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Chapter

Roles of the Serotonergic System in Coping with Traumatic Stress

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Abstract

Post-Traumatic Stress Disorder (PTSD) is characterized by substantial physiological and/or psychological distress following exposure to trauma. Intrusive fear memories often lead to persistent avoidance of stimuli associated with the trauma, detachment from others, irritability and sleep disturbances. Different key structures in the brain are involved with fear conditioning, fear extinction and coping. The limbic system, namely, the amygdala complex in close relationship with the hippocampal hub and the prefrontal cortex play central roles in the integration and in coping with fear memories. Serotonin acting both as a neurotransmitter and as a neurohormone participates in regulating the normal and pathological activity of these anatomic structures. We review the literature analyzing how the different actors of the serotoninergic system (5-HT receptors, transporters and anabolic and catabolic pathways) may be involved in regulating the sensitivity to highly stressful events and hopefully coping with them.

Keywords: 5-HT, 5-HT receptors, amygdala, hippocampus, limbic structures, PTSD, prefrontal cortex, SERT

1. Introduction

Following exposure to traumatic events as a succession of inescapable stressful stimuli or life-threatening accidents, most people adapt and cope with the stress and return to their normal life when the stressful event (s) has (ve) stopped. However a minority of them, 6-8% of people [1, 2] develop PTSD characterized by a variety of symptoms precisely defined by “the American Psychiatric Association’s Diagnostic and Statistical manual of Mental Disorders” [3]. It includes intrusive memories of the traumatic event, nightmares, irritability, sleep impairment, attention deficit and/or emotional withdrawal. Post-traumatic stress disorder is often associated with several comorbidities such as inflammation [4], chronic pain and heightened risk of neurodegenerative disease. This disorder is more often than we believe difficult to treat as many patients suffer from it during several years after the traumatic event has stopped. For instance, 40 years after the Vietnam War, 11% of the veterans still experienced PTSD [5]. This disorder is primarily due to an overload of traumatic sensory stimuli inducing continuous overproduction of cortisol in the brain and body [6] generating secondary cascades of deregulations that prevent a return to the original homeostatic biological state by the parasympathetic brake, essential for the patient [6–8]. These biological impairments lead to the anchoring of fear memories in the limbic cerebral circuits which include primarily
the amygdala complex (AMY) handling the emotional processing related to stress associated with memory processing of the hippocampal-cortical circuits [6, 9, 10].

The fact that a minority of people undergoing traumatic events don’t recover and develop long-lasting PTSD suggests that among the population different genetic/epigenetic predispositions unique for each individual impact the way patients are able to cope or not with stressful events [6]. Impairments of the limbic circuitry and activity are among the key features explaining various PTSD symptoms. Numerous examples have shown that the serotoninergic system is well positioned to modulate the activity of the amygdalo-hippocampal-prefrontal hub. The serotoninergic system is widely known to play a critical role in mood regulation and it is not surprising that different pharmacological treatments initially proposed to relieve PTSD symptoms modulate serotoninergic systems [11–14]. Among them serotonin reuptake inhibitors (SSRIs; i.e. citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) causing high extracellular 5-HT levels are classically used for their anxiolytic effects and treatment of depression and for their relative minor side effects [12–15].

We will review how the limbic system is modulated by changes in 5-HT homeostasis by acting through 5-HT transporter or receptors during development and in adults.

We analyze knowledge obtained from relevant adult rodent models and extend them to human data when possible. Indeed, rodent models, appear useful for understanding the etiology of PTSD, as the “fear circuitry” and the endocrine responses to stress are fairly conserved across species. However, they lack the complexity of the cognitive treatment mediated by highly developed cortical circuits observed in primates [6, 16–18]. We will also review literature clearly demonstrating that imbalance in the serotonergic system during development associated or not with genetic alterations may modify the way patients are able to cope with stressful events.

2. Anatomy and physiology of limbic circuits implicated in the stress response

Regardless of its intensity, stress induces primarily stimulation of the Hypothalamic-Pituitary-Adrenal (HPA) axis that coordinates the body-brain biological response through a highly regulated neurohormonal cascade. Corticotrophin releasing hormone (CRH) or factor (CRF) is released from hypothalamic neurons, letting adrenocorticotropic hormone (ACTH) out of pituitary cells, which in turn stimulates the secretion of cortisol (CORT) into the bloodstream by the adrenal cortex. Cortisol activates glucocorticoid receptors (GR) that are widely distributed in the brain, mainly along the HPA axis itself and in major limbic structures such as the amygdala complex (AMY), the hippocampal formation (HIP) and the prefrontal cortex (PFC). When the stress is qualified as “adaptive”, activation of hypothalamic GR decreases HPA axis activity, creating a negative feedback loop leading to corticoid levels returning to normal with the stress responses turned off [6–8, 19]. In parallel the HPA axis interacts with the limbic structures afore mentioned which in turn participate to the feedback inhibition and feed-forward stimulation of the HPA axis that regulate stress responses [20–22]. When stressful events are perceived as particularly severe and/or persistent, the stressors can cause long-lasting changes in active stimulation of the HPA axis modifying the “body-brain” responses to CORT and CRH. In this context, corticoids flowing continuously in the brain and the body generate long lasting modifications/alterations of the limbic and cortical circuits contributing to induce a large array of PTSD symptoms [6–8] (Figure 1).
The amygdala complex is considered as “a hub” of cerebral emotional processing, receiving inputs from sensory areas (including sensory thalamus), autonomic system, HIP and cortical regions such as the infra-limbic (IL) prefrontal cortex. By « computing » information stored in the HIP and cortical structures, AMY attributes an emotional valence to the event and plays a crucial role in fear learning and extinction [10, 23, 24]. In patients suffering PTSD, exaggerated responses to emotional stimuli induce hyperactivation of AMY, which become hypertrophic by the increased complexity of their glutamatergic neurons [6, 25]. Then in PTSD, the different subnuclei of AMY are modified in their connections and their complex regulation of inhibitory GABA neurons network. The basolateral nucleus (BLA) that receives sensory information stimulates abnormally the central nucleus (CE), which regulates the output of fear behavior [10, 26–28]. Different Pavlovian rodent models analyzed the neural basis for encoding association of two stimuli, a neutral stimulus (a sound, a light) and a painful stimulus.
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(a footshock). They revealed that the lateral nucleus of the amygdala (LA) receives inputs of both stimuli, conveyed information to the basal nucleus (BA), then to the output CE which coordinates the expression of defensive behaviors such as freezing [29–31]. Recently, it was suggested that the BA may not be implicated in the defensive behavior but rather in avoidance [32]. The extended amygdala as the bed nucleus of the stria terminalis (BNST) is also largely implicated in anxiety [10, 26, 28] and its role will be developed later. The reciprocal connections of AMY with HIP and PFC, in particular IL cortex (in rodents) that participate in the inhibition of learned fears are defective in PTSD patients leading to the persistence of fearful memories and other emotional symptoms [24].

