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Review

Stress, serotonin, and hippocampal neurogenesis in relation to depression and antidepressant effects

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ABSTRACT

Chronic stressful life events are risk factors for developing major depression, the pathophysiology of which is strongly linked to impairments in serotonin (5-HT) neurotransmission. Exposure to chronic unpredictable stress (CUS) has been found to induce depressive-like behaviours, including passive behavioural coping and anhedonia in animal models, along with many other affective, cognitive, and behavioural symptoms. The heterogeneity of these symptoms represents the plurality of corticolimbic structures involved in mood regulation that are adversely affected in the disorder. Chronic stress has also been shown to negatively regulate adult hippocampal neurogenesis, a phenomenon that is involved in antidepressant effects and regulates subsequent stress responses. Although there exists an enormous body of data on stress-induced alterations of 5-HT activity, there has not been extensive exploration of 5-HT adaptations occurring presynaptically or at the level of the raphe nuclei after exposure to CUS. Similarly, although hippocampal neurogenesis is known to be negatively regulated by stress and positively regulated by antidepressant treatment, the role of neurogenesis in mediating affective behaviour in the context of stress remains an active area of investigation. The goal of this review is to link the serotonergic and neurogenic hypotheses of depression and antidepressant effects in the context of stress. Specifically, chronic stress significantly attenuates 5-HT neurotransmission and 5-HT_{1A} autoreceptor sensitivity, and this effect could represent an endophenotypic hallmark for mood disorders. In addition, by decreasing neurogenesis, CUS decreases hippocampal inhibition of the hypothalamic–pituitary–adrenal (HPA) axis, exacerbating stress axis overactivity. Similarly, we discuss the possibility that adult hippocampal neurogenesis mediates antidepressant effects via the ventral (in rodents; anterior in humans) hippocampus' influence on the HPA axis, and mechanisms by which antidepressants may reverse chronic stress-induced 5-HT and neurogenic changes. Although data are as yet equivocal, antidepressant modulation of 5-HT neurotransmission may well serve as one of the factors that could drive neurogenesis-dependent antidepressant effects through these stress regulation-related mechanisms.

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1. Introduction

Major depression is a recurrent and debilitating mental disorder with a lifetime prevalence of up to 20% in the general population, among the highest for psychiatric disorders (Kessler et al., 2003). Its diagnosis is based upon the presence of persisting affective, cognitive and behavioural symptoms (see Table 1), with a depressive episode requiring at least five of these symptoms (including depressed mood or anhedonia) persisting for at least two weeks to meet diagnostic criteria (American Psychiatric Association, 2013). Despite advancements in the development of therapeutics, current treatment options have not reached optimal efficacy. For instance, pharmacological antidepressant treatments typically require several weeks of treatment before improvement of symptoms can be observed (Jacobs et al., 2000). In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, the largest prospective, randomized antidepressant trial to date, 16% of participants dropped out due to tolerability issues, only 36.8% achieved remission after a first level treatment with an antidepressant, and 40% of remittances subsequently led to relapses (McGrath et al., 2008). A large proportion of remitted patients also suffer from residual symptoms that may fluctuate over time (Judd et al., 1998). These clinical limitations owe in part to gaps in knowledge about depressive pathophysiology, which is increasingly being recognized as involving multiple levels, encompassing disturbances in molecular signalling and in modulatory network function.

The aetiology of depression is still largely unknown, and theories vary widely in scope and perspective. For example, depression has been proposed to be an evolutionary adaptation to social environments (Allen and Badcock, 2006), or as a consequence of deleterious social environment (Billings et al., 1983). Cognitive theories span from earlier psychoanalytical perspectives of depression as a product of subconscious libidinal drive (Silverman, 1976) to more modern and supported cognitive theories concerning negative and irrational cognitive distortions regarding the self as well as ruminative cognitive patterns (Possel, 2011), and other psychosocial theories suggest particular personality factors such as introversion and pessimism might predispose to depression (Akiskal et al., 1983). More recent theoretical focus has largely been on biological factors, including a wealth of information supporting stress as a causal factor in depression, largely concerning chronic stress-related HPA dysregulation and toxicity from excessive glucocorticoid release (Lupien et al., 2009), though other theories posit that a downregulation of hippocampal neurogenesis underlies the disorder (Kempermann and Kronenberg, 2003), or suggest genetic or epigenetic factors for developing depression (Karg et al., 2011; Menke et al., 2012). The diathesis-stress model accounts for the interaction of a number of factors as crucial for the aetiology of depression. In particular, it posits that a depressive episode is triggered by a combination of a biological predisposition or intrinsic vulnerability (the diathesis) and a precipitating stressful event that may occur much later in life (Monroe and Simons, 1991). The diathesis may stem from genetic liabilities impacting different neurobiological systems involved in stress adaptation and affective processing (as discussed in later sections) or from postnatal or peri-adolescent events, such as child abuse, which directly impact early development of the nervous system (Kendler et al., 2002, 2006; Kendler et al., 2004). The effect of stress, on the other hand, can be modulated by many other factors such as personality, intrapsychic conflict, and presence (or absence) of social support, which could affect how stressful events are perceived in terms of controllability and agency. These environmental and stress factors could in turn influence biological systems, such as causing excessive glucocorticoid release or other HPA dysregulation, particularly in tandem with genetic polymorphisms influencing physiological response to stress, leading to changes in limbic and cortical brain areas as well as depressive (including cognitive) symptoms. Thus theories of depression to date involve evolutionary, social, environmental, interpersonal, psychoanalytical, cognitive, personality, behavioural, endocrine, cellular, and genetic and epigenetic factors and levels of analysis.

However, at the neurochemical level, the most widely accepted hypothesis concerns the depletion of monoamines, most notably of the indoleamine serotonin (5-hydroxytryptamine, 5-HT), in the brains of depressed patients. Indeed, conventional antidepressants that enhance 5-HT transmission, such as inhibitors of 5-HT reuptake, are the primary choice for first-line pharmacotherapy (Bambico et al., 2009a; Bambico and Gobbi, 2008). However, it is important to point out that some findings do not entirely support a simplistic explanation of depression as purely arising from a serotonergic deficit. For example, a decrease in 5-HT tone does not precipitate a full-blown clinical depressive phenotype in healthy individuals, although this has been shown to occur in some individuals with a history of depressive episodes. Moreover, not all depressed patients respond substantially to treatment with 5-HT agonists (Albert et al., 2012; Neumeister et al., 2002). In addition, although typically chronic treatment with antidepressants is necessary for therapeutic efficacy in treating depressive symptoms

Table 1
Symptoms of a depressive episode, at least five of which must persist for at least two weeks to meet diagnostic criteria, with depressed mood or anhedonia requisite (DSM-V; American Psychiatric Association, 2013).

Depressed mood most of the day, nearly every day
Compromised ability to experience pleasure (anhedonia) or interest in activities most of the day, nearly every day
Feelings of worthlessness or unreasonable guilt nearly every day
Sleep disturbance (insomnia or hypersomnia) nearly every day
Fluctuations in weight or appetite changes nearly every day
Psychomotor agitation or retardation nearly every day
Fatigue nearly every day
Diminished ability to think or concentrate nearly every day
Recurrent thoughts of death or suicidal ideation

in patients or reversing depression-like endophenotypes in animal models (Jacobs et al., 2000), extracellular 5-HT levels increase rapidly after administration (Hervas and Artigas, 1998), suggesting that restoration of 5-HT activity is not immediately sufficient for depressive amelioration and that additional longer-term mechanisms are likely involved. As such, other potentially contributing neurobiological etiological factors underlying depression (and its treatment) have been proposed, including deficits in other neurotransmitters and in neurotrophic factors such as brain-derived neurotrophic factor (BDNF), changes in hippocampal neurogenesis, HPA dysregulation, and circadian rhythm disruption (Hasler, 2010; Jacobs et al., 2000). Notably, these factors do not exist in isolation and frequently influence each other; for example (as discussed later in this article, in Sections 4.2 and 4.4), BDNF and 5-HT positively modulate hippocampal neurogenesis, which in turn regulates HPA function and response to stress.

