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Review

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Input-output specific orchestration of aversive valence in lateral habenula during stress dynamics

Taida HUANG[1,2,3,4], Xiaonan GUO[2], Xiaomin HUANG[4], Chenju YI[4,5,6]✉, Yihui CUI[2,3]✉, Yiyan DONG[1]✉

[1]*Department of Neurology and International Institutes of Medicine, The Fourth Affiliated Hospital, Zhejiang University School of Medicine, Yiwu 322000, China*
[2]*Department of Neurology of Sir Run Run Shaw Hospital and School of Brain Science and Brain Medicine, Zhejiang University School of Medicine, Hangzhou 310058, China*
[3]*NHC and CAMS Key Laboratory of Medical Neurobiology, MOE Frontier Science Center for Brain Science and Brain-Machine Integration, Zhejiang University, Hangzhou 310058, China*
[4]*Research Centre, The Seventh Affiliated Hospital, Sun Yat-sen University, Shenzhen 518107, China*
[5]*Guangdong Provincial Key Laboratory of Brain Function and Disease, Guangzhou 510080, China*
[6]*Shenzhen Key Laboratory of Chinese Medicine Active substance screening and Translational Research, Shenzhen, 518107, China*

Abstract: Stress has been considered as a major risk factor for depressive disorders, triggering depression onset via inducing persistent dysfunctions in specialized brain regions and neural circuits. Among various regions across the brain, the lateral habenula (LHb) serves as a critical hub for processing aversive information during the dynamic process of stress accumulation, thus having been implicated in the pathogenesis of depression. LHb neurons integrate aversive valence conveyed by distinct upstream inputs, many of which selectively innervate the medial part (LHbM) or lateral part (LHbL) of LHb. LHb subregions also separately assign aversive valence via dissociable projections to the downstream targets in the midbrain which provides feedback loops. Despite these strides, the spatiotemporal dynamics of LHb-centric neural circuits remain elusive during the progression of depression-like state under stress. In this review, we attempt to describe a framework in which LHb orchestrates aversive valence via the input-output specific neuronal architecture. Notably, a physiological form of Hebbian plasticity in LHb under multiple stressors has been unveiled to incubate neuronal hyperactivity in an input-specific manner, which causally encodes chronic stress experience and drives depression onset. Collectively, the recent progress and future efforts in elucidating LHb circuits shed light on early interventions and circuit-specific antidepressant therapies.

Key words: Lateral habenula; Neural circuits; Aversion; Stress dynamics; Depression-like state; Head-to-head comparison

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1 Introduction

Compelling evidence has considered stressful events as the major risk factors for depressive disorders. Meanwhile, stress is inevitable in our daily life. Although short-term exposure to moderate stress promotes motivation and memory, chronic stress exerts deleterious effects on the human brain and causes depression onset (McEwen, 1998; McEwen et al., 2015).

Commonly involved in stressful events, aversive valence is processed within specialized neural circuits across the brain (Malezieux et al., 2023; Parekh et al., 2022; Russo and Nestler, 2013). During chronic stress, persistent maladaptations of specific neural circuits underlie the pathogenesis of depression. Accumulating evidence suggests an essential and common role of the lateral habenula (LHb) in encoding aversion and depression-like state, ranging from zebrafish to rodents and to humans (Amo et al., 2014; Andalman et al., 2019;

✉ Chenju YI, yichj@mail.sysu.edu.cn
Yihui CUI, yihuicui@zju.edu.cn
Yiyan DONG, yiyandong@zju.edu.cn
Chenju YI, https://orcid.org/0000-0002-8686-4525
Yihui CUI, https://orcid.org/0000-0002-7362-6237
Yiyan DONG, https://orcid.org/0000-0002-4664-4579
Taida HUANG, https://orcid.org/0009-0000-5781-226X

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Caldecotthazard et al., 1988; Cerniauskas et al., 2019; Cui et al., 2019; Cui et al., 2018a; Cui et al., 2018b; Hikosaka, 2010; Hu et al., 2020; Huang et al., 2019; Lecca et al., 2016; Li et al., 2011; Li et al., 2013; Matsumoto and Hikosaka, 2007, 2009; Morris et al., 1999; Proulx et al., 2014; Shabel et al., 2019; Stamatakis and Stuber, 2012; Tian and Uchida, 2015; Wang et al., 2017; Wirtshafter et al., 1994; Yang et al., 2018; Zheng et al., 2022). However, during the accumulation of stress and the progressive development of depression-like state, the spatiotemporal dynamics of LHb-centric neural circuits remain elusive. In this review, we attempt to delineate a framework in which LHb orchestrates aversive valence in an input-output specific manner.

