impairment in object location memory suggesting deficits in spatial learning. Indeed, impairment in novel object recognition and location memory has been reported in both genetic [83–85] and stress-based [27,86–89] models of depression. On similar lines, our earlier studies have demonstrated that neonatal administration of CLI causes profound spatial learning deficits in partially baited radial arm maze test [22–25]. Likewise, neonatal blockage of 5-HTT leads to impaired fear extinction learning and recall [53]. In addition, neonatal administration of citalopram decreases social novelty-seeking behavior at postnatal days 30 and 60 [90]. Moreover, deficits in recognition memory and recall are widely reported in MDD patients [91]. Interestingly, the CLI-induced decline in novel object and location recognition memory were reversed by chronic ICSS of LH-MFB. A recent study demonstrates that chronic stimulation of MFB in Flinders Sensitive Line (FSL) rats improves spatial learning in double H maze [92]. Numerous studies suggest that stimulation of fornix or PFC ameliorates cognitive decline in Alzheimer's disease and other neurogenerative disorders [93,94]. In the present study, we selected MFB

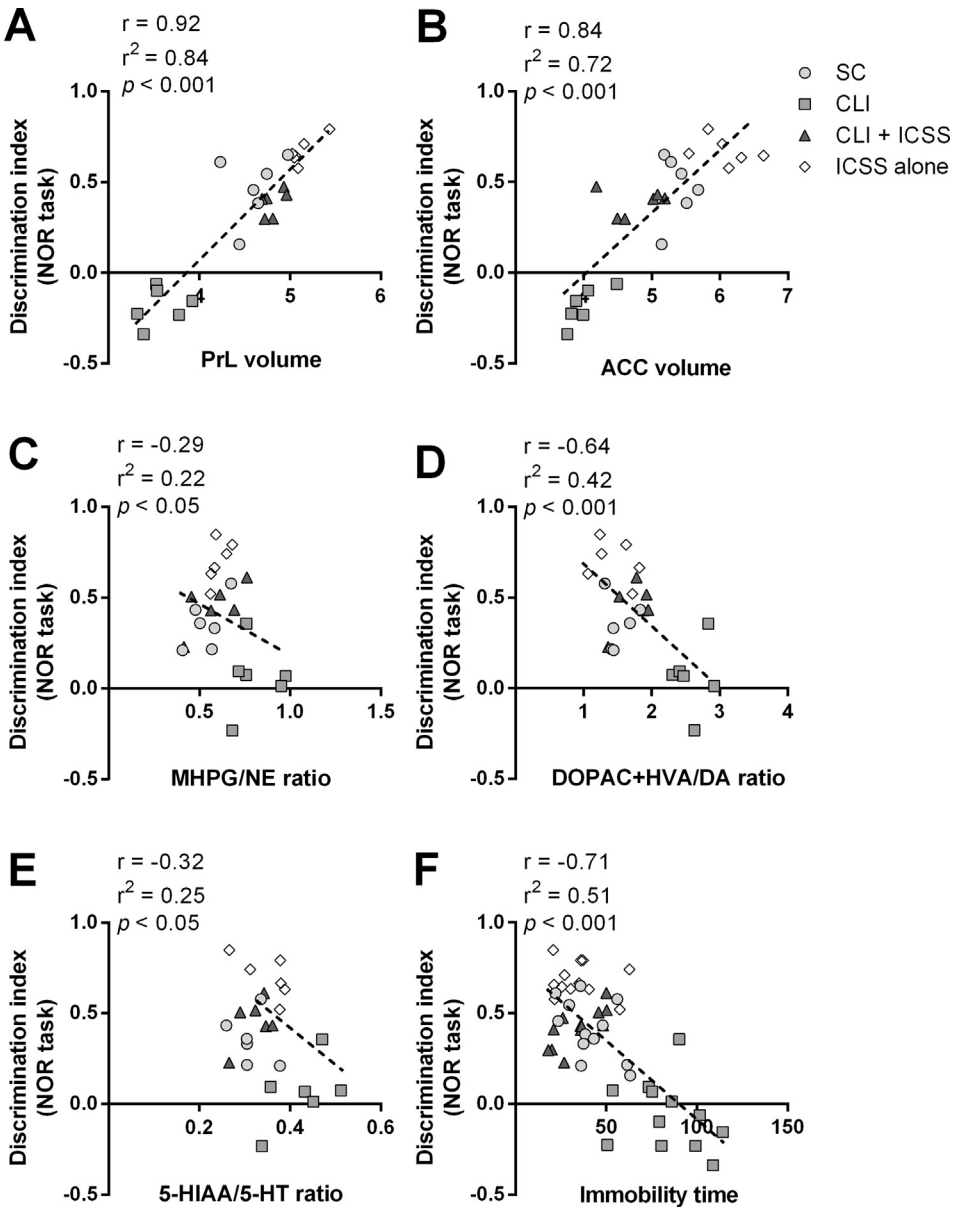

Fig. 8. Correlation between novel object recognition memory and alterations in the PFC. Correlation between discrimination index in NOR task and volumes of PrL (A), ACC (B); MHPG/NE ratio (C), DOPAC + HVA/DA ratio (D) and 5-HIAA/5-HT ratio (E) in the PFC. Correlation between behavioral despair and recognition memory (F). Groups as described in Fig. 3.