5-HT is produced from the essential amino acid L-tryptophan in neurons of midbrain raphe nuclei, primarily by the dorsal raphe (DR), which contains about half of the mammalian nervous system's 5-HT neurons and represents a major source of 5-HT projections in the central nervous system, including the spinal cord (Dahlstroem and Fuxe, 1964; Descarries et al., 1982). Virtually all corticolimbic structures that are involved in mood regulation and the stress response, and which express receptors for 5-HT, are extensively innervated by DR-originating axons. These include the prefrontal cortex (PFC), amygdala, hippocampus and nucleus accumbens (NAc) (Holmes, 2008; Steinbusch, 1981). Not surprisingly, depressive symptomatology is extremely complex and overlaps with that of other neuropsychiatric disorders, such as the negative symptoms seen in schizophrenia. It has been hypothesized that disturbances in 5-HT activity in these postsynaptic targets underlie the wide range of emotional, cognitive, vegetative, and endocrine symptoms found in depression (Blier and de Montigny, 1999; Ressler and Nemeroff, 2000). Genetic (Caspi et al., 2003; Lesch, 2004; Levinson, 2006), brain imaging (Rosa-Neto et al., 2004), tryptophan depletion (Delgado et al., 1999; Leyton et al., 2000), and post-mortem studies (Mann et al., 2000) have provided further evidence in support of this view.

The origin of 5-HT impairment in depression is multifaceted and is likely due to the interaction of many intrinsic (e.g. genetic predisposition, gender and personality factors) and extrinsic factors (e.g. drug use, insufficient social support and stress) (Jans et al., 2007). Among environmental elements, stress has been given considerable attention as one of the most potent precipitating factors for depression. The emergence of depressive symptoms does indeed proceed in many cases from an experience with a stressful stimulus of one form or another, with which the organism is incapable of coping (Jans et al., 2007). Furthermore, the impact of genetic factors has been shown to be modulated by stress (Kendler et al., 1995; Pucilowski et al., 1993; Silberg et al., 1999). Under normal conditions, the stress response is integral to survival and proper biological and psychological functioning. However, an individual subjected repeatedly to stress, especially where it finds itself unable to neutralize the source of stress, may eventually succumb to despair. In this case, the accumulated psychological and physical demands (allostatic load) of the stressful experiences will have become detrimental to the central nervous system. These consequences are conducive in potentiating one's vulnerability to depression and other neuropsychiatric disorders. The neural transmission of monoamine transmitter systems has been examined in response to the depressogenic nature of stressful stimuli. It is gradually being recognized from neurochemical and electrophysiological studies that 5-HT neural excitability is greatly influenced by stress and other depressogenic factors, as well as manipulations or agents possessing antidepressant activity. This impact of stress on 5-HT activity could influence the spontaneous and evoked single-spiking and burst-firing activity of 5-HT neurons, as well as the function of their presynaptic and postsynaptic receptors. Stress could also affect different levels of the monoamine metabolic pathway (synthesis, intracellular trafficking, degradation, and reuptake), which could in turn influence electrochemical signalling (Holmes, 2008). Notably, environmental context may also play a role in the interaction between stress and monoaminergic antidepressant effects, as a recent study has shown that an enriched environmental context during treatment with the selective serotonin reuptake inhibitor (SSRI) fluoxetine leads to behavioural, glucocorticoid, and hippocampal and hypothalamic BDNF recovery from chronic stress, whereas fluoxetine treatment in a stressful context (after enriched housing) exacerbates these consequences of chronic stress (Branchi et al., 2013). Future studies may further elucidate whether environmental context, as well as other as yet unconsidered factors, modulates response to antidepressants and stress.

Chronic stress has also been shown to affect several aspects of hippocampal neuroplasticity. In particular, it potently decreases adult hippocampal neurogenesis (Dranovsky and Hen, 2006), the process by which new granule cell neurons are added throughout life to the dentate gyrus of the hippocampus. Given that hippocampal neurogenesis can regulate the hypothalamic–pituitary–adrenal (HPA) axis (Schloesser et al., 2009; Snyder et al., 2011), this consequence of chronic stress may exacerbate affective and behavioural responses to stress (Raison and Miller, 2003) in addition to predisposing an individual to subsequent depressive episodes in response to stress. Notably, treatments with antidepressant efficacy have been shown to increase hippocampal neurogenesis, including antidepressant medication (serotonergic as well as non-serotonergic (Banasr et al., 2006; Dranovsky and Hen, 2006) and non-pharmacological interventions such as electroconvulsive shock (Perera et al., 2007), transcranial magnetic stimulation (Ueyama et al., 2011), and exercise (Glasper et al., 2010; Kiuchi et al., 2012); the neurogenic efficacy of non-serotonergic therapies suggests that antidepressant-stimulated neurogenesis may also be regulated by non-serotonergic pathways. In fact, hippocampal neurogenesis may be required for the actions of some antidepressant agents, particularly serotonergic medications (Airan et al., 2007; Jiang et al., 2005; Santarelli et al., 2003; Surget et al., 2008), and this requirement may involve inhibition of the HPA axis by adult-born neurons in the hippocampus (Snyder et al., 2011).

This review considers the effects of short-term and chronic stress on 5-HT and neurogenesis-related neurophysiology, primarily within the context of stress-related animal models of depression. The central 5-HT system will be extensively discussed, particularly in relation to the influences of acute (Section 2) and chronic (Section 3) stress on 5-HT activity, as well as hedonic and motivational behaviour (Section 3.1). The role of presynaptic and postsynaptic 5-HT_{1A} receptors in the control of 5-HT activity, which have also been exhaustively studied in the past regarding receptor mechanisms of antidepressant action and stress adaptation, will be also be examined (Section 3.2). Finally, the potential role of hippocampal neurogenesis (Section 4) in depression and antidepressant effects (Section 4.1), its regulation by monoamines and neurotrophic factors (Section 4.2), its relationship with antidepressant response (Section 4.3), and the particular function of ventral (in rodents) or anterior (in primates) hippocampal neurogenesis in mediating response to stress and antidepressant effects (Section 4.4) will be discussed, along with a timeline of important stages in hippocampal neurogenesis and when neurogenic manipulations at various stages should have functional consequences on behaviour (Section 4.5). 5-HT and neurogenic responses to stress and influences on affective behaviour explored throughout this review are summarized in Fig. 1. We also propose a link between these two systems by suggesting that stress-induced neurogenic deficits contribute to 5-HT dysfunction through HPA dysregulation,