2 Neuronal hyperactivity and burst firing in the LHb as common biomarkers of depression-like state

LHb neurons are predominantly glutamatergic and spontaneously active, mainly classified into three distinct firing patterns: silent, tonic, and burst (Cui et al., 2019; Cui et al., 2018a; Cui et al., 2018b; Hu et al., 2020; Weiss and Veh, 2011; Wilcox et al., 1988; Yang et al., 2018). Tonic neurons fire with single action potentials (APs), while burst neurons typically fire with a cluster of high-frequency (~100 Hz) APs. Compared with silent and tonic neurons, burst neurons exhibit more hyperpolarized resting membrane potentials (RMP), which elicit burst firings (Chang and Kim, 2004; Weiss and Veh, 2011) via the sequential activation of T-type voltage-sensitive calcium channels (T-VSCCs) and N-methyl-D-aspartate receptors (NMDARs) (Cui et al., 2019; Cui et al., 2018a; Cui et al., 2018b; Yang et al., 2018).

Accumulating evidence has identified the neuronal hyperactivity of LHb as a common biomarker of depression-like state (Andalman et al., 2019; Caldecotthazard et al., 1988; Cerniauskas et al., 2019; Cui et al., 2019; Cui et al., 2018a; Cui et al., 2018b; Hu et al., 2020; Huang et al., 2019; Lecca et al., 2016; Li et al., 2011; Li et al., 2013; Morris et al., 1999; Proulx et al., 2018; Yang et al., 2018; Zheng et al., 2022). However, the neuronal coding mechanisms underlying depression remain elusive. Intriguingly, recent studies have unraveled that LHb burst firing encodes depression-like state. In various animal models of depression induced by chronic stress, the LHb burst firing activity is consistently increased in both *in vitro* brain slices and *in vivo* freely moving animals (Cerniauskas et al., 2019; Cui et al., 2019; Cui et al., 2018a; Cui et al., 2018b; Hu et al., 2020; Huang et al., 2019; Seo et al., 2018; Yang et al., 2018; Zhang et al., 2023). Furthermore, the causality between LHb burst and depression-like state has been substantiated via bidirectional manipulations. Optogenetic induction of LHb burst in naïve mice instantly recapitulates depression-like behaviors under chronic stress, whereas the blockade of LHb burst exerts rapid antidepressant effects (Cui et al., 2019; Cui et al., 2018a; Hu et al., 2020; Yang et al., 2018).

Notably, the drastically increased burst firings in LHb are probably attributed to the enhanced function of astrocytic Kir4.1, an inwardly rectifying potassium channel (Cui et al., 2018b). Kir4.1 is expressed at the astrocytic processes which tightly surround the neuronal soma in LHb, buffering excessive extracellular potassium ions due to neuronal firings. In depression-like animals, overexpressed Kir4.1 augments the effect of potassium buffering, subsequently hyperpolarizing LHb neurons and driving burst firings (Cui et al., 2018a; Cui et al., 2018b; Hu et al., 2020). Despite such progress, it remains unclear what drives the upregulation of Kir4.1 during the accumulation of chronic stress and the progression of depression-like state. Plausibly, enhanced LHb neuronal activity during stress drives the compensatory upregulation of astrocytic Kir4.1 for maintaining neuronal homeostasis. Therefore, chronic stress repeatedly evokes Kir4.1 upregulation and finally causes the decompensation of Kir4.1 overexpression and enhanced LHb burst.