The HIP is known to play a critical role in learning and memory integrating contextual information to regulate behavior (Reviewed by [33]). In PTSD, it mediates memory-related problems including persistent re-experiencing of traumatic events and impaired context-dependent modulation of memory as well as increased salience of negative emotional memories deficits in working and verbal memory [6, 34]. Studies in rats have shown that the dorsal HIP (homologous to the human posterior HIP) is mostly associated with cognitive performance while the ventral HIP (homologous to the human anterior HIP) rather participates in the regulation of stress response and affect [35]. Hippocampal volume is reduced in individuals with PTSD compared to controls. The HIP morphology is highly plastic and size reduction could indicate predisposition for PTSD while increase in volume may underlie positive responses to treatment. The HIP reciprocal connections to other brain areas are critical in these regulations; importantly, the HIP interacts with the AMY to regulate emotional arousal and consolidation of fear memories (as previously mentioned [10, 27, 36] and with the PFC to regulate memory [37].

The prefrontal part (PFC) of the frontal lobe plays essential roles in attention, working memory, decision-making and regulation of emotion [38]. Its role is crucial for PTSD patients in the regulation of fear, learning, expression, and extinction [39]. Interestingly the anterior cingulate cortex (ACC) and the medial PFC (mPFC) display abnormal levels of activation in PTSD patients [40]. The human ventromedial PFC (vmPFC; analogous to the IL cortex in rodents) plays a key role in the extinction of fear memories by processing “safety signals” and interacting with the AMY to inhibit fear expression [41]. In PTSD patients, impaired vmPFC activation leads to altered emotional processing and impaired retention of fear extinction learning. Other cortical structures such as the insular cortex (visceral regulation) intervene in the emotional processing and interoception that are altered in PTSD patients.

Going back to everyday life stress regulation, the response to an adaptive stress involves motivation and action giving rise to pleasure by activation of reward circuit or strengthening/operant conditioning circuit (as salivation in the Pavlovian conditioned dogs) present in most vertebrate species. Following a stress the dopaminergic neurons of ventral tegmental area (VTA) projecting towards limbic areas (the medial PFC, the AMY and the accumbens) “integrate” the emotional/pleasure valence linked to this event [42, 43]. When the stressor is adaptive, dopaminergic neurons of VTA and the accumbens are activated by different brain structures in particular AMY generating escape as adaptive behavior. When the stressor is too strong, the VTA-reward/action system becomes less efficient. When the stressor happens to be severe and/or permanent, the adaptive behavior VTA-reward/action system is decreased/abolished and the adaptive “way out” motor system is inhibited [44]. Interestingly, the activity of VTA neurons could be modulated by the noradrenergic and serotoninergic neurons. A small subset of the noradrenergic locus coeruleus (LC) neurons could activate VTA, playing therefore a role in resiliency to stress [45]. Similarly, several studies have shown that dorsal raphe serotoninergic
neurons could modulate the activity of VTA neurons. Recently, it was shown using optogenetic tools coupling to behavioral tests, that stimulation of dorsal raphe neurons induces reward seeking in mice. Moreover, this behavior was abolished by the specific inhibition of 5-HT-containing axons reaching the VTA and induces conditioned place aversion [46]. Depending on the targets reached by serotoninergic neurons their activation may lead to various and sometimes opposite roles in behavior [47]. We will discuss these recent findings in section 4.

3. Lay-out of the 5-HT system

3.1 Serotonin synthesis, storage and degradation

Serotonin is synthesized from the essential amino-acid L-tryptophan. In the blood stream, L-tryptophan is linked to serum-albumin but a free proportion that decreases with age and physiological status freely crosses the BBB (10% at postnatal day 12 when BBB is thought fully functional in rat [48]). In 5-HT-producing cells, tryptophan is then transported, accumulated and hydroxylated by the tryptophan hydroxylase (Tph) enzymes. Tryptophan hydroxylase type 2 (Tph2) is expressed in serotoninergic neurons of the raphe nuclei and myenteric neurons [49, 50] while Tph1 is expressed in the gut enterochromaffin cells, the pineal gland and various peripheral tissues [51, 52] and possibly in the placenta depending on the species [53]. 5-hydroxytryptophan is then further decarboxylated into 5-HT by the aromatic amino-acid decarboxylase (AADC). It has been shown that the availability of tryptophan to synthesize 5-HT depends on the inflammatory status of the organism. Interestingly, patients suffering PTSD develop a pro-inflammatory status with increased circulating pro-inflammatory cytokines [6]. Indoleamine 2,3-dioxygenase (IDO) is generated following inflammation and can lead to 5-HT depletion in the organism [54]. Such a state may impact the levels of 5-HT in PTSD patients and favor the emergence of depressive-like status.

5-HT producing cells express the SERT and vesicular monoamine transporter type 2 (VMAT2) allowing respectively 5-HT uptake and storage in those cells [55]. In the CNS these transporters regulate the level of 5-HT, not only at the synaptic cleft, but also when 5-HT is release along 5-HT-containing (5-HT+) axons in a « volume-transmission » manner [56]. The use of SSRIs have been used for treatment of PTSD symptoms [6]. In various rodent models, SSRIs were shown to relieve some of the PTSD-like symptoms (reviewed in [57]). Indeed, administration of SSRIs or ketamine ameliorate PTSD-like behavioral deficits in restraint paired forced swimming test (or other stressors) [58]. These models are attempting to reproduce unpredictable stress as those observed by soldiers experiencing war zones [59–61]. Similarly, exposure to a predator induces hyperarousal, avoidance and fear, [62–64] increases anxiety-like behavior and reduces fear extinction. In these models, animals also respond to sertraline reducing anxiety-like behavior and cue avoidance [65, 66]. Interestingly, SSRI treatment appears efficient only when administered chronically, at least for 3–6 month in patients. Initially depressive symptoms worsen by 5-HT increase activating the inhibitory 5-HT1 autoreceptors in the raphe nuclei, before they get desensitized following chronic treatment. Alternatively, the delayed therapeutic effects of SSRIs may be due to neuroplastic changes that need time to develop in mature brain [62, 67].