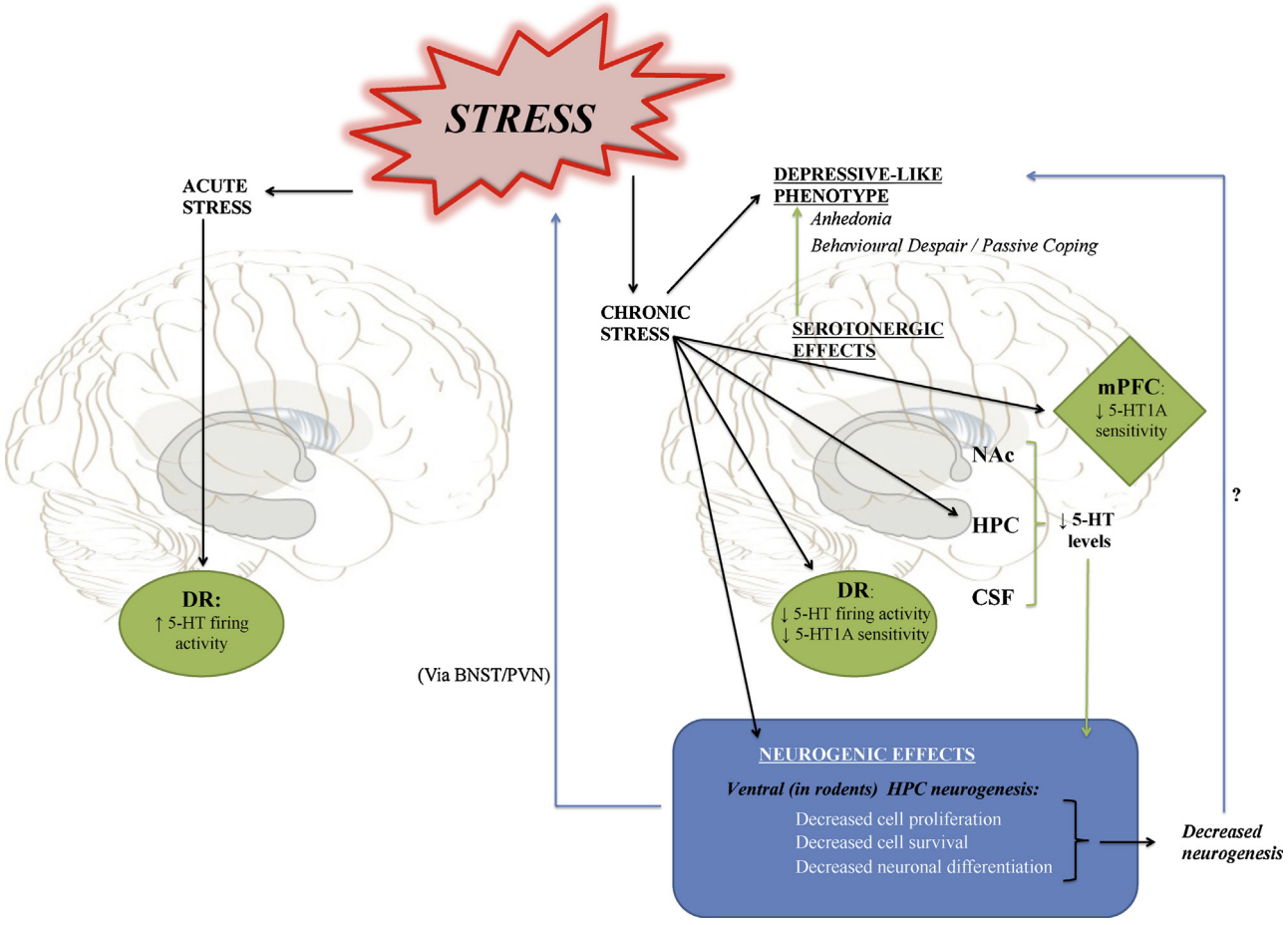

Fig. 1. Model of serotonergic (5-HT; green arrow), neurogenic (blue arrow), and behavioural effects of stress. Acute stress (dotted box) increases dorsal raphe (DR) 5-HT firing. Chronic stress leads to monoaminergic changes (solid box), decreased neurogenesis (blue box), and depressive symptoms or endophenotypes. Decreases in ventral hippocampal (in rodents; anterior hippocampal in humans) neurogenesis, which may underlie depressive/depression-like phenotypes, impairs regulation of the hypothalamic–pituitary–adrenal (HPA) axis, leading to HPA dysregulation and resulting monoaminergic and behavioural effects of chronic stress. Restoration of ventral hippocampal neurogenesis (e.g. through serotonergic antidepressant treatment) reinstates hippocampal regulation of HPA activity and reverses depression-like behavioural phenotypes. BNST, bed nucleus of the stria terminalis; CSF, cerebrospinal fluid; HPC, hippocampus; mPFC, medial prefrontal cortex; NAc, nucleus accumbens; PVN, paraventricular nucleus of the hypothalamus. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

and that antidepressants acting on 5-HT may drive hippocampal neurogenesis-dependent antidepressant effects through stress regulation.

2. Acute effects of stress on serotonergic neuronal activity

Under normal conditions, stress sets into motion a cascade of physiological mechanisms (i.e. autonomic and endocrine), paralleled by cognitive and affective processes, which rapidly prepare for the mobilization of energy (glycogenolysis). This equips the organism with an arsenal of defensive behaviours, such as escape, aggression, and avoidance, to address the source of danger. Acute stress exposure modulates the activity of the central 5-HT system as an important neurophysiological component of the stress response. Acute or short-term exposure to various noxious (physical) stimuli and psychological (situational) stressors have been found to influence the synaptic transmission of monoamines in varying degrees (Lanfumey et al., 2008; Sapolsky, 2003; Schultz, 2007). These responses are rather rapid, transient (may last for several seconds beyond stimulus offset) electrochemical changes that aim to re-establish homeostasis in the organism, and are generally commensurate to the demand imposed by the stressful situation (i.e. allostatic load) (Lanfumey et al., 2008; Sapolsky, 2003; Schultz, 2007).

Many electrophysiological studies have examined how various external stimuli and events might influence central 5-HT neural activity. These entail monitoring changes in the electrical discharge pattern of 5-HT neurons while awake animals are being exposed to the stimuli or are under anaesthesia immediately following exposure to stimuli. In freely moving cats, DR 5-HT neurons are resistant to any effect of acute physical or psychological stress on action potential firing, such as following exposure to restraint, loud (100 dB) white noise, confrontation with a dog, or to an injection of formalin into the extremities (Shima et al., 1986; Wilkinson and Jacobs, 1988). Similarly in anesthetized rats, DR 5-HT neurons are unaffected by repeated light flashes (Mosko and Jacobs, 1974). In anaesthetized rats, prior exposure to 30 min of restraint produces at most a slight non-significant increase in the mean firing activity of DR 5-HT neurons (Bambico et al., 2009b). However, some aversive stimuli, such as a foot shock (Schweimer and Ungless, 2010) or defensive encounter with an intruding conspecific in the home cage or experimenter (Walletschek and Raab, 1982), as well as innocuous (non-noxious) stimuli such as clicks (auditory) and light flashes (visual), are able to increase the firing rate of these neurons in awake cats and tree shrews or anesthetized rats (Heym et al., 1982; Trulson and Jacobs, 1979; Trulson and Preussler, 1984; Walletschek and Raab, 1982). In studies with anesthetized rats investigating the response of DR 5-HT neurons to prior restraint, interspike interval (ISI) histograms showed a clear disruption in the rhythmicity of firing in about half of 5-HT neurons monitored, compared to an otherwise Gaussian profile normally exhibited

under non-stress conditions; moreover, the probability of encountering 5-HT neurons that fired in burst was markedly increased by stress exposure (about 50% in comparison to 18% under control, non-stress condition) (Bambico et al., 2009b). Crawford et al. (2010) proposed that the excitability of these 5-HT neurons in response to acute stress, particularly exhibited by 5-HT neurons in the lateral wings and the medial extent of the DR, is consistent with the their unique intrinsic active and passive membrane properties (greater membrane resistance, hyperpolarized spike threshold, smaller activation gap, larger tau, long afterhyperpolarization duration, increase in current-induced firing rate). These characteristics are argued to contribute to greater converging input and consequent output, necessary for a role for stress adaptation. In agreement with these electrophysiological studies, several neurobiological studies have detected an increase in immediate-early gene expression (such as c-fos) in the DR, indicating enhanced activation of 5-HT neurons in this midbrain nucleus, following acute stress exposure (Amat et al., 2005; Commons, 2008; Crawford et al., 2010; Grahn et al., 1999; Hale et al., 2008; Takase et al., 2004). Corroborating stress-induced activation of DR 5-HT neurons, in vivo microdialysis has also correlated acute stress exposure with significant increases in the extracellular/tissue levels or 5-HT efflux, detected within the DR, medial PFC (mPFC), amygdala and hippocampus, which could be related to the rapid increase in amount of transmitter released per electrical impulse (Bambico et al., 2007; Gartside et al., 2000; Holmes, 2008; Mo et al., 2008; Sheikh et al., 2007). This has been observed following a wide range of different stimuli (such as electric shock, tail pinch, exposure to an elevated platform or predator, social defeat, restraint/immobilization), but not for all forms of aversive stimuli and contexts (Amat et al., 2005; Holmes, 2008; Maier and Watkins, 2005). The exact synaptic and neurophysiological mechanisms that drive increases in tonic or burst-firing activity in DR 5-HT neurons by acute stress have not been completely clarified. A number of hypotheses have been proposed, including a role for excitatory glutamatergic feedback (Crawford et al., 2010; Crespi, 2009, 2010; Rouchet et al., 2008) and alterations in the function of small-conductance calcium-activated potassium (SK) channels (Crespi, 2009, 2010; Rouchet et al., 2008) that are expressed in midline and lateral wing DR 5-HT neurons. The role of glutamatergic inputs from the mPFC to the DR has been the subject of recent investigations regarding the DR 5-HT-activating consequences of acute stress; this has been explained in relation to the ability of the mPFC to communicate synaptic information to DR 5-HT neurons about the controllability of acute stressors (Amat et al., 2005, 2008, 2010; Maier et al., 2006; Maier and Watkins, 2005), as will be discussed in the following sections. Amat et al. (2005) have determined through measurements of c-fos expression that inescapable stressors possess the capacity to activate 5-HT neurons, particularly those located in the caudal region of the DR, and that this activation is associated with the behavioural consequences of acute stress. Such activation can be driven by modifications in mPFC-DR glutamatergic excitatory input to GABAergic and 5-HT neurons in the DR (Amat et al., 2005; Maier et al., 2006). Other stress-associated events may act in concert with these mechanisms in modulating 5-HT activity. These include enhancement in tryptophan hydroxylase (TPH)2-mediated intracellular synthesis, vesicular monoamine transporter (VMAT)2-mediated vesicular packaging of transmitter, and reduction in 5-HT cleavage by monoamine oxidase (MAO)-A and in reuptake by the 5-HT transporter (5-HTT). In an extensive review, Holmes (2008) suggested that these are also subject to genetic variability (strain and species-dependence in animal studies), and are likewise sensitive to conventional and putative antidepressants. More investigations are warranted to clearly understand how properties of stressors, such as severity, chronicity, controllability, and aversiveness interact to affect 5-HT activity, and to determine whether and which discrete 5-HT neuronal subgroups are influenced by stress.