3 Input-specific integration of aversive valence in LHb subregions

The LHb receives extensive inputs mainly from the basal forebrain and the midbrain (Herkenham and Nauta, 1977; Hu et al., 2020; Proulx et al., 2014; Zahm and Root, 2017). Notably, multiple upstream inputs selectively project to different LHb subregions. The entopeduncular nucleus (EPN) (Cerniauskas et al., 2019; Shabel et al., 2012; Stephenson-Jones et al., 2016) and the central amygdala (CeA) (Zhou et al., 2019) specifically project to the lateral part of LHb (LHbL). In contrast, the medial part of LHb (LHbM) receives inputs selectively from the medial septum (MS) (Zhang et al., 2018a), the bed nucleus of stria terminalis (BNST)

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(Lecca et al., 2023), the median raphe nucleus (MRN) (Szonyi et al., 2019), and glutamate neurons in the lateral preoptic area (LPO) (Barker et al., 2017).

Numerous studies have suggested that various upstream regions convey aversive information onto LHb (Amo et al., 2014; Barker et al., 2017; Benekareddy et al., 2018; Calvigioni et al., 2023; Cerniauskas et al., 2019; Faget et al., 2018; Hong and Hikosaka, 2008; Ip et al., 2023; Knowland et al., 2017; Lazaridis et al., 2019; Lecca et al., 2023; Lecca et al., 2017; Li et al., 2019b; Lin et al., 2022; Mathis et al., 2021; Root et al., 2014a; Shabel et al., 2012; Stamatakis et al., 2016; Stephenson-Jones et al., 2020; Stephenson-Jones et al., 2016; Szonyi et al., 2019; Tooley et al., 2018; Trusel et al., 2019; Wang et al., 2023a; Wang et al., 2023b; Warden et al., 2012; Zhang et al., 2018a; Zheng et al., 2022; Zhou et al., 2019). Moreover, substantial evidence has revealed the physiological relevance of various inputs onto LHb in encoding aversion or depression-like state under stressful stimuli, including EPN (Cerniauskas et al., 2019; Li et al., 2019b; Stephenson-Jones et al., 2016), ventral pallidum (VP) (Knowland et al., 2017; Stephenson-Jones et al., 2020), LPO (Barker et al., 2017), MS (Zhang et al., 2018a), CeA (Zhou et al., 2019), the medial prefrontal cortex (mPFC) (Lin et al., 2022; Mathis et al., 2021), BNST (Lecca et al., 2023), the sensory thalamic reticular nucleus (sTRN) (Wang et al., 2023b), and the lateral hypothalamus (LH) (Calvigioni et al., 2023; Lazaridis et al., 2019; Lecca et al., 2017; Trusel et al., 2019) (Fig. 1). Nevertheless, systematic head-to-head comparisons are still lacking among these inputs, hindering the elucidation of how distinct inputs differentially encode the aversive valence of various stressors.

To fulfill this gap, our recent studies conducted systematic functional mappings of various upstream inputs onto LHb in mice (Zheng et al., 2022). Initially utilizing the pathway-specific c-fos mappings of LHb inputs via an unbiased whole-brain manner, we identified five major upstream inputs activated by restraint stress, including LH, EPN, lateral septum (LS), LPO, and MS. Notably, the activation levels of these inputs onto LHb are consistent with the synaptic connectivity characterized by the optogenetics-assisted *in vitro* slice electrophysiology. Furthermore, via pathway-specific fiber photometry, we parallelly monitored the real-time calcium activity of these inputs in response to restraint stress. Intriguingly, the LH-LHb pathway exhibits substantially stronger calcium response to restraint, indicating LH as the most physiologically relevant input onto LHb when encoding aversive valence of restraint stress (Zheng et al., 2022). Consistent with our findings, other studies reveal that LH inputs onto LHb are selectively responsible for the avoidance learning under footshock stress (Lecca et al., 2017; Trusel et al., 2019), collectively suggesting the predominant role of LH in the immediate transmission of aversive information onto the LHb.