as a target because it is known to produce rapid and long-lasting antidepressant effects both in humans [11,74] and animal models of depression [12]. To the best of our knowledge, this is the first study to demonstrate that ICSS of LH-MFB ameliorates non-spatial and spatial learning deficits in a neonatal CLI model of depression. Additionally, we observed a procognitive effect of LH-MFB self-stimulation in saline administered rats. The procognitive effects of LH-MFB self-stimulation have been demonstrated in many previous studies [32,33,39,40,45,95]. Further, this enhanced learning in self-stimulated rats was associated with increased levels of neurotransmitters, spine density, synapses and dendritic arborization [34–36,41–44]. Together, we demonstrate that repeated self-stimulation of LH-MFB ameliorates affective symptoms and learning deficits in a neonatal CLI model of depression.

Functional abnormalities in the PFC are often associated with despair behavior, anhedonia and emotional reactivity - the core features of depression [76,96]. These impaired prefrontal cortical functions following depression cause learning deficits. For instance, impaired autobiographic memory and cognitive speed in depressed patients were associated with poor activation and/or reduced grey matter volumes of PFC [97–99]. Similarly, in many preclinical studies affective symptoms and cognitive decline were associated with reduced trophic support, neurochemical deficits and reduced volume in the PFC [22,26,100–102]. Further, PFC is involved in pathophysiological changes in reward processing during MDD [103,104]. Here, we demonstrate that neonatal CLI administration causes a reduction in the volumes of PrL and ACC subregions of the PFC. Our results are in concordance with earlier studies which demonstrated a significant decline of PFC volumes in MDD patients [7,99,105,106] as well as in various animal models of depression [102,107,108]. The observed decrease in the volumes is plausible due to dendritic retraction [35,109], reduced spinogenesis [110],