5-HT is catabolized by monoamine oxidases A or B (MAOA or MAOB; located in the mitochondria and by catechol-O-methyltransferase (COMT) [68, 69]. MAOA has higher affinity for 5-HT than MAOB and is co-expressed with MAOB in rodent serotoninergic neurons [70]. MAOs are also expressed by many non-aminergic
structures, in particular MAOB is expressed in glial cells throughout the brain [71] and our unpublished results). MAOA mRNA has been detected in the deep layers of the rodent prefrontal cortex [72]. MAOs may thus regulate the amount of 5-HT locally, throughout the brain and in the peripheral tissues where they are also expressed [70, 71]. Interestingly, MAOs expression and protein synthesis are tightly regulated and have been shown to be sensitive to environmental factors such as inflammation [73] and stress. Indeed, glucocorticoids increase MAOA in the brain through the stimulation of the Kruppel-like factor11 and cell-division associated 7-Like protein pathways [74]. Animals under chronic stress show increased MAOA and 5-HIAA/5-HT ratio suggesting a higher 5-HT turnover levels [75]. MAOA inhibitors have been shown to reverse the decreased neurogenesis and dendritic plasticity in the hippocampus of chronically stressed rats [76].

3.2 Transducing pathways

At least fourteen 5-HT receptor subtypes have been identified in the mammalian brain and periphery ([77–79]; see [80] for the latest classification). Isoform diversity, alternative splicing of some subtypes and RNA editing add to the complexity of serotoninergic receptor functions. With the exception of 5-HT\textsubscript{3} receptors, all 5-HT receptors are coupled to G-proteins. According to their second messenger coupling pathways, 5-HT receptors have been categorized into four groups. 5-HT\textsubscript{1} and 5-HT\textsubscript{3} receptors are coupled to Gi/Go proteins and exert their inhibitory effects on adenylyl cyclase, inhibiting cAMP formation. Within the raphe nuclei, 5-HT\textsubscript{1A} receptors are acting as autoreceptors inhibiting the release of 5-HT by serotoninergic neurons. After the start of SSRI treatment, they are proposed to be responsible for the initial worsening of depressive symptoms [13, 81]. 5-HT\textsubscript{2} receptors are coupled to Gq proteins and stimulate phospholipase C to increase the hydrolysis of inositol phosphates and elevate intracellular Ca\textsuperscript{2+}. 5-HT\textsubscript{4,6,7} receptors are coupled to Gs proteins and are positively linked to adenylyl cyclase and increase cAMP formation. 5-HT\textsubscript{3} receptors are ligand-gated ion channel receptors and are a unique 5-HT receptor able to mediate fast response to neurotransmitter release [82]. It is generally admitted that, in the limbic structures 5-HT\textsubscript{1A} receptors are mainly expressed by glutamatergic neurons. 5-HT\textsubscript{1} receptors are expressed by subtypes of interneurons expressing mainly the vasoactive intestinal peptide (VIP), cholecystokinin (CCK) or calretinin (CR) (but never expressing parvalbumin (PV) and rarely somatostatin (SOM)). 5-HT\textsubscript{2} receptors are expressed in both neuronal populations [83–85]. 5-HT\textsubscript{7} receptor expression has been shown in the deep layers of the rodent prefrontal cortex. For additional precision, see also [86].

4. Serotoninergic projections and modulation of limbic structures

4.1 Serotoninergic neurons and projections: focus on mature limbic systems

Different subsets of 5-HT+ neurons of brainstem raphe nuclei (average of 26 000 neurons in rodents) send diffuse axonal networks to specific brain areas throughout the brain. Pioneer studies using 5-HT or SERT Immunolabeling, coupled or not to retrograde tracing [87–89] provided a general description of these 5-HT projections towards numerous areas including the cerebral cortex. More recently, anterograde tracing (injection of adeno-associated viruses) in raphe nuclei of mice conditionally expressing the green fluorescent protein/channel rhodopsin under the control of the SERT or TPH2 promoter [47, 90, 91] have provided evidence that limbic structures receive 5-HT afferences from topographically
organized subpopulations of dorsal DR (the largest 5-HT+ nuclei in rodent and pri-
mates) and median raphe nuclei (MnR). Using genetic activation of specific 5-HT+ pro-
jections, some studies allowed to correlate activation/inhibition of specific
5-HT+ subgroups/aффerences to behaviour. Interestingly they revealed that DR and
MnR 5-HT+ neurons should be apprehended as neuronal populations having the
ability to release a large numbers of neurotransmitters and neuropeptides in addi-
tion to 5-HT [92, 93]. Such a diversity in subtypes, targeting and functions is already
underlined by the complexity observed in 5-HT+ developmental programming
(i.e. specification and axonal targeting; see [93, 94]).

As a whole, it is generally admitted that exposure to a severe/inescapable shock
as in predator exposure, social defeat or other stress conditions [95] induces a surge
of 5-HT in the vicinity of DR/MnR and in the corticolimbic structures such as the
AMY, HIP and mPFC. Only a few studies have reported a decrease of serotonin-
gic activity following severe stressful situation. That may match with the genuine
possibility of specific individual/strain to cope with stress [96]. Interestingly,
around 80% of 5-HT+ neurons in the ventral portion of the DR (DRv) and MnR
express the vesicular glutamate transporter type 3 (Vglut3) and send axons to AMY
and HIP. These neurons can release 5-HT and/or glutamate and then modulate
the activation of AMY and HIP [93, 94, 97]. Generally, low frequency stimulation
(<10Hz) induces glutamate release resulting in fast excitation of the targeted neu-
ron while higher frequency stimulations (10-20Hz) induce 5-HT release suggesting
that these neurons could rapidly switch their neurotransmitter output depend-
ing on activation [97]. A subgroup of DR 5-HT+/Vglut3+ neurons projecting to
the nucleus accumbens (NAC) and orbitofrontal cortex (OPFc) to specifically
receive inputs and integrate information from “reward encoding regions” such as
the ventral pallidum. Conversely, another group of DR 5-HT+/Vglut3+ neurons
specifically receives inputs from the “fear encoding regions” (periaqueducal grey
(PAG) and LC) and project to the BA. This last subpopulation appears to potentiate
fear via the 5-HT1A and 5-HT2A receptor pathways and to impair fear extinction
[98]. Interestingly, in rats some DRv 5-HT+/Vglut3+ neurons are sensitive to CRH
released by the AMY that induces a decrease of TPH2 in them and ameliorates
stress-induced anhedonia [99]. The level of TPH2 regulation by CRH could be the
signature of a resilience status [99]. In the MnR 5-HT+/Vglut3+ neurons appear
to integrate selectively negative events and may play a central role in depression-
related mood disorders [100]. Subgroups of MnR 5-HT neurons express the type 2
CRH receptor. These examples illustrate the complexity of the 5-HT neuron-driven
behaviors. Possible co-transmission based on gene expression suggests that DR and
MnR 5-HT+ neurons could potentially also co-release GABA, dynorphin, galanin,
cholecystokinin (CCK), nitric oxide (NO), CRH and other neuropeptides for
which a role remains to be established (Reviewed in [93]).