Further *in vivo* delineation of LH neuronal firing parameters in freely moving mice unraveled a consistent switch of intra-burst firing frequency from 20 Hz to 40 Hz in response to various stressors (e.g., restraint, tail suspension, footshock, social defeat) (Zheng et al., 2022). Consequently, 40-Hz phasic firings of LH neurons universally serve as a unique coding pattern responding to stressful stimuli. Moreover, this phasic 40-Hz firing pattern in LH neurons reliably induces a summation of excitatory post-synaptic potentials (EPSPs) in LHb neurons, which subsequently allows the calcium influx to form a plateau potential and evoke the LHb burst firings (~100 Hz). Such pairings of pre-synaptic 40 Hz and post-synaptic 100 Hz also exist under *in vivo* conditions, suggesting the unique spatiotemporal dynamics of LH-LHb circuit when encoding aversive valence of stressors.

4 A physiological form of Hebbian plasticity at LH-LHb synapses encodes chronic stress and triggers depression-like state

During the pathogenesis of depression, it remains an open question how chronic stress accumulates and gradually sculpts neural circuits. Through an unbiased deconstruction of five major inputs onto LHb, we disclose that LH-LHb pathway is selectively potentiated and coincides with the onset of depression-like state induced by chronic restraint stress (CRS) or chronic social defeat stress (CSDS) (Zheng et al., 2022). This pathway-specific synaptic potentiation plays a determinant role in the development of depression-like state, according to the fact that silencing the LH-LHb pathway during chronic stress prevents depression-like behaviors (despair-like and anhedonia-like phenotypes).

Coincidently, the 40 Hz-100 Hz pairings in LH-LHb circuit comply with the temporal window of Hebbian plasticity, thereby reliably inducing long-term potentiation (LTP) both in *in vitro* brain slices and *in vivo* freely moving animals (Fig. 1). Remarkably, this specific form of LTP, named as the EPSPs-burst dependent plasticity

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(EBDP), selectively occurs at the LH-LHb circuit (Zheng et al., 2022). Furthermore, utilizing a phasic 40-Hz photostimulation protocol in the LH-LHb pathway to mimic stress experience, the chronic induction of LH-LHb EBDP is sufficient to incept the persistent depression-like state even in stress-naïve mice. Collectively, our discovery unveils a physiological form of Hebbian plasticity in encoding chronic stress and depression-like state.

To further validate the Hebb's postulate that "cells fire together, wire together", rigorous control experiments have been designed as the "pre-only" and "post-only". The pre-only experiment demonstrates that pre-synaptic 20-Hz firings of LH neurons merely evoke separate EPSPs in LHb neurons (no post-synaptic firings), thus failing to induce LTP. The post-only experiment is realized by the induction of rebound burst firings in post-synaptic LHb neurons, which also fails to induce LTP, probably attributed to the lack of pre-synaptic firings. To test the necessity of pre- and post-synaptic pairings in the behavioral levels, the pre-only and post-only stimulation were induced in mouse models of subthreshold stress, and both failed to facilitate depression-like state (Zheng et al., 2022). Collectively, the requirement of pre- and post-synaptic pairings restricts the LTP induction in LHb, serving as a homeostatic mechanism against the detrimental effects of daily stress.

The entire glutamatergic LH-LHb projections have been classified into functionally distinct subpopulations, among which $Esr1^+$ LH-LHb projections selectively mediate depression-like state after chronic mild shocks (Calvigioni et al., 2023). In addition to the essential role of LH-LHb circuit in gating both despair- and anhedonia-like phenotypes (Calvigioni et al., 2023; Zheng et al., 2022), other studies unraveled additional circuit mechanisms in distinct animal models of depression. For instance, both of the EPN-LHb and VP-LHb circuits specifically mediate the despair-like phenotype induced by chronic mild stress (CMS) (Cerniauskas et al., 2019) and CSDS (Knowland et al., 2017), respectively. Besides, the CeA-LHb circuit serves as a therapeutic target responsible for the depression-like state comorbid with chronic pain (Zhou et al., 2019).