3. Effects of chronic stress on behaviour and 5-HT activity

3.1. Chronic stress and other models of depression

As depression is a complex, symptomatically heterogenous disorder, existing animal models may be limited in reproducing all of the pathological dimensions of depression, and face a particular obstacle in demonstrating face validity. Nevertheless, these models can be very useful testing tools, as they reproduce particular endophenotypes related to specific components of depression symptomatology. Fig. 2 illustrates some of these animal models of depression and tests for depressive-like behaviour.

Vulnerability to a depressive-like state can be precipitated by a number of validated experimental manipulations that mimic early life adversity, genetic liabilities, stress, and other predisposing factors (Monroe and Simons, 1991). The maternal separation model of early life adversity involves periodic separation of neonates from the dam (Leussis et al., 2012). Genetic manipulations, such as with 5-HT transporter knockout (SERT$^{-/-}$) mice (Olivier et al., 2008) and cannabinoid CB1 receptor knockout (CB1$^{-/-}$) mice (Valverde and Torrens, 2012), have shown depressive-like phenotypes. Similarly, congenital learned helplessness (cLH) rats are selectively bred for learned helplessness behaviour (Weiss et al., 1998), and Flinders Sensitive Line (FSL) rats are selectively bred for increased responses to cholinesterase inhibitors (Overstreet, 1993). Olfactory bulbectomy (complete ablation of the olfactory bulb) has been used to model depression (Song and Leonard, 2005), and causes widespread neuronal degernation and remodelling in limbic, raphe, and other brain regions (Harkin et al., 2003). Pharmacological models are also used, including psychostimulant (such as amphetamine) withdrawal (Barr et al., 2002) and clomipramine treatment in neonates (Vogel et al., 1990). Finally, multiple models involve repeated exposure to stress or stress hormones, including chronic administration of corticosterone (Rainer et al., 2011), chronic restraint stress (Chiba et al., 2012), chronic social defeat by a dominant conspecific (Avgustinovich et al., 2005), prolonged social isolation (Brenes Saenz et al., 2006), repeated foot shock (Swiergiel et al., 2008), and chronic unpredictable mild stress (CUS) exposure (Willner et al., 1992), which have been shown to increase glucocorticoid levels and induce depressive-like phenotypes.

Although the neurobiological foundations of these models may be argued to be distinct from that of depression, these models are typically validated by behavioural tasks with quite remarkable predictive validities in screening for antidepressants, including the forced swim test (FST), tail suspension test (TST), and learned helplessness test (LH) measuring stress coping impairment or behavioural despair, the sucrose preference test (SPT) measuring anhedonia-like reactivity, the novelty-suppressed feeding test (NSFT) examining anxiety-like behaviour, and the social interaction test (SIT) examining sociality (Cryan and Holmes, 2005; Dulawa and Hen, 2005; Lucki, 1997; McArthur and Borsini, 2006; Nestler et al., 2002; Willner, 1990).

Of these models, CUS merits particular examination due to its widespread use and validation (Willner, 1997, 2005). In this model, multiple varied non-debilitating inescapable and uncontrollable physical, psychological, and circadian stressors are applied in an unpredictable (occurring at any time) and randomized fashion for several weeks, whereas control (unstressed) animals are not exposed to any of the stressors and may be housed in pairs throughout the course of the experiment (Bambico et al., 2009b; Bekris et al., 2005; Moreau et al., 1992, 1995; Willner et al., 1992). Table 2 shows some of the commonly used micro-stressors, whose combinatory and cumulative effects are sufficient to produce

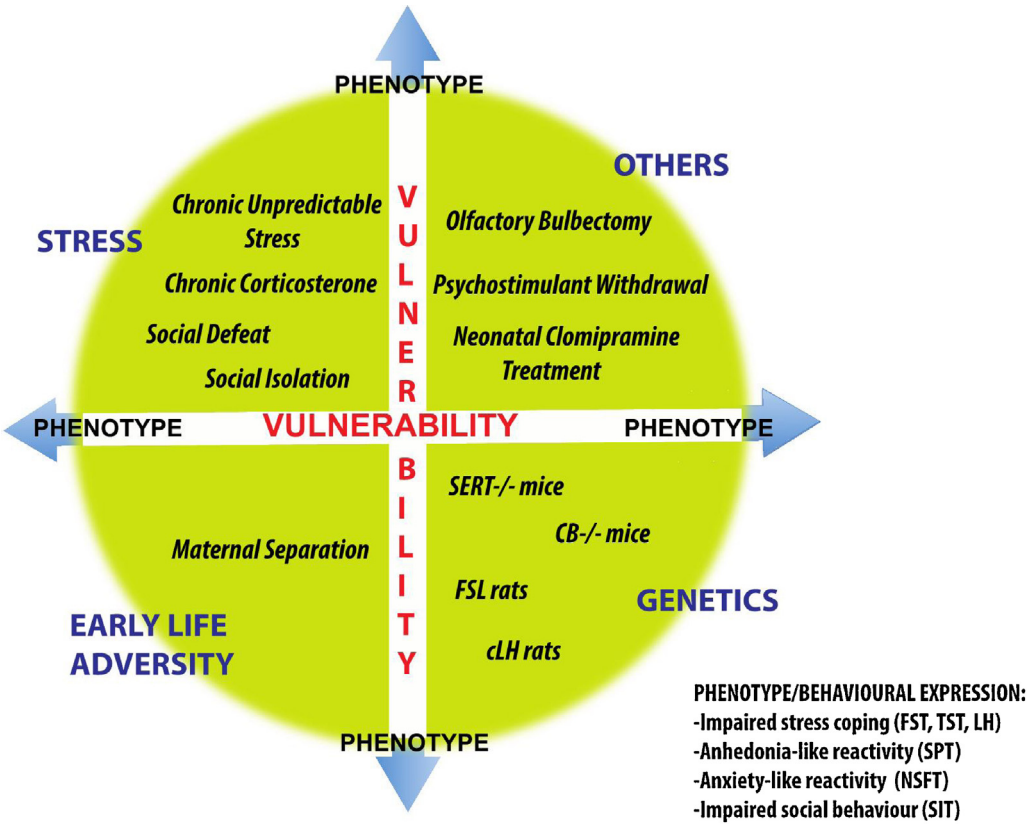

Fig. 2. Animal models of depression vulnerability and depressive-like reactivity. Vulnerability to a depressive-like state can be precipitated by a number of experimental manipulations that mimic early life adversity, genetic liabilities, stress, and other predisposing factors (within the circle). Following development of depression vulnerability, enhanced expression of depressive-like phenotypes/behavioural reactivity can be assayed by the forced swim test (FST), tail suspension test (TST) and learned helplessness test (LH) that measure impairment in stress coping; by the sucrose preference test (SPT) for anhedonia-like reactivity; by the novelty-suppressed feeding test (NSFT) for anxiety-like reactivity; and by the social interaction test (SIT) for perturbed sociality. Other behavioural and physiological measures not shown here include exploratory behaviour in an open field, intracranial self-stimulation for reward sensitivity, changes in sleep architecture, and modifications in neuroendocrine response (corticosterone assays and dexamethasone challenge). $CB1^{-/-}$, cannabinoid CB1 receptor knockout; cLH, congenital learned helplessness; FSL, Flinders Sensitive Line; $SERT^{-/-}$, serotonin transporter knockout.

depressive-like behaviours. CUS exposure delays or prevents habituation, has increased physical and psychological demand, progressively increases corrective behavioural/physiological reactivity, and adversely alters neural systems involved in subsequent stress appraisal (Fairbank et al., 1991; Roman et al., 2004), effects than could otherwise be more effectively overcome with short-term exposure and with one kind of stressor (homotypic). CUS can therefore lead to the eventual exhaustion of physical and cognitive resources, which eventually translates to depression-relevant behavioural responses. These depressive-like consequences develop only after an extended duration (Bambico et al., 2009b; Banasr and Duman, 2008; Grippo et al., 2005, 2006; Kim et al., 2003), with the exact time of onset varying, likely due to differences in the CUS protocol (intensity, duration, types and combination of stressors), animal strain, and handling procedures used across different laboratories. Depressive-like features cover a large spectrum that includes alterations in emotional and hedonic reactivity, cognitive function, motivational states and grooming behaviour and body weight, features analogous to those found in depressed patients, and which could accordingly be prevented or reversed by chronic treatment with antidepressants (Moreau et al., 1992, 1995; Willner, 1997, 2005; Willner et al., 1987, 1992).