4.2 The amygdala complex

Serotoninergic axonal projections to the AMY mainly arise from 5HT+ DR
neurons while only rare axons arise from MnR. The 5-HT+ axonal density is
strong in BA, moderate in LA, and moderate to low in CE, intercalated nuclei
and BNST [87, 89, 91]. 5-HT axons target both glutamatergic principal neurons
(PN, not interneurons) bearing 5-HT1C receptors in LA and, 5-HT2A/1A receptors
in BA and a variety of GABAergic interneurons [101]. GABAergic interneurons
expressing PV bear 5-HT2A receptors receive inputs from glutamatergic PN and
project reciprocally on them and on somatostatin-expressing (SOM+) GABAergic
neurons. 5-HT exerts most of its effects on PV+ GABAergic neurons that express
the strongest levels of 5-HT2A receptors and facilitate GABAergic inhibition. Following
inescapable stress 5-HT$_{2A}$-receptor mediated facilitating actions are severely impaired. 5-HT$_{2A}$ receptor-mRNA is downregulated following the surge of 5-HT in the AMY leading to hyperactivity of PN neurons [102]. Neuropeptide Y-containing (NPY+) (5-HT$_{2C}$+ and 5-HT$_{3A}$+ receptor) and CCK+ and VIP+ (5-HT$_{1A}$+ receptor) also project on glutamatergic PN (Figure 2 in [15]). Within the BA and LA the role of 5-HT$_{3A}$ remains to be clarified. Glutamatergic principal neurons of LA and BA send numerous efferents to CE and to a lesser extent to BNST. These plastic efferent fields are sensitive to environmental conditions and in PTSD patients this could be

Figure 2.
The amygdala complex is modulated by serotonin via various 5-HT receptor expressions. A, The major GABAergic neuron subtypes modulating the function of the amygdala complex are represented in the left panel. They could be subdivided into four main classes: the somatostatin-containing (SOM; orange), the 5-HT$_{3A}$-expressing (5-HT$_{3A}$; green), the parvalbumin-containing (PV; bleu) and the neuropeptide Y-containing (NPY; pink). The 5-HT$_{3A}$-expressing GABAergic neurons could be further subdivided into three classes: the vasoactive intestinal peptide-containing (VIP), the cholecystokinin-containing (CCK) and the calretinin-containing (CR) GABAergic neurons. Their activities are modulated by serotoninergic axons arising from the dorsal raphe nucleus (violet arrows). B, In the amygdala complex, the lateral amygdala (LA) glutamatergic neurons (principal neurons, PN; black) that receive thalamic inputs stimulate glutamatergic neurons (principal neurons; PN) of the basal complex (BA; black). These neuronal populations are modulated by 5-HT$_{2A}$/2C receptors and 5-HT$_{1A}$ autoreceptors. Glutamatergic BA neurons send outputs to the ventral hippocampus (vHPC) and to the ventromedial prefrontal cortex (vmPFC). LA and BA stimulate neurons of the central amygdala (CE). The central amygdala (CE) is mainly composed of GABAergic neurons. Lateral CE (CEL) contains GABAergic projection neurons that express somatostatin (SOM+) and are modulated by 5-HT$_{2A}$ receptors. These neurons send outputs to the medial CE (CEM) that drives the anxiogenic pathway. CEM modulates the periaqueductal gray (PAG) and brainstem to induce freezing behaviour. By contrast, CEL receives corticotropin-releasing factor inputs (CRF+; yellow) that suppresses anxiety-like behaviour and anxiogenic pathway. Cross-talk between CRF+ and CEL neurons are continuous (double headed arrow).
responsible for the increased sensitivity of CE and BNST [103, 104]. The lateral part of the CE (CEL) receives major inputs from BA and LA but also from ventral HIP or sensory regions. CE is mainly populated by GABAergic interneurons. When avoidance of stressful stimulus is possible CRH+ GABAergic neurons are activated and SOM+ GABAergic projection neurons are inhibited [105]. Following fear conditioning, SOM+ GABAergic projection neurons disinhibiting the medial part of the CE (CEM) allowed a range of defensive behaviour as freezing [105–107] and fear recall [108]. Direct cross-talk between CRH+ and SOM+ neuronal populations allow the specific appropriate action [105].

Interestingly, 5-HT_{2A} receptors are expressed by SOM+ neurons of the CEL and the selective 5-HT_{2A} receptor inactivation in CEL increases innate freezing behaviour but decreases learned freezing induced by predator odor. Innate freezing behaviour and risk assessment are processed by the dorsal PAG while learned freezing is processed by the ventral PAG. These data suggest that 5-HT_{2A} receptor control innate freezing behaviour by the AMY-hypothalamus-dPAG pathway [109, 110]. As innate and acquired fears are controlled by antagonistic mechanisms, drugs that treat one type of fear could worsen the other one, leading to paradoxical results.

Risperidon is largely used to treat various psychiatric disorders including PTSD. Although its main therapeutic target acts by antagonizing dopamine-D2 receptors, it is also targeting 5-HT_{2} and therefore should be used carefully.