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5 Output-specific assignment of aversive valence from LHb subregions to the midbrain

Accumulating evidence suggests the existence of topographically organized projections from the two major LHb subdivisions to their major downstream targets in the midbrain and hindbrain (Herkenham and Nauta, 1979; Proulx et al., 2014; Metzger et al., 2021). Indeed, LHbL mainly sends excitatory projections to the inhibitory gamma-aminobutyric acid (GABA) neurons in the rostromedial tegmental nucleus (RMTg) (Cerniauskas et al., 2019; Goncalves et al., 2012; Jhou et al., 2009b), subsequently inhibiting dopamine (DA) neurons in the ventral tegmental area (VTA) (Hong et al., 2011; Jhou et al., 2009a; Li et al., 2019b; Li et al., 2019c; St Laurent et al., 2020; Vento et al., 2017) and serotonin (5-HT) neurons in the dorsal raphe nucleus (DRN) (Li et al., 2019a). Consequently, activation of the LHbL-RMTg pathway elicits behavioral phenotypes of avoidance (Stamatakis and Stuber, 2012) and passive coping (Proulx et al., 2018). Furthermore, LHbL also inhibits RMTg via the trace aminergic signaling (Yang et al., 2023), indicating a biphasic modulation from LHbL to RMTg. Without any relay nucleus, LHbM directly projects to the VTA (Bernard and Veh, 2012; Goncalves et al., 2012), DRN (Bernard and Veh, 2012; Cerniauskas et al., 2019; Sego et al., 2014), MRN (Bernard and Veh, 2012; Szonyi et al., 2019), hypothalamus (Quina et al., 2015), laterodorsal tegmentum (LDT) (Quina et al., 2015; Yang et al., 2016), and locus coeruleus (LC) (Mathis et al., 2021) (Fig. 1).

In addition to the subregion-dependent projection patterns from LHb, post-synaptic cell-type specificity in the downstream targets also manifests the topographical organization of LHb innervations. For instance, LHbM selectively innervates GABA neurons in the LDT, engaged in the innate fear processing (Yang et al., 2016). LHbM also innervates both monoaminergic and GABAergic neurons in the VTA (Meye et al., 2016; Omelchenko et al., 2009) and DRN (Takahashi et al., 2022; Zhou et al., 2017), suggesting a complex circuitry of direct excitation and feedforward inhibition. In the LHbM-VTA pathway, LHbM-innervated DA neurons are selectively located in the medial part of VTA and encode aversion (Lammel et al., 2012). Indeed, activation of the LHb-VTA pathway evokes aversive state (Cerniauskas et al., 2019; Lammel et al., 2012), behavioral despair and motivational deficit (Cerniauskas et al., 2019). Besides, LHbM also directly innervates VTA glutamate neurons (Faget et al., 2016), whose function requires future investigations. In the LHbM-DRN pathway, recent evidence reveals its pro-depressive role that photostimulation induces real-time aversion (Cerniauskas et al., 2019) and increases the susceptibility to social defeat stress (Liu et al., 2021), whereas chemogenetic inhibition

attenuates the passive coping phenotype (Coffey et al., 2020). Notably, the LHb homolog in zebrafish, the ventral habenula (vHb), selectively activates 5-HT neurons in MRN and causally mediates the active avoidance from electrical shocks (Amo et al., 2014). In contrast, other studies also indicate that LHbM in mice selectively projects to the glutamate neurons in MRN, and encodes aversive information (Szonyi et al., 2019).