Table 2
Stressors used in the chronic unpredictable stress (CUS) model of depression.

Lighting conditions and disturbance in the circadian cycle
Frequent, intermittent on-off switching of lights
Abrupt reversal of the light/dark cycle
Stroboscopic lights
Food and water availability
Restricted food supply
Restricted water supply
Water deprivation
Food deprivation
Housing conditions
Isolation
Group housing
Cage tilt
Used mouse cage exposure
Damp bedding
Ecological challenges
Foreign object exposure
Cold room
Noise
Predator odour
Restraint
Forced swim

CUS possesses face (symptom profile, including anhedonia), construct (theoretical background), predictive (treatment profile), and etiological (causation) validity as a model of depression (Willner, 2005), and its validity may surpass that of other models (including those that also involve repeated stress), many of which fail to show validity in each of these three domains or to show the same depression-relevant chronicity of behavioural endophenotype duration (Willner, 1997). The efficacy of long-term, but not short-term, antidepressant treatment in reversing behavioural and

biochemical sequelae associated with CUS reliably mirrors the temporal delay of antidepressant treatment effect in depressed patients (predictive validity) (Willner, 1997, 2005; Willner et al., 1987).

CUS also mimics from the human milieu the role of stress in the aetiology of depressive disorders. Epidemiological studies have indicated that chronic exposure to stressful life events in the human population is considered a major risk factor for developing depression (Firk and Markus, 2007; Kendler et al., 2004). Interestingly, the distinct pattern of depressive symptoms has been found to be dependent upon the characteristics (e.g. the kind and severity) of the stressful event(s) experienced (Keller et al., 2007). This association of stress and depression has also been supported by experiments among healthy individuals, such as those demonstrating that a stressful experience and associated changes in cortisol responses greatly magnify self-reported depressive symptoms and the effects of mood-impairing manipulations including tryptophan depletion (Pruessner et al., 2003; Richell et al., 2005). In recent years, evidence for the strong link between stress and genetics as an essential factor in the pathogenesis of depressive disorders has been rapidly mounting (El Hage et al., 2009; Jans et al., 2007). Polymorphisms in genes encoding glucocorticoids and attendant receptors or other elements of the HPA axis, such as the CRF-R1 and NR3C1 genes (for review, see El Hage et al., 2009), in the 5-HT transporter-linked promoter region (5-HTTLPR) of the 5-HT transporter-encoding SLC6A4 gene (chromosome 17, 11 in mouse), or of the Htr1A promoter region on the 5-HT_{1A}-encoding gene on chromosome 5 (13 in mouse) confer greater tendency to develop depression or depressive symptoms after stressful life events, such as childhood trauma (Caspi et al., 2003; Jacobs et al., 2006; Kaufman et al., 2004; Keller et al., 2007; Kendler et al., 2004, 2005; Le Francois et al., 2008; Zalsman et al., 2006). In particular, the 5-HTTLPR s/s genotype, associated with reduced 5-HTT expression, and the G(−1019) variant of the Htr1A promoter region, which is associated with reduced 5-HT_{1A} receptor expression, have been found to impair affective regulation (Caspi et al., 2010; Le Francois et al., 2008; Lesch et al., 1996). Moreover, CUS exposure in both humans and animals is argued to profoundly influence epigenetic regulation that may produce gradual but stable behavioural and neurobiological adaptations seen in depression (for review, see Tsankova et al., 2007; Zhang and Meaney, 2010). In particular, chronic but not acute exposure to stress has been determined to decrease the function of the enzyme histone deacetylase (HDAC5) in the mouse NAc, leading to increased histone acetylation and transcription of target genes and hypersensitivity to the behavioural effects of chronic stress (Renthal et al., 2007). Furthermore, CUS increases hippocampal HDAC activity and decreases histone acetylation (Ferland and Schrader, 2011). Finally, resilience or susceptibility to stress is also a feature of both chronic stress animal models of depression and depressive aetiology in humans (Russo et al., 2012). Specifically, the subset of animals submitted to CUS that are susceptible to developing anhedonia also show decreased hippocampal expression of synapse-related genes, increased thymopoietin, and increased glucocorticoid levels, similar to findings in depressed patients (Brown et al., 2004; Christiansen et al., 2012; Duric et al., 2013; Goldstein et al., 2000; Henningsen et al., 2012).

3.2. Chronic unpredictable stress alters serotonergic neural activity

The underlying neurobiological underpinnings of CUS-induced depressive-like behaviours are likely multi-factorial and may include neurodegenerative, morphological and immunological processes, as well as impairments in intracellular signalling and hippocampal neurogenesis. Indeed, CUS results in the attenuation of cell proliferation and neurogenesis (Jayatissa et al., 2009; Mineur et al., 2007), extracellular signal-regulated kinase (Erk) phosphorylation (Qi et al., 2006), vascular endothelial growth factor (VEGF) expression (Bergstrom et al., 2008), and an increase in long-term depression (Holderbach et al., 2007) in key limbic structures, notably the hippocampus and the PFC. It also enhances pro-inflammatory cytokines and immunosuppressant processes (Pitychoutis et al., 2009; Rasheed et al., 2008). At the neurochemical level, CUS can directly impact the 5-HT system, the impairments of which correlate with several dimensions of depressive symptomatology.

3.2.1. Effect of CUS on DR serotonergic neural activity

Following CUS, spectrophotometric and neurochemical analyses have found an increase in MAO-A (Bhutani et al., 2009) and a global depletion of 5-HT (Ahmad et al., 2010; Bhutani et al., 2009; Dang et al., 2009a,b; Rasheed et al., 2008). There have also been reports of reductions in 5-HT release, tissue concentration, and synaptic activity in key corticolimbic structures, such as the hippocampus and NAc (Bekris et al., 2005; Kang et al., 2005; Luo et al., 2008; Yi et al., 2008). These changes are consistent with those observed in a subgroup of depressed patients who display reductions of the 5-HT metabolite 5-hydroxyindoleacetic acid (5-HIAA) in cerebrospinal fluid (van Praag, 1996), although some studies on 5-HT metabolites in depressed patients provide mixed results (Belmaker and Agam, 2008). Moreover, experimentally-induced depletion of 5-HT through a diet lacking the 5-HT precursor tryptophan produces greater depressed mood among healthy subjects with a family history of depression (Benkelfat et al., 1994; Klaassen et al., 1999a,b), and triggers a relapse among remitted depressive patients (Delgado et al., 1999), likely involving a direct attenuating effect on 5-HT action potential firing. CUS has been shown to induce a significant decline of about 35% in the mean spontaneous neural firing activity of 5-HT neurons recorded from the DR, a significant decrease in the number of spontaneously active neurons, anhedonia-like reductions in the preference for and intake (absolute and relative) of sucrose in the SPT (Bambico et al., 2009b), which is a depression-related endophenotype thought to be instigated by dysregulation in dopaminergic neurotransmission (Willner, 2005), and enhanced immobility (passive behavioural coping or behavioural despair) in the FST (Banasr and Duman, 2008). Conversely, the observed enhancement in 5-HT neurotransmission is widely considered to be a benchmark of antidepressant-like activity (Bell et al., 2001; De Montigny, 1981).

3.2.2. CUS downregulates presynaptic 5-HT_{1A} autoreceptor function

Among the numerous subtypes of 5-HT receptors, the 5-HT_{1A}, a Gi/Go-protein-coupled receptor, is one of the most commonly studied in relation to the neurobiology underlying mood disorders and antidepressant response (Holmes, 2008). The activity of DR 5-HT neurons is negatively regulated by these receptors, which may be localized on somatodendritic compartments (presynaptic autoinhibitory receptors) of 5-HT neurons or postsynaptic targets of 5-HT terminals (Hall et al., 1997; Pazos et al., 1987). Postsynaptic 5-HT_{1A} receptors, such as those in the ventral (infralimbic) regions of the medial PFC (mPFC), exert inhibitory and excitatory control over DR 5-HT neuronal activity (Hajos et al., 1999; Martin-Ruiz and Ugedo, 2001) by modulating glutamatergic excitatory input to DR GABAergic and 5-HT neurons (Amat et al., 2005; Bambico et al., 2007), as discussed in the next section. For this position to influence 5-HT neural activity, presynaptic and postsynaptic 5-HT_{1A} receptors are implicated in the therapeutic mechanisms of antidepressants and are putative antidepressant targets (Blier et al., 1998).