The activity of the bed nucleus of the stria terminalis (BNST) is correlated with fear mediated by uncertain threats [111]. It integrates fear, reward and stress-related circuits. BNST receives inputs from various limbic structures including BA and CE. The BNST displays a rich array of 5-HT receptors which define the three cell types I-III identified in this structure [112]. The 5-HT_{1A} receptor is the most abundant in BNST and the global effect of increased 5-HT in the BNST is a hyperpolarization of type I BNST neurons [113, 114]. Such hyperpolarization is associated with suppression of anxiety [115]. By contrast, type III cells express 5-HT_{2C} receptors and CRH and send outputs to the same hypothalamic and brainstem targets to which the CE projects and stimulate the anxiogenic pathway [116]. 5-HT_{2C} receptor-mRNA splicing/editing that leads to overexpression of 5-HT_{2C} receptors enhances anxiety and innate fear behaviour [117]. Specific 5-HT_{2C} receptor antagonists are now considered as possible compounds to treat anxiety disorders including PTSD as they relieve anxiety symptoms in patients and are well tolerated [118]. Interestingly, high-frequency BLA stimulations in rat models of anxiety or PTSD reduce anxiety-like behaviour following exposure to predator odor. These results can be compared to those observed after deep brain stimulation in humans [119].

4.3 The hippocampal formation

A dense serotoninergic innervation from the MnR is present in the hippocampus proper and has a powerful modulatory influence on hippocampal functions and memory formation [120]. In the CA1-CA3 hippocampal fields, stimulation of serotoninergic axons potentiates excitatory synapses and has positive effects on spatial memory processing in the dorsal hippocampus. Conversely, optogenetic silencing of CA1 5-HT terminals within the dorsal hippocampus inhibits spatial memory. Systemic modulation of 5-HT_{4} receptor function can impact memory formation. PTSD patients display memory deficits in encoding and retrieval as well as in extinction learning such as fear extinction. In these patients, the hippocampal volume is smaller [121]. This is a consequence of the damage caused by the continuous release of cortisol associated with an increase of glutamate release (Figure 3).

MnR also sends axons to the ventral part of the hippocampus that is more specifically involved in anxiety-related disorders. Indeed, rats infused bilaterally
with 5,7-dihydroxytryptamine (that induces a drastic reduction (80%) of 5-HT levels in the ventral hippocampus) spend less time in the open arm of an elevated plus maze. This suggests that reducing 5-HT levels in the ventral hippocampus increases anxiety-like behavior [122]. In the same line of evidence, a rat strain selected for high levels of anxiety displayed reduced stress-induced 5-HT activation [123]. Increased anxiety-like behavior has been associated with decreased 5-HT\textsubscript{1A} receptor numbers in the ventral hippocampus [124] while reduced anxiety-like behavior has been reported to be associated with global overexpression of 5-HT\textsubscript{1A} receptors [125]. 5-HT\textsubscript{2} receptors are expressed in both glutamatergic and GABAergic neurons of the hippocampus. 5-HT\textsubscript{2} receptors modulate 5-HT-induced outward currents in hippocampal pyramidal neurons and facilitate GABAergic transmission [85]. The precise roles of hippocampal 5-HT\textsubscript{2} receptors in the control of anxiety-like phenotype remains to be investigated.
The modulation of 5-HT<sub>7</sub> receptors appears promising for the treatment of PTSD. 5-HT<sub>7</sub> receptors are expressed by CA3 neurons and activation of 5-HT<sub>7</sub> receptors hyperpolarizes these neurons and induces freezing. By contrast, infusion of 5-HT<sub>7</sub> antagonists in the ventral hippocampus decreases freezing behaviour induced by contextual fear conditioning [126, 127]. Since blockade of MnR 5-HT<sup>+</sup>/CRH2+ neurons reverse the effect mediated by 5-HT released in the ventral hippocampus, it has been speculated that 5-HT<sub>7</sub><sup>+</sup> CA3 neurons would receive specific 5-HT<sup>+</sup>/CRH2+ inputs [127]. 5-HT<sub>7</sub> receptor antagonists are already used for the treatment of colonic intestinal symptoms and could be safely used for the treatment of fear-related disorders [128].

5-HT<sub>4</sub> receptor antagonists appear to modulate stress induced defecation but not freezing suggesting that this role may engage different sub-circuits [127]. 5-HT<sub>4</sub> receptor agonists may act rapidly and reduce immobility in forced swimming test, decrease sucrose intake following chronic mild stress and have been shown to display antidepressant potential. Drugs acting on 5-HT<sub>1A</sub> receptors should be carefully considered and used depending on the level/type of stress induced by the trauma [129].

### 4.4 The prefrontal cortex

The serotonergic system appears a potent regulator of the PFC circuitry acting through a variety of 5-HT receptors [85, 92, 130]. Throughout the rodent PFC, pyramidal neurons largely express 5-HT<sub>1A</sub>, 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors. Some pyramidal neurons co-express 5-HT<sub>1A</sub>/5-HT<sub>2A</sub> receptors [131] whereas 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors are expressed by overlapping populations [132]. The 5-HT<sub>2A</sub> receptor is more strongly expressed by layer 5 neurons [133–135]. 5-HT<sub>4</sub> receptors are expressed by PFC glutamatergic neurons [136] and pyramidal neurons of deep layers express transiently (P2-P14) 5-HT<sub>7</sub> receptors [137]. GABAergic interneurons express a large array of 5-HT receptors that mainly segregated in two subpopulations: 1/ the PV<sup>+</sup> fast-spiking interneurons and the SOM<sup>+</sup> interneurons both localized in deep cortical layers and expressing 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptors [130] and 2/the slow-spiking interneurons (VIP<sup>+</sup>, CR<sup>+</sup>) located in the superficial cortical layers and expressing 5-HT<sub>3A</sub> receptors [83, 84, 138]. This variety of 5-HT receptor expression allows 5-HT to finely tune the excitability of pyramidal neurons, and therefore control the mPFC top-down exerted on other structures, such as the AMY, the HIP and raphe nuclei.