6 Feedback loops from the midbrain encode heterogeneous emotional valences

Recent studies have also documented feedback loops from the VTA, DRN, and MRN to the LHb (Fig. 1). For instance, negative feedback circuits exist in the VTA-LHb and DRN-LHb projections. VTA GABA neurons have been demonstrated to inhibit LHb neurons, encoding an appetitive valence (Lammel et al., 2015; Stamatakis et al., 2013). LHb also receives excitatory inputs from VTA glutamate neurons, exhibiting a behavioral phenotype of real-time place aversion (Lammel et al., 2015; Root et al., 2014a; Yoo et al., 2016). Meanwhile, other studies reveal the predominant co-release of glutamate and GABA in the VTA-LHb pathway, which unexpectedly causes the inhibitory net effect (Root et al., 2020; Root et al., 2014b; Yoo et al., 2016). It becomes more puzzling that activation of the glutamatergic VTA-LHb projections elicits behavioral outcomes of both place aversion and positive reinforcement (Yoo et al., 2016). In the DRN-LHb negative feedback circuit, DRN neurons release 5-HT to inhibit the LHb activity, alleviating both aversion and depression-like behaviors (Shabel et al., 2012; Zhang et al., 2018b). Moreover, potential positive feedback loop occurs within the LHbM-MRN circuit, since the LHbM forms reciprocal connections with the glutamate neurons in MRN (Szonyi et al., 2019). Future studies are warranted to clarify the exact roles of these reciprocal circuits during the pathogenesis of depression.

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7 Discussion

Here we propose a mechanistic framework which delineates the functional role of LHb-centric circuitry via an input-output specific manner. The LHb subregion-selective innervation patterns provide a novel perspective to dissect heterogeneous LHb neuronal subpopulations via distinct downstream targets and upstream inputs. Given that systematic head-to-head comparisons are rare among parallel LHb inputs or outputs, future endeavors will clarify the physiological relevance level of distinct LHb circuits under various stressors.

Given that pathway-specific (from mPFC, VP, LH, EPN, or CeA to LHb) synaptic potentiation encodes depression-like state induced by different stressors (Fig. 1), corresponding synaptic depression might serve as a novel antidepressant strategy. Indeed, recent studies have already pointed out the fascinating possibility of projection-specific synaptic depression under the control of endocannabinoid (eCB) system (Winters et al., 2023). Remarkably, as the deep brain stimulation (DBS) in LHb exhibits antidepressant efficacy even in treatment-resistant depressed (TRD) patients (Sartorius et al., 2010; Wang et al., 2021; Zhang et al., 2022), the topographical input-output selectivity embedded in LHb subregions might further inspire the circuit- and cell-type specific DBS therapy, based on the elaborate modifications of stimulation parameters (Alagapan et al., 2023; Riva-Posse et al., 2020; Spix et al., 2021). Due to the invasive drawback of DBS, non-invasive transcranial magnetic stimulation (TMS) therapies have provided a more promising avenue based on the personalized functional connectome (Cole et al., 2022; Cole et al., 2020; Fox et al., 2012; Williams et al., 2018). Considering the interconnectivity between cortical and subcortical regions, superficial cortical targets covered by the TMS are emerging as promising candidates to disrupt the LHb activity and take rapid antidepressant actions. Collectively, potential progress will benefit the precise antidepressant treatments targeting specific neural circuits and patient subpopulations.

Recent studies have indicated a dual valence encoded within a neurotransmitter-specific neural circuit, as the majority of LHb-projecting glutamate neurons in the LH respond to both aversive and appetitive stimuli (Rossi et al., 2021). Moreover, diverse neuronal subpopulations in LHb have been identified (Aizawa et al., 2012; Proulx et al., 2014), warranting the functional characterizations via ensemble-defined single-cell recordings/imagings *in vivo* (Sylwestrak et al., 2022). The recent establishment of single-cell RNA sequencing (scRNA-seq) has precisely characterized the molecular profiles of distinct LHb neuronal ensembles (Hashikawa et al., 2020; Wallace et al., 2020), especially in an output-specific manner under depression-like

state (Cerniauskas et al., 2019). Intriguingly, from zebrafish to mice, the evolutionary conservation of LHb has been substantiated in both of the transcriptional (Hashikawa et al., 2020) and the circuit (Stephenson-Jones et al., 2012) levels, indicating the essential role of LHb in orchestrating aversive valence across species. Collectively, all aspects of the aforementioned endeavours will disentangle the functional identities of LHb neurons at an unprecedented spatiotemporal resolution.