Alterations in the function and levels of 5-HT_{1A} receptors in depressive pathology are not as consistently reported in humans as in animal models. As shown in Table 3, human brain imaging and

Table 3
Evidence of disrupted 5-HT_{1A} receptor function in depressed patients and animal models of depression, and related effects of antidepressants. Note that some findings are equivocal in the literature. $SERT^{-/-}$, 5-HT transporter knockout; $CB1^{-/-}$, cannabiniod receptor knockout; SSRI, selective 5-HT reuptake inhibitor; TCA, tricyclic antidepressant.

	5-HT_{1A} changes	Reference (species)
Animal models		
$SERT^{-/-}$ mice	↓ (desensitized) presynaptic	Fabre et al. (2000), Gobbi et al. (2001), Li et al. (2000) and Lira et al. (2003)
$CB1^{-/-}$ mice	↓ presynaptic	Aso et al. (2008, 2009)
Chronic stress (CUS)	↓ presynaptic	Bambico et al. (2009b) (rat); Froger et al. (2004) (mouse); Lanfumey et al. (1999) (mouse)
Chronic corticosterone treatment	↓ presynaptic	Rainer et al. (2011) (mouse)
Maternal separation	↓ presynaptic	Gartside et al. (2003) (rat)
Neonatal clomipramine treatment	↓ presynaptic	Kinney et al. (1997) (rat); Maudhuit et al. (1995) (rat); Maudhuit et al. (1996) (rat)
Acute stress exposure	↔ presynaptic	Laaris et al. (1997) (rat); Steciuk et al. (2000) (rat)
Chronic SSRI treatment	↓ presynaptic	Le Poul et al. (1997) (rat)
Chronic TCA treatment	↑ postsynaptic (hippocampus)	Bijak et al. (1996) (rat)
Depressed patients (5-HT_{1A} mRNA, 5-HT_{1A} receptor density and function)	↑ presynaptic	Stockmeier et al. (1998)
	↓ presynaptic, also distribution volume	Arango et al. (2001), Meltzer et al. (2004) and Rabiner et al. (2004)
	↔ presynaptic	Bhagwagar et al. (2004)
	↓ postsynaptic, medicated and unmedicated patients	Drevets et al. (2007), Hirvonen et al. (2008), Neumeister et al. (2004) and Sargent et al. (2000)
	↔ postsynaptic, midbrain	Stockmeier et al. (1998)
	↓ neuroendocrine response to agonist	Pitchot et al. (2005)
	↓ hypothermic response to agonist	Cowen et al. (1994)

postmortem studies on depressed patients have obtained divergent findings (van Praag, 2004). These equivocal findings could arise from the difficulty of delineating depression-specific changes from those associated with comorbidities, including other neuropsychiatric conditions and history of drug use, as well as from those incurred by medications. However, animal models have consistently shown reductions in somatodendritic 5-HT_{1A} autoreceptor sensitivity in the DR. This has been demonstrated in ex vivo and in vivo electrophysiological experiments on CUS-exposed rats or mice by a diminution in the inhibitory response of DR 5-HT neurons to a local application of the 5-HT_{1A} agonist/partial agonist 8-OH-DPAT or ipsapirone (Table 3). Interestingly, CUS-induced 5-HT_{1A} desensitization was accompanied by a reduction in spontaneous 5-HT firing activity (Bambico et al., 2009b), effects that were recapitulated in 5-HT transporter null ($SERT^{-/-}$) mutant mice (Fabre et al., 2000; Gobbi et al., 2001; Li et al., 2000; Lira et al., 2003) and neonatal clomipramine treatment models of depression (Kinney et al., 1997; Maudhuit et al., 1995, 1996). These observations are striking given that chronic SSRI administration decreases 5-HT_{1A} autoreceptor binding in depressed patients (Gray et al., 2013). In rodent electrophysiology models, SSRIs acutely decrease 5-HT neuronal firing activity, and following chronic administration desensitize 5-HT_{1A} autoreceptors to restore normal 5-HT neuronal firing activity (Bambico et al., 2009a; Bambico and Gobbi, 2008; Blier and de Montigny, 1999). As SSRI-mediated and CUS-induced 5-HT_{1A} autoreceptor desensitization are associated with opposing behavioural profiles, it is likely that these progress via somewhat unrelated mechanisms. SSRI-induced 5-HT_{1A} autoreceptor desensitization appears to determine the gradual restorative increase in DR 5-HT firing activity with chronic SSRI treatment. A more complex process might be at play though, as acute and not chronic SSRI treatment has been reported to internalize DR 5-HT_{1A} autoreceptors (Riad et al., 2004, 2008). CUS-induced desensitization, however, is paralleled by a lower basal 5-HT neuronal firing tone (Bambico et al., 2009b). It can therefore be hypothesized as a compensatory response to the primary CUS-induced decrease in 5-HT tone, possibly among a presumed subpopulation of 5-HT neurons (about 16%) with low or null expression of these 5-HT_{1A} autoreceptors (Kiyasova et al., 2013).

There is a long-standing view that 5-HT_{1A} autoreceptor desensitization is essential for the therapeutic mechanism of SSRIs. 5-HT_{1A} autoreceptors are desensitized by chronic treatment with SSRIs, whereas postsynaptic 5-HT_{1A} receptors, particularly those in the hippocampus, are sensitized by chronic tricyclic antidepressant (TCA) treatment and electroconvulsive shock administration (for review, see Bambico et al., 2009a; Bambico and Gobbi, 2008; Hill et al., 2009; Sharp et al., 2007). It is recognized that the desensitizing action of SSRIs occurs to disengage negative regulation of 5-HT neuronal activity, but may also tap into other 5-HT_{1A}-related intracellular processes. However, SSRI treatment has been shown to reverse CUS-induced behavioural deficits (for review, see Willner, 1997, 2005), suggesting that the occurrence of 5-HT_{1A} desensitization with CUS does not completely abrogate the therapeutic action of SSRIs. This has been similarly observed in $CB1^{-/-}$ (Steiner et al., 2008) (Aso et al., 2008, 2009) and 5-$HT_{1A}^{-/-}$ (Santarelli et al., 2003) mice, which are responsive to the antidepressant effects of SSRIs (paroxetine) and TCAs (imipramine and desipramine), respectively, despite the absence or desensitization of 5-HT_{1A} autoreceptors. More recently, Richardson-Jones and colleagues generated mice with high and low 5-HT_{1A} autoreceptor expression in the DR, without affecting postsynaptic 5-HT_{1A} receptors, by genetically engineering the Htr1A gene that encodes 5-HT_{1A} (Richardson-Jones et al., 2010). They found that high-DR 5-HT_{1A} mice showed a blunted physiological response to acute stress, increased passive behavioural coping and a non-response to fluoxetine despite displaying gradual desensitization of 5-HT_{1A} autoreceptors. Conversely, low-DR 5-HT_{1A} mice were more responsive. It appears from these studies that SSRIs may still be therapeutically active in the presence of desensitized 5-HT_{1A} autoreceptors, but not in their complete absence, and that the interplay between the sensitivity and expression of these receptors may more reliably determine the severity of the depressive-like state and the response to SSRIs. This notion corroborates some clinical studies (Rabiner et al., 2004) but not others (Lan et al., 2013; Miller et al., 2013), and therefore

warrants further investigation on the differential role of 5-HT_{1A} receptor expression, internalization, and sensitivity in the partial or lack of response to SSRIs among a subgroup of patients.