#### 4.4.1 Prefrontal cortex and amygdala

The global effect of 5-HT application in vitro or the stimulation of endogenous 5-HT release in vivo in PFC is inhibitory and mediated by 5-HT<sub>1A</sub> receptors. 5-HT<sub>1A</sub> receptor stimulation (via LY341495) appears to play antidepressant role as shown by the reduction of the immobility time in 24h forced swim test which is partially reversed by infusion of the 5-HT<sub>1A</sub> receptor antagonist WAY100635 in the mPFC [139]. Regulation of the GABAergic tone in the AMY (BLA) appears to be sensitive to mPFC top down-down control. 5-HT depletion in the mPFC increases expression of the immediate early gene c-fos in the BLA in the forced swimming test. It reduces GABA release induced by stress in the AMY [140, 141]. Moreover, unilateral 5-HT depletion in mPFC and infusion of an inhibitor of GABA synthesis into the contralateral BLA, selectively decrease immobility in the forced swimming test by inducing a “disconnection” between the PFC and the AMY [140].

The 5-HT<sub>2A</sub> receptor is the major excitatory serotonin receptor in the brain. 5-HT<sub>2A</sub> receptors have been implicated in mediating specific aspects of
stress-induced responses. Indeed, stressful events as those induced by a six week isolation in rat, induces 5-HT$_{2A}$ upregulation participating in anchoring the associative memory related to the stressful event [142, 143]. In humans, the density of 5-HT$_{2A}$ receptors in the mPFC was negatively associated with reduced threat-related right AMY reactivity [144].

**4.4.2 Medial prefrontal cortex and hippocampus**

mPFC and HIP form a functional neural networks as their activities are highly synchronized. Specific oscillatory activities, detectable by EEG, correlate with specific behaviors [85] and may provide means for regulating neural communications. Synchronous firing between different neuronal populations should more efficiently in driving the firing of downstream neurons. Such process is important for complex cognitive tasks that require coordination of long-range networks across the brain. Interestingly, in humans transcranial stimulation or deep-brain stimulation in mPFC can assist major treatment-resistant depression probably by stimulating the afore-mentioned pathway [145].

**4.4.3 Prefrontal cortex and raphe nuclei**

PFC and raphe nuclei form a functional loop. PFC is reciprocally connected to both the DR and MnR [146] and exerts a top-down control on 5-HT neurons. Descending excitatory fibers from the PFC exert complex functional regulation of 5-HT neuronal activity with an overall inhibitory effect mediated by 5-HT$_{1A}$ autoreceptors and feedforward inhibition [147, 148]. 5-HT$_{2C}$ receptors, the targets of antidepressant (mirtazapine, agomelatine) and antipsychotic drugs are expressed by GABAergic interneurons of the PFC and may function in a negative feedback loop involving reciprocal interactions between GABAergic and serotonergic neurons [149]. 5-HT$_{4}$ and 5-HT$_{7}$ receptors also exert a top-down control on DR and MnR 5-HT$^{+}$ neurons. 5-HT$_{4}$ receptor activation is associated with hypophagia induced by stress [150]. Selective activation of 5-HT$_{4}$ receptors in the PFC has been shown to induce modifications of SERT (downregulation) and 5-HT$_{1A}$ receptors and an increase in 5-HT release in the raphe [150]. 5-HT$_{7}$ receptors are transiently co-expressed with SERT in layers 5-6 neurons of mPFC during the P2-P14 period in mice, and modulate the development of mPFC neurons [137]. While SERT inhibition (SSRI treatment) during the P2-P14 period induces an increase in the number of mPFC synaptic contacts on DR neurons, ablation of 5-HT$_{7}$ (as observed in SERT-KO mice) induces a reduction of synaptic contacts in mPFC to DR [72, 137]. Therefore 5-HT$_{7}$ receptor inhibition counteracts the developmental effect mediated by SERT inhibition. SSRI treatment at P2-P14 or 5-HT$_{7}$ overexpression induces anxiety and depressive-like symptoms in adult mice. Such P2-P14 period is likely to correspond to the last trimester of pregnancy in humans [151]. During this period fetuses/babies (via the maternal milk) are highly impacted by maternal SSRI intake (see section 5). Since SERT-KO mice are not developing altered behavior, 5-HT$_{7}$ receptor antagonists appear as good candidate for the treatment of mood disorder during pregnancy or post-partum [152, 153].

Interestingly, the developmental maturation of the prefrontal cortex lasts far further into adolescence, up to the age of 20-24 years in humans [154]. Whether stress impacts the development apart the mature functions of mPFC is thus difficult to shape. Furthermore, the developmental expression of SERT in fetuses or infants is not known and much work has to be done to clarify the possible period of vulnerability to SSRI intake in humans (see [138] and section 5).
5. Sensitive periods for 5-HT in brain development: focus on limbic structures

When reviewing the role of 5-HT in the predisposition to develop PTSD or to cope with stress, it is necessary to untangle what is due to developmental modifications of the neuronal circuits apart from what is specifically due to modifications occurring at mature stages. During development, environmental stimuli sculpt neuronal circuits by an experience-dependent axon/synaptic refinement and pruning over the course of different critical periods, specific for each structure/function (i.e. the prefrontal system maturing all along development [154]). These processes have been shown to be highly sensitive to the imbalance in 5-HT levels depending on numerous genetic/epigenetic modifications of genes encoding the various actors of different 5-HT systems [93, 138, 151].

5.1 Subsets of 5-HT subgroups are differently implicated in response to stress

Although more complex, the development of 5-HT neurons largely depends on two transcription factors Lmx1b and Pet-1 [93, 94, 155, 156]. In Pet-1 knockout (KO) mice only few 5-HT+ neurons are preserved [155]. They correspond to 5-HT+ neurons located in the hypothalamic paraventricular nucleus (PVH), the ventral PAG and the ventral medulla, all projecting to the AMY while other brain targets are deprived of 5-HT+ axons. In conflict models, these mice show decreased levels of anxiety but enhanced freezing in fear conditioning tests. This suggests that 5-HT neurons could mediate anxiogenic effects in unconditioned anxiety tasks mainly through the innervation of forebrain areas such as the medial PFC and HIP, which receive no 5-HT innervation in Pet-1KO mice. Conversely data also suggests in Pet-1KO, that 5-HT might inhibit fear responses through the remaining 5-HT innervation toward specific AMY and PAG subnuclei [94, 156]. Further studies are needed for a better understanding of the contradictory effects of 5-HT on fear/anxiety responses in this model. Alternatively, compensatory mechanisms may occur in Pet1-KO mice that remain to go into in depth.