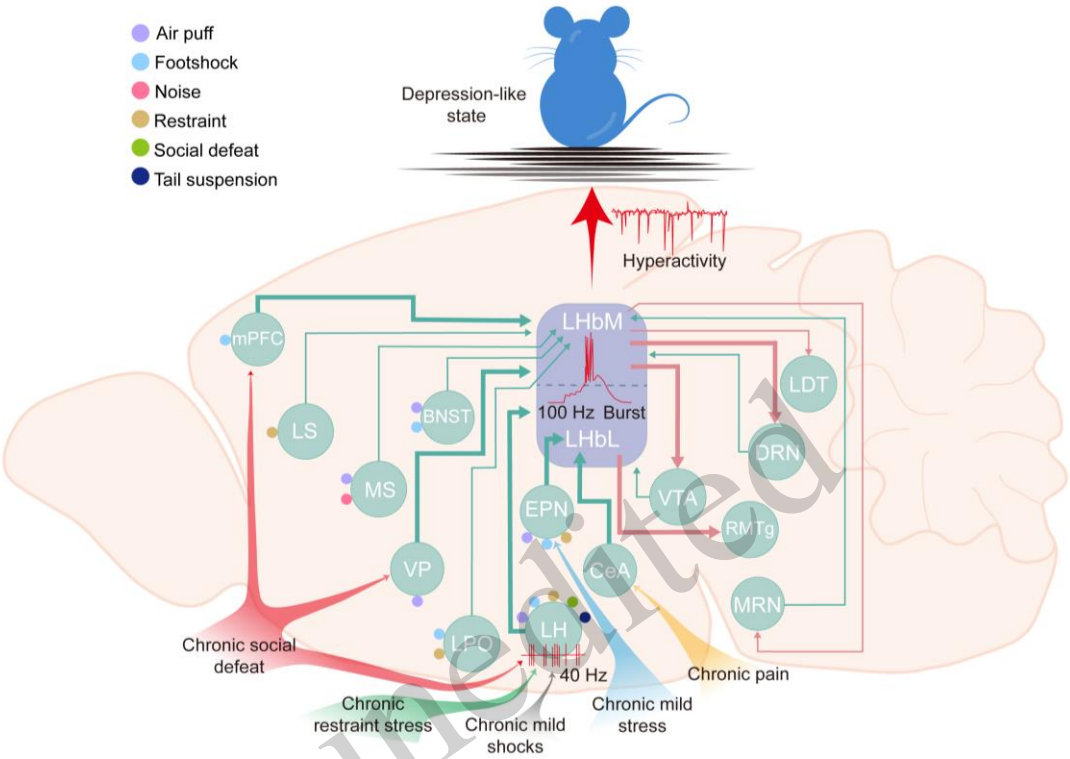

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Fig. 1 LHb orchestrates aversive valence of various stressors via specific input-output configurations. Aversive valence of various stressors is integrated via diverse upstream inputs (green lines) onto LHb, and assigned to dissociable downstream targets (red lines). Different stressors are annotated by different colored circles. Pathway-specific enhancement of neuronal activity (bold lines) mediates the depression-like behaviors induced by different animal models of chronic stress. Particularly, multiple stressors universally evoke the phasic 40-Hz firings in LH, subsequently inducing ~100-Hz burst firings in LHb. Such repeated pairings of pre-synaptic 40-Hz and post-synaptic 100-Hz firings comply with the Hebbian rule of LTP, and sufficiently incept the persistent depression-like state in stress-naïve mice.

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Author contributions

Conceptualization, Yihui CUI, Yiyan DONG, Chenju YI; writing - original draft, Yiyan DONG, Yihui CUI, Taida HUANG, Xiaonan GUO; writing - review & editing, Yiyan DONG, Taida HUANG, Yihui CUI, Chenju YI, Xiaomin HUANG; visualization, Taida HUANG; funding acquisition, Yihui CUI, Yiyan DONG, Chenju YI, Taida HUANG, Xiaomin HUANG; supervision, Yiyan DONG, Yihui CUI, Chenju YI. All authors have read and approved the final manuscript.

Compliance with ethics guidelines

Taida HUANG, Xiaonan GUO, Xiaomin HUANG, Chenju YI, Yihui CUI, Yiyan DONG declare that they have no conflict of interest.

This review does not contain any studies with human or animal subjects performed by any of the authors.

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