3.2.3. CUS alters postsynaptic 5-HT_{1A} heteroreceptor function: possible influence on medial prefrontal glutamatergic feedback

In addition to the effects of CUS on presynaptic 5-HT_{1A} autoreceptors, an impact on postsynaptic 5-HT_{1A} heteroreceptors is likely to contribute to the behavioural and neurophysiological impairments found in CUS-exposed animals, including impairments in midbrain 5-HT neuronal activity. Postsynaptic 5-HT_{1A} heteroreceptors located in different corticolimbic regions, such as the PFC, amygdala, and hypothalamus, have been suggested to indirectly modulate DR 5-HT activity (Bosker et al., 1997; Holmes, 2008). Of these, the mPFC is of particular interest as it abundantly expresses 5-HT_{1A} and serves as the origin of most cortical projections to the DR (Gabbott et al., 2005; Hajos et al., 1999; Peyron et al., 1998). 5-HT_{1A} receptors in the mPFC, like 5-HT_{1A} autoreceptors in the DR, exert regulatory feedback onto DR 5-HT neurons via a long-range loop (Celada et al., 2001; Gabbott et al., 2005; Hajos et al., 1999; Martin-Ruiz and Ugedo, 2001; Peyron et al., 1998). Application of the selective 5-HT_{1A} agonist 8-OH-DPAT directly into the mPFC inhibits the spontaneous and glutamate-mediated neuronal firing of the major projection neurons therein (Araneda and Andrade, 1991; Ashby et al., 1994; Borsini et al., 1995; Cai et al., 2002). This could, in turn, inhibit DR 5-HT neuronal firing activity, as has been demonstrated under conditions where DR somatodendritic 5-HT_{1A} autoreceptor activity was inhibited by pertussis toxin blocking intracellular signalling of Gi/Go proteins (Martin-Ruiz and Ugedo, 2001). Interestingly, following CUS it was observed that a systemic injection of 8-OH-DPAT that could activate these mPFC 5-HT_{1A} receptors failed to attenuate DR 5-HT neuronal firing activity (Bambico et al., 2009b). As DR somatodendritic 5-HT_{1A} autoreceptors were desensitized in these CUS-exposed animals, this decrease in the ability of 8-OH-DPAT to inhibit 5-HT neurons suggests that mPFC 5-HT_{1A} receptors themselves were desensitized by CUS, and as 5-HT_{1A} receptors are inhibitory, their desensitization in the mPFC would translate into a hyperactivation of mPFC glutamatergic projections to the midbrain. The desensitization of mPFC 5-HT_{1A} receptors following CUS concurs with observations from other animal models, as well as with the significant reduction of PFC 5-HT_{1A} receptor binding and 5-HT_{1A} sensitivity found in treated and untreated depressive patients (Drevets et al., 2007). However, contradictory findings have also been reported, such as reports of an increase in postsynaptic 5-HT_{1A} receptor density (Vicentic et al., 2006; Ziabreva et al., 2003), mRNA levels (Neumaier et al., 2002), or sensitivity (Arborelius et al., 2004) in the rodent model of maternal separation and congenital learned helplessness. Nevertheless, data from brain imaging studies on depressed patients appear to converge at abnormal hyperactivation in cortical regions such as the anterior cingulate and the subgenual cortex (Price and Drevets, 2010), structures that are considered analogous to the mPFC in the rodent. Indeed, the most parsimonious hypothesis that could explain this hyperactivity is a desensitization or downregulation of inhibitory 5-HT_{1A} receptors in the PFC.

The mPFC-DR circuit is an important locus for cognitive appraisal of stressful situations, and likely subserves some of the cognitive, executive, and memory-related dysfunctions associated with depression, such as disturbance in concentration and learning, negative and irrational cognitive distortions regarding the self, increased rumination, and despair (Amat et al., 2005; Celada et al., 2001; Price and Drevets, 2010). The prelimbic/infralimbic region of the mPFC is postulated to be the cortical detector and processor of stress controllability. It functions to inhibit the stress-induced activation of 5-HT neurons of the caudal DR when the stimulus is perceived to be controllable or escapable (Amat et al., 2005, 2008, 2010). This could well explain the opposing effects of aggressiveness/offensiveness- (controllable) and defensiveness-related (uncontrollable) stimuli on DR 5-HT neuronal activity observed in tree shrews made to confront a conspecific intruder or an experimenter (Walletschek and Raab, 1982). Electrical stimulation of the mPFC also elicits antidepressant-like effects, enhances DR 5-HT activity, and increases the postsynaptic release of monoamines, notably 5-HT (Hamani et al., 2010a,b; Juckel et al., 1999), which could provide the neurochemical basis for the efficacy of subgenual cingulate (Cg25) deep brain stimulation as an antidepressant treatment for intractable depression (Mayberg et al., 2005). As the mPFC forms a reciprocal feedback circuit with the DR (Celada et al., 2001; Martin-Ruiz et al., 2001), repeated experience of loss of control and unpredictability, as well as the associated allostatic load observed with CUS, could progressively impair both the mPFC and the DR, as well as their interaction. Functionally, this could translate to alterations in neural excitability in the mPFC, as has been demonstrated (Wilber et al., 2011), and to decreases in spontaneous single-spiking and burst-firing activity of 5-HT DR neurons (Bambico et al., 2009b). Behaviourally, these effects could translate into passive behavioural coping, anhedonia, and other depression-related markers. Interestingly, Maier and colleagues have shown that prior experience to an otherwise controllable (escapable) aversive stimulus (such as tail shock) potently blocks the behavioural and neurochemical alterations produced by subsequent uncontrollable (inescapable) stressor (tail shock) (Amat et al., 2005, 2008, 2010; Maier et al., 2006; Maier and Watkins, 2005), and possibly the progressive cascade of adverse consequences of CUS. Similarly, predictable chronic mild stress may have antidepressant, anxiolytic, and pro-neurogenic effects in the hippocampus (Parihar et al., 2011). These results indicate that controllable or predictable stress exposure may inoculate against the deleterious effects of stress seen in paradigms such as CUS, and suggest an interaction between the processes involved in neural responses to controllable and uncontrollable stress.

Thus chronic stress induces changes to 5-HT systems in the brain, including the hippocampus, associated with depression and depressive-like phenotypes, which can be reversed by antidepressant treatment. However, chronic stress also impacts hippocampal neurogenesis, which is itself regulated by 5-HT, and the effects of stress on neurogenesis can also be reversed by monoaminergic antidepressant treatment. In the following section we discuss how this regulation of neurogenesis occurs, and how neurogenesis interacts with ADs, 5-HT, and stress to mediate the opposing effects of stress and antidepressant treatment on depression-related pheonotypes.

4. The role of hippocampal neurogenesis in mediating affect, antidepressant action, and stress response

4.1. Neurogenesis in depression

Soon after the discovery of adult hippocampal neurogenesis in humans (Eriksson et al., 1998), it was theorized that basal deficits in hippocampal neurogenesis may underlie symptoms of psychiatric disorders, particularly depression (Kempermann, 2002). This theory was largely based on findings indicating decreased hippocampal volume in depressed patients and increased neurogenesis with administration of antidepressant medication and therapies (Kempermann, 2002; Kempermann and Kronenberg, 2003), supported by recent studies indicating decreased numbers of granule cells and decreased granule cell layer volume in the anterior and mid-dentate gyrus (DG) in unmedicated depressed patients relative to controls, as well as increased hippocampal neurogenesis and increased granule cell layer volume in depressed

Table 4
Summary of findings regarding direction of influence of monoamines and neurotrophic factors on hippocampal neurogenesis. Serotonin and norepinephrine, as well as neurotrophic factors, appear to positively regulate hippocampal neurogenesis, although transgenic BDNF reduction may increase proliferation but decrease survival and neuronal differentiation, whereas findings on the influence of dopamine are mixed (particularly regarding the effects of pharmacological antagonism). BDNF, brain-derived neurotrophic factor; IGF, insulin-like growth factor; NRG1, neuregulin-1; VEGF, vascular endothelial growth factor.

	Agonism	Antagonism	References (species)
Monoamines			
Serotonin	↑	↓	Banasr et al. (2004) (rat); Diaz et al. (2012) (mouse)
Norepinephrine	↑	↓	Jhaveri et al. (2010) (mouse and rat); Kulkarni et al. (2002) (rat); Masuda et al. (2012) (rat)
Dopamine	↑	↕?	Hoglinger et al., (2004) (mouse); Veena et al. (2011) (rat and mouse); Yang et al. (2008) (mouse)
Neurotrophic factors			
BDNF	↑	↕	Sairanen et al. (2005) (mouse); Schmidt and Duman (2010) (mouse); Waterhouse et al. (2012) (mouse)
IGF	↑	↓	Aberg et al. (2000) (rat); Beck et al. (1995) (mouse); Glasper et al. (2010) (mouse)
VEGF	↑	↓	Jin et al. (2002) (rat); Sun et al. (2006) (mouse)
NRG1	↑	?	Mahar et al. (2011) (mouse)

patients who had taken antidepressants relative to unmedicated patients (Boldrini et al., 2009, 2012, 2013). A particularly exciting recent report by Spalding et al. has revealed that adult hippocampal neurogenesis in humans is substantial and that neuronal turnover is high in comparison to rodents, supporting the possibility that human hippocampal neurogenesis is sufficient to support a role in affective and cognitive phenomena such as depression and response to stress and antidepressants (Spalding et al., 2013). In addition, the delay in efficacy of antidepressants (in both humans and animal models) appears to mirror the time required for newly proliferated neurons to become functional and hyperplastic (Ge et al., 2007; Jacobs et al., 2000).