5.2 5-HT synthesis

In the mouse, a single-nucleotide polymorphism (SNP) has been identified in the Tph2 gene that leads to a significant decrease in brain serotonin levels [157]. This polymorphism may account for the different susceptibility to anxiety and stress-related event across mouse strains (the C57BL/6J strain being more resistant). In humans, several polymorphisms inducing a loss of function of the Tph2 gene have been detected and were associated with increased incidence of depression and anxiety or with exaggerated response of the AMY to, for instance, threatening faces. Such a loss of function appears relatively frequently in humans [158, 159]. TPH1 governs an average of 90% of 5-HT synthesis that occurs at the periphery. Peripheral 5-HT is then delivered in the blood (mainly stored in platelets) or during development by maternal/placental supply to the embryo prior BBB closure [160, 161]. Analysis of the impacts of maternal TPH1 deficiency on cortico-limbic development of the embryo is undergoing and suggests that TPH1 may durably alter vulnerability to stressful events (G. Vodjdani personal communication).

5.3 Vesicular storage of monoamines

In serotonergic cell bodies and axons 5-HT is stored into vesicles preventing its degradation. Evidences that VMAT2 may play a role in regulating stress-related
pathology was first discovered by reserpine treatment given to patients. Reserpine blocks VMATs function and induced depressive-like symptoms in humans. Reserpine's effect appears due to a defective storage of both catecholamine and 5-HT [162]. Mice displaying an altered copy of the VMAT2 allele display exaggerated corticosterone levels in response to forced swim test but respond normally to classic tests measuring anxiety-like behavior. Together this suggests that VMAT2 might play a role in regulating "depressive-like" behavior [163]. Magnitude to the antidepressant-like response appears to depend on the VMAT2 gene that is differentially modified in the BALB/c versus A/J mouse strain [164]. However, the relative contribution of catecholamines and 5-HT remains to be clearly established.

5.4 5-HT transporter

As discussed above, SSRIs are largely used for their anti-depressant and anti- anxiogenic effects in adults. However, despite the fact that they are largely used in pregnant women (2-13% of women [165]) suffering mood disorders, it has been clearly shown that they have paradoxical long-term effects on fetuses and infant development. When administered during perinatal periods SSRIs increased the risk to develop anxiety and depression in infancy. SSRIs cross the placenta, are detectable in breast milk and reach the developing brain where they disturb the development of neuronal circuitry. During gestation SSRIs induced a reduction of blood flow in the middle cerebral artery and reduced fetal head growth [166, 167]. SSRIs impair motor movements, speech perception at 6-10 months of age, increased irritability and altered psychomotor development in children [168, 169]. When given during pregnancy, they induce a two-fold increased predisposition to develop autism-spectrum disorder [170]. Such alterations appeared correlated with higher dosage of SSRIs [171].

These various developmental roles are mainly related to the different developmental time windows in which SERT is expressed by a large array of glutamatergic neurons, increasing extracellular 5-HT levels and modulating the synaptic and axonal maturation of these neurons. Such a role has been first illustrated by pioneer studies analyzing the development of the somatosensory and visual system. In these systems, 5-HT excess acting via 5-HT<sub>1B</sub> receptors, reduced glutamate release and induced the maintenance of immature features by SERT<sup>+</sup> axons [172–177]. In the limbic system SERT expression has been described in the HIP, the AMY, the mPFC (for exhaustive list and time-window of expression see Table 1 in [173] and Figure 3 in [178]). However, in these regions, SERT<sup>+</sup> neurons do not appear to express 5-HT<sub>1B</sub> receptors during development and are modulated by excess 5-HT via other pathways that remained to be identified.

Similarly, genetic downregulation of the SERT causes depression-related behaviors of developmental origin. In humans, a lesser-expressing form of Slc6a4, the so-called short allele variant (Slc6a4s), has been associated with an increased risk of developing depression in response to early-life stress [179, 180]. This mutation also induces a decreased volume and activity of vmPFC, a structure actively implicated in the control of stress-coping response, which is hypoactive in depressive patients (review in [181]). Interestingly, in mice a subset of glutamatergic neurons located in the layer 5-6 of the IL cortex that transiently express SERT during early postnatal life (P2-P11) project to the DR. Conditional SERT ablation in those neurons leads to a 40% increase in the number of functional PFC synapses onto both 5-HT and GABA neurons of the DR, an effect that is reproduced by postnatal fluoxetine administration. Alteration of this neuronal population has been shown to mediate the depressive- and anxiety-like symptoms observed in adults previously subjected to early postnatal exposure to SSRIs. Thus, this neuronal population provides
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a top–down control of emotional deficits induced by exposure to SSRIs during early postnatal life, resulting in long-lasting effects on mood. Interestingly, 5-HT blockade during the P2-P11 period also impacts the development of prelimbic (PL) pyramidal neurons that neighbor IL neurons but in a reverse way. These neuronal populations which normally play a role in promoting fear extinction or inhibiting fear extinction respectively are permanently altered by SERT blockade leading to the emergence of affective and fear-related altered behaviours [72, 182].

Long life expression changes in SERT expression, such as those observed in mice knockout for SERT (SERT-KO) or overexpressing SERT (SERT-OE) result in altered development of limbic structures. SERT-KO mice display impaired recall of fear extinction compared to wild-type littermate controls. In these mice, BA and LA principal glutamatergic neurons display abnormal dendritic spine density [183]. Conversely, SERT-OE mice have lower extracellular 5-HT levels [184] and exhibit impaired fear learning [185]. Genetic manipulation of SERT during development induces compensatory mechanisms leading to modified levels of 5-HT1A [11] and 5-HT2A Receptor expression [185, 186] in the AMY. Constitutive low levels of 5-HT2A receptors in BA and LA may result in a reduced GABAergic tone in this structure that would be hyperresponsive to traumatic reminders or even innocuous stimuli [102].

It is to note that other risk alleles could interact within a context of SERT deficiency and further increase the risk for abnormal neural circuitry development. For instance, it has been observed in rodents that PTEN (a phosphatase and tensin homolog), a gene associated to autism spectrum disorders [187] interacts with SERT haploinsufficiency to modify brain size and social behaviors [188].