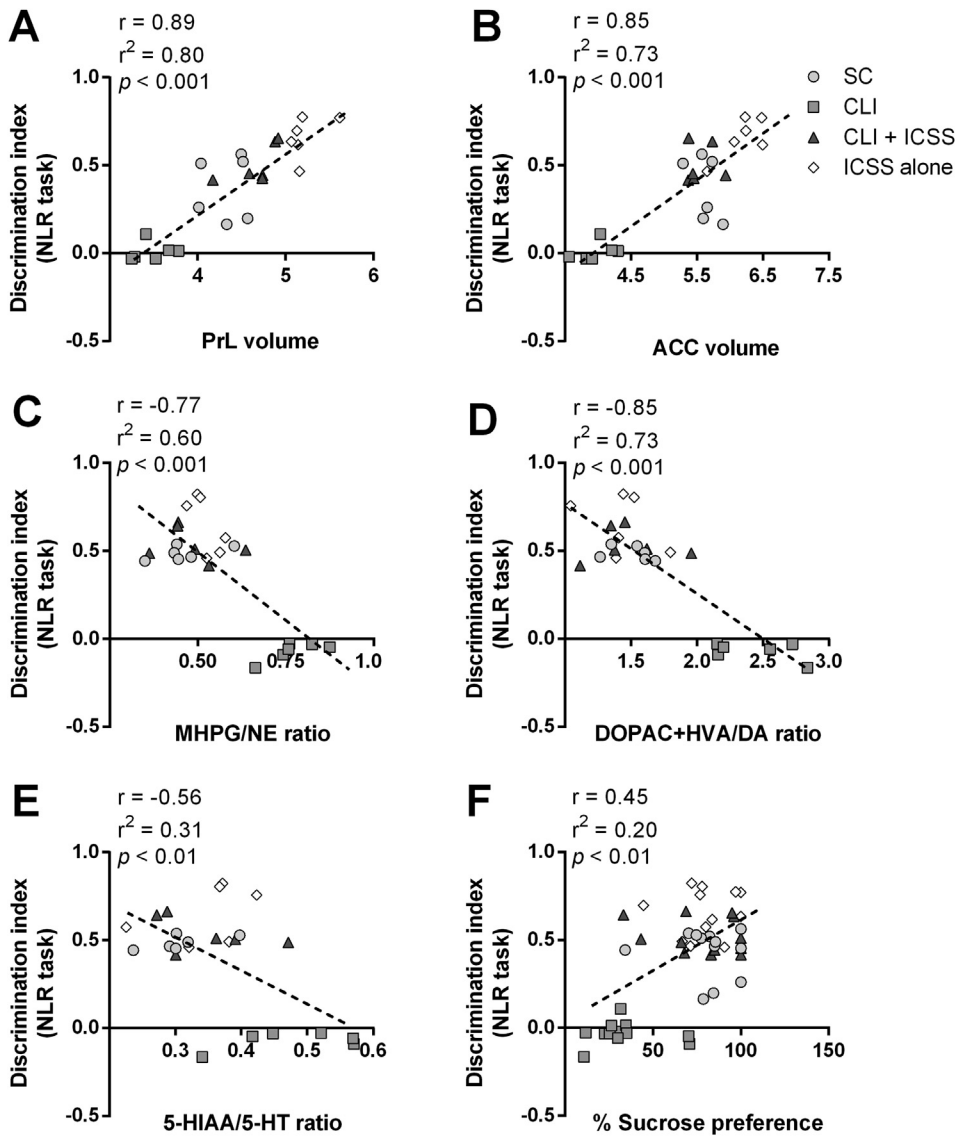

Fig. 9. Correlation between novel location recognition memory and alterations in the PFC. Correlation between discrimination index in NLR task and volumes of PrL (A), ACC (B); MHPG/NE ratio (C), DOPAC + HVA/DA ratio (D) and 5-HIAA/5-HT ratio (E) in the PFC. Correlation between anhedonia and recognition memory (F). Groups as described in Fig. 3.

loss of synapses [111] and/or glial loss [27,112] in the PFC. Remarkably, ICSS of LH-MFB reverses the CLI-induced volume loss in the PFC. Indeed, a recent study shows that electrical stimulation of PFC causes robust structural changes in the hippocampus, thalamus and increases angiogenesis, glial and synaptic density [113]. Furthermore, the reversal of CLI-induced PFC volume loss significantly correlated with improved mood and performance in NOR and NLR task. Of note, recognition memory involves a complex interaction between prefrontal-hippocampal-perirhinal neuronal networks [82,114,115]. In context with wider literature, the prefrontal-hippocampal circuitry is involved in novel location recognition, whereas perirhinal cortex and hippocampus are involved in novel object recognition. In a seminal study by Weible, Rowland, Pang, Kentros [116], they demonstrated that neuronal firing in the PFC particularly ACC is involved in the novel object recognition memory. For instance, some neurons fire near to identical objects during familiarization phase of NOR, and when the familiar object was replaced with a novel object, the rate of firing in these neurons was doubled. Further, the firing pattern was decreased near familiar object and increased near novel object. Interestingly, another set of neurons fired exclusively near familiar object. Thus, this demonstrates that PFC neurons can be effectively activated during novel object recognition. Moreover, they also demonstrate a similar kind of firing response during the NLR task, suggesting the involvement of PFC.

Remarkably, a recent study demonstrates that chemogenetic inhibition of PFC (involving PrL cortex) following familiarization phase impairs recognition memory in both NOR and NLR task [117]. Furthermore, through series of experiments, they showed that concurrent subthreshold inactivation of PFC and hippocampus impairs NOR and NLR memory [117]. This indicates that PFC and hippocampus are involved independently as well as in combination for consolidation of recognition memory in NOR and NLR task. On similar lines, enhanced c-fos was observed in PFC when rats were exposed to NOR task [118,119]. Moreover, PFC is crucially involved in novelty-seeking behavior [120–122]. Recently, we demonstrated that astroglial loss in the PrL and ACC were correlated with impaired novel object recognition memory following stress [27]. In contrast to above studies, the lesion of PFC did not impair the novel object and location recognition memory [68,114]. However, the

lesion of cingulate cortex impairs the novel location recognition memory [68]. Together, these studies suggest that PFC might be important for information processing pertaining to the object, and it is possible that PFC can mediate some of the aspects of novel object and location recognition memory with other limbic structures.