5.5 Monoamine oxidases

MAOA blockade was one of the first treatments used in humans to relieve symptoms of depression. However they showed side effects since they increased anxiety-like behavior and caused resistance to chronic mild stress habituation [189]. MAOA-KO mice display increase 5-HT levels in the brain that normalized with age (by 6 months). These mice show exaggerated unconditioned and conditioned fear behavior as well as increase aggressive-like behavior [190]. Such increased outbursts of aggressive behavior were also observed in a Dutch family by men lacking MAOA gene (MAOA is located on the X chromosome [191]). More common variants located on the MAOA promoter leading to a low MAOA activity induce, in humans, various social and emotional alterations. They were associated with increased responses of the HIP and AMY to threatening faces and with a reduction of grey matter volume in anterior cingulate cortex, insula and HIP and increased orbitofrontal volumes [192, 193]. Interestingly, human carrier of a hyperactive MAOA form tends to be more prone to depressive-like behavior [194]. By contrast, human carriers of the hypoactive form of MAOA show higher subjective stress, lesser glucocorticoid responses and blunted HPA axis response to chronic stress reflecting HPA axis exhaustion [195]. However, such alterations probably of developmental origin, could not be attributed specifically to 5-HT increase but could also be due to the norepinephrine increase characterized in early developmental and adulthood of MAOA-KO mice [190]. Various interindividual DNA methylations were detected on the promoter core of MAOA in peripheral circulating white cells and appear to predict efficiently the MAOA brain endophenotype and the susceptibility to stressful events [196]. Interestingly, the levels of MAOA methylation return to normal during the process of cognitive therapy of patients undergoing panic disorders. This study suggests that modification of MAOA methylation is part of a process that mediates fear extinction [197, 198].
6. Conclusion

5-HT appeared early on the scale of evolution and is highly conserved across species. 5-HT modulates nearly all the functions that are needed to sustain life and is also implicated in the formation of brain circuits. Despite the fact that 5-HT was one of the first neurotransmitters/neurohormones discovered, the large number of receptors that mediate its role make it difficult to apprehend how 5-HT regulate these functions. Indeed, some 5-HT receptor expressions and time of expressions (they may be transiently expressed) are still to be determined in rodents and in humans. Even regions and times of SERT expression remains to be established in humans. The treatment of PTSD is complex depending on the delay from the stressful event and although SSRIs associated with various psychotherapies were...
initially largely prescribed, alternative pharmacological treatments are emerging. Some of them rely on 5-HT and modulate specific receptors, but a large array of pharmacological treatments currently used or clinically tested modulate other neurotransmitters, neurohormones or neuropeptides. They however all have a common goal: to decrease the strength of traumatic memories, to eliminate the pathological memories by reconsolidation blockade or even reducing the association between the traumatic event and the negative emotional valence. Anyway, the history of a patient and its genetic/epigenetic makeup he bears largely impact the way he will cope with a stressor. Regarding this last point it is clear that individual specificities of the 5-HT system will influence how people are coping with stress (Figure 4).

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Abbreviation list

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>5-HT</td>
<td>5-hydroxytryptamin</td>
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<tr>
<td>5-HIAA</td>
<td>5-hydroxyindolacetic acid</td>
</tr>
<tr>
<td>AADC</td>
<td>aminoacid decarboxylase</td>
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<tr>
<td>ACTH</td>
<td>adrenocorticotropic hormone</td>
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<tr>
<td>AMY</td>
<td>amygdala complex</td>
</tr>
<tr>
<td>BA</td>
<td>basal nucleus of amygdala</td>
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<tr>
<td>BBB</td>
<td>brain blood barrier</td>
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<tr>
<td>BLA</td>
<td>basolateral nucleus of amygdala</td>
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<tr>
<td>BNST</td>
<td>bed nucleus of the stria terminalis</td>
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<tr>
<td>cAMP</td>
<td>cyclic adenosin monophosphate</td>
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<tr>
<td>CA1-CA3</td>
<td>hippocampal fields</td>
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<tr>
<td>CCK</td>
<td>cholecystokinin</td>
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<tr>
<td>CE</td>
<td>central nucleus of amygdala</td>
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<tr>
<td>CEL</td>
<td>lateral part of the CE</td>
</tr>
<tr>
<td>CEM</td>
<td>medial part of the CE</td>
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<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>COMT</td>
<td>catéchol-O-méthyltransferase</td>
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<tr>
<td>CORT</td>
<td>cortisol/corticosterone</td>
</tr>
<tr>
<td>CR</td>
<td>calretinin</td>
</tr>
<tr>
<td>CRH or CRF</td>
<td>corticotrophin releasing hormone/factor</td>
</tr>
<tr>
<td>DR</td>
<td>dorsal raphe nuclei</td>
</tr>
<tr>
<td>vDR</td>
<td>ventral dorsal raphe</td>
</tr>
<tr>
<td>GABA</td>
<td>gamma aminobutyric acid</td>
</tr>
<tr>
<td>GR</td>
<td>glucocorticoid receptors</td>
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<tr>
<td>HIP</td>
<td>hippocampal formation</td>
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<tr>
<td>HPA</td>
<td>hypothalamic-pituitary-adrenal axis</td>
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<tr>
<td>IDO</td>
<td>indoleamine 2,3-dioxygenase</td>
</tr>
<tr>
<td>IL</td>
<td>infralimbic cortex</td>
</tr>
<tr>
<td>KO</td>
<td>knockout</td>
</tr>
<tr>
<td>LA</td>
<td>lateral nucleus of the amygdala</td>
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</tbody>
</table>
LC        locus coeruleus
MAOA      monoamine oxidase A
MAOB      monoamine oxidase B
MnR       median raphe nucleus
NAc       nucleus accumbens
NO        nitric oxide
NPY       neuropeptide Y
OPFc      orbitoprefrontal cortex
OE        over expression
PAG       periaqueductal grey
PFC       prefrontal cortex
PL        prelimbic cortex
PN        principal glutamatergic neurons
PTSD      post-traumatic stress disorder
PV        parvalbumin
PVH       paraventricular nucleus of the hypothalamus
SERT      serotonin transporter
SNP       single-nucleotide polymorphism
SOM       somatostatin
SSRI      serotonin reuptake inhibitor
TH        tyrosine Hydroxylase
Tph       tryptophan hydroxylase
Tph1      tryptophan hydroxylase type1
Tph2      tryptophan hydroxylase type 2
Vglut3    vesicular glutamate transporter 3
VIP       vasoactive intestinal polypeptide
VMAT 2    vesicular monoamine transporter 2
vmPFC     ventromedial prefrontal cortex
VTA       ventral tegmental area

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