Accordingly, it is possible that ICSS-induced reversal of recognition memory deficits in CLI rats might be due to the restoration of PFC functioning. Moreover, ICSS-induced increase in the volumes of PFC in neonatal vehicle-administered rats might be associated with procognitive effects. Thus, we speculate that amelioration of CLI-induced reward processing deficits by ICSS of LH-MFB could modulate the structure and function of the PFC. Given that recognition memory is not a unitary process and attributed to activation of multiple neuronal circuits including PFC and hippocampus, we speculate that improved NOR/NLR performance following ICSS of CLI-administered rats might also involve hippocampal circuitry. Interestingly, chronic stress-induced morphological changes in CA3 region of the hippocampus were reversed by chronic ICSS treatment [36]. Further, ICSS alone is known to increase spine density, dendritic branching, neurogenesis and several plasticity markers in the hippocampus [34,36,43,44,46,123]. Consequently, it is possible that ICSS-induced improved learning in CLI rats might be attributed to increased progressive plasticity in both PFC and hippocampus. Moreover, the procognitive effect of ICSS alone could be mediated via prefrontal and/or hippocampal networks.

Several studies on animal models of depression have consisted demonstrated that monoaminergic deficits in PFC were associated learning impairments. For instance, hypodopaminergic states in the PFC were associated with persistent depressive behavior and cognitive deficits [22,124,125]. Further, the decrease in DA levels was accompanied with profound dendritic retraction and cognitive decline [35,36]. Similarly, NE and its downstream effectors are crucially involved in depression associated pathology [126,127]. Optimum levels of NE are required for the maintenance of cognitive function and mood [128,129]. Furthermore, impairment in the serotonergic system is widely reported in anxiety and depressive disorders [130,131]. Serotonergic circuitry in the PFC determines the susceptibility to mood-related disorders in adulthood [48,53].

In the present study, we found a significant decrease in NE, DA and 5-HT levels in the PFC following CLI administration. CLI rats also had a significant increase in neurotransmitter to metabolite ratio, suggesting enhanced catabolism of the monoamines in the PFC. Remarkably, chronic ICSS of LH-MFB reverses CLI-induced neurochemical alterations in the PFC. Several studies demonstrate that chronic stimulation of either nucleus accumbens, VTA, PFC or lateral habenula restores monoamine levels in various animal models of depression [35,132–134]. Additionally, chronic self-stimulation of LH-MFB alone also produced a significant increase in NE and DA levels in the PFC. Our observations are consistent with several studies which show that ICSS of VTA and/or LH-MFB in naïve rats produces a robust increase in NE and DA levels [35,36,41].

We speculated that restoration of monoamines levels and its metabolism in the PFC of CLI rats following ICSS might have improved learning. Indeed, we observed a significant correlation between the beneficial effect of ICSS on recognition memory and monoamine metabolism in the PFC. Although we correlated neurochemical changes in PFC with NOR/NLR memory, it is possible that the positive effects of ICSS might also involve the hippocampus. Moreover, our earlier studies demonstrate that ICSS ameliorates stress-induced cognitive deficits by reversal of monoamine deficits in both PFC and hippocampus [35,36]. Furthermore, ICSS alone increases hippocampal monoamine levels [41], suggesting the potential involvement of hippocampal circuitry in ICSS-mediated enhanced learning and memory.

Conclusions

Together, we demonstrate that repeated self-stimulation of LH-MFB ameliorates recognition memory deficits in a neonatal CLI model of depression. Further, improved recognition memory following ICSS treatment was associated with restoration of volumes and neurochemical changes in the PFC. The present study provides the structural and neurochemical correlates of improved recognition memory in CLI rats following chronic ICSS of LH-MFB. We speculate that brain stimulation rewarding experience could be evolved as a potential therapeutic strategy to treat affective disorders and associated cognitive deficits.

Contributions

S.C., T.R.R., and B.S.S.R. conceptualized and designed the experiments; S.C. and S.J.T. performed the experiments and analyzed the data; S.C., S.J.T., B.N.S, T.R.R., and B.S.S.R. wrote the manuscript.

Compliance with ethical standards

Conflict of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2019.01.020.

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