However, in presenting a balanced view of the role of hippocampal neurogenesis in depression and antidepressant effects, it is important to consider evidence that fails to support or contradicts this view. Recent studies have brought into question whether decreased neurogenesis underlies depression (Eisch and Petrik, 2012; Hanson et al., 2011; Petrik et al., 2012). Whether ablating neurogenesis in animals is sufficient to induce a depressive phenotype remains controversial (Perera et al., 2011; Schloesser et al., 2009; Snyder et al., 2011; Surget et al., 2008; Vollmayr et al., 2003; Wang et al., 2008). Further disputing the role of HPC neurogenesis deficits in depressive aetiology is the fact that depressed patients have not been demonstrated to have significantly reduced hippocampal neurogenesis (Boldrini et al., 2009), although granule cells and granule cell layer volume are reduced (Boldrini et al., 2013), leaving the neurogenic hypothesis of depression in doubt (Hanson et al., 2011; Petrik et al., 2012). Consequently, a more supported hypothesis has emerged: that adult hippocampal neurogenesis is involved in mediating response to antidepressant treatments (Hanson et al., 2011). This is supported by studies showing that increases in hippocampal neurogenesis are associated with antidepressant effects mirroring the developmental latency of new neurons (Mahar et al., 2011), that antidepressant treatments increase hippocampal neurogenesis (Boldrini et al., 2009; Malberg et al., 2000), and that the behavioural effects of antidepressants may require intact neurogenesis (Perera et al., 2011; Santarelli et al., 2003; Wang et al., 2008). However, in understanding the importance of adult hippocampal neurogenesis in the mechanism of exogenous monoamine-related agents, it is important to discuss the regulation of neurogenesis by endogenous monoaminergic systems.

4.2. Monoaminergic and neurotrophic factor regulation of neurogenesis

Hippocampal neurogenesis has been shown to be regulated by a variety of monoamines and neurotrophic factors, as shown in Table 4. The hippocampus receives dense innervation by 5-HT fibres (Gage and Thompson, 1980; Gasbarri et al., 1994). Ablation of 5-HT neurons in the DR and median raphe decrease neurogenesis, and these effects are reversed by 5-HT re-innervation (Brezun and Daszuta, 2000a,b). Regarding 5-HT receptors, effects of 5-HT-mediated signalling on hippocampal neurogenesis appear to be receptor subtype-specific. Pharmacological studies suggest that 5-HT_{1A} stimulation is pro-neurogenic, 5-HT_{1B} stimulation does not produce an effect, 5-$HT_{2A/C}$ antagonism decreases proliferation, 5-HT_{2B} stimulation increases neurogenesis (and has antidepressant-like effects; notably, blocking activity of this receptor ablates behavioural and neurogenic efficacy of SSRIs), and 5-HT_{2C} stimulation does not affect neurogenesis (Banasr et al., 2004; Diaz et al., 2012). In addition, suppression of 5-HT transporter expression increases hippocampal neurogenesis and causes antidepressant-like behaviour (Ferres-Coy et al., 2013).

Apart from the influence of the 5-HT system, the dopaminergic and norepinephrinergic systems have also been shown to influence neurogenesis, although the findings are not as clear as those regarding 5-HT. Dopamine depletion reduces hippocampal cytogenesis, an effect that is reversed by ropinirole administration (Hoglinger et al., 2004), although in other studies a transient increase is observed after depletion (Park and Enikolopov, 2010). D2 receptor activation by quinpirole increases subgranular zone proliferation (Yang et al., 2008), and D3 knockout or blockade also increases proliferation (Egeland et al., 2012), suggesting a receptor-specific regulation. However, the effects of dopaminergic antagonists (e.g. haloperidol) on hippocampal neurogenesis are mixed (Veena et al., 2011), and merit further experimental investigation. Although dopamine transporter-immunoreactive fibres have been identified near neurogenic cells in the subgranular zone (Hoglinger et al., 2004), dopaminergic subgranular zone innervation is thought to be limited (Kempermann, 2011), suggesting that the regulation of hippocampal neurogenesis by dopamine may be due to an indirect mechanism, potentially involving reciprocal interactions with the 5-HT and norepinephrinergic systems (Guiard et al., 2008a,b).

Norepinephrine depletion decreases hippocampal progenitor proliferation (Kulkarni et al., 2002). Norepinephrine has been shown to positively modulate hippocampal neural precursor cell proliferation in a β-adrenergic receptor-dependent (but not α1- or α2-dependent) manner (Jhaveri et al., 2010; Masuda et al., 2012), although in other studies α2-receptor blockade increases cell survival and dendritic arborisation (Rizk et al., 2006). These effects may result from direct norepinephrine input onto neurogenic cells (Rizk et al., 2006).

Neurotrophic factors have also been shown to increase adult hippocampal neurogenesis and modulate antidepressant-related behaviours, particularly BDNF, insulin-like growth factor (IGF), VEGF, and neuregulin-1 (NRG1). Notably, many of these factors can be administered peripherally to induce these effects (Aberg et al., 2000; Duman et al., 2009; Mahar et al., 2011; Schmidt and Duman, 2010), suggesting that peripheral levels of neurotrophic factors may modulate hippocampal neurogenesis and mood. Infusion of BDNF, both peripherally and centrally, increases neuronal survival and overall hippocampal neurogenesis, and also produces antidepressant-like effects (Scharfman et al., 2005; Schmidt and Duman, 2010; Shirayama et al., 2002). Decreases in BDNF are predominantly detrimental to neurogenesis, although results are mixed; proliferation is largely unchanged in $BDNF^{+/-}$ mice (Rossi et al., 2006; Waterhouse et al., 2012) (though one study reports an increase in proliferation in these animals (Sairanen et al., 2005) and another reports increased proliferation but decreased neuronal differentiation in mice largely lacking dendritic BDNF (Waterhouse et al., 2012)), but these animals show decreased survival (Sairanen et al., 2005) and a lack of effectiveness for environmental enrichment on increasing neurogenesis (Rossi et al., 2006), and DG-specific knockdown of BDNF leads to decreased neurogenesis through decreased neuronal differentiation (Taliaz et al., 2010). BDNF-hypomorphic mice also show depression-like behaviour and behavioural resistance to antidepressants (Adachi et al., 2008; Taliaz et al., 2010). Notably, BDNF may contribute to the modulation of neurogenesis in response to both stress and antidepressants, as hippocampal BDNF levels decrease in response to chronic stress (Larsen et al., 2010; Shi et al., 2010; Smith et al., 1995a,b) and increase in response to antidepressant treatments (Altar et al., 2003; Czubak et al., 2009; Gersner et al., 2010; Hanson et al., 2011; Musazzi et al., 2009; Nibuya et al., 1995).

Peripherally administered IGF increases hippocampal neurogenesis by stimulating DG proliferation and neuronal differentiation (Aberg et al., 2000), and also produces antidepressant effects (Duman et al., 2009), whereas IGF-knockout mice display decreased numbers of hippocampal granule cells (Beck et al., 1995). Blocking IGF activity decreases proliferation in both sedentary and exercised animals (Glasper et al., 2010).

VEGF administration increases hippocampal neurogenesis by promoting cell proliferation (Jin et al., 2002). In contrast, VEGF-knockout mice display decreased numbers of immature neurons and reduced proliferation (Sun et al., 2006). Hippocampal VEGF levels increase after antidepressant treatment, and VEGF (through signalling with Flk-1) may also be necessary for antidepressant-induced proliferation and antidepressant-like behavioural effects (Warner-Schmidt and Duman, 2007). Stress-induced depressive-like behaviour and decreases in DG cell survival are reversed by exercise, but this effect is abolished with VEGF antagonists (Kiuchi et al., 2012), similar to effects seen with IGF antagonists (Glasper et al., 2010).

NRG1 has been shown to cross the blood–brain barrier (Carlsson et al., 2011; Kastin et al., 2004), and peripheral administration of NRG1 increases ventral hippocampal neurogenesis by rapidly increasing proliferation, possibly through direct stimulation of ErbB3 receptors in DG cells, leading to antidepressant-like effects four weeks after administration (Mahar et al., 2011). This delayed effect mirrors the latency for newborn cells to have differentiated into hyperplastic neurons (Ge et al., 2007). It remains to be determined whether other epidermal growth factor-related proteins have similar effects, or whether NRG1 antagonism leads to neurogenic deficits.

Thus monoamines (including 5-HT) and neurotrophic factors have been shown to modulate hippocampal neurogenesis, and this represents one avenue by which stress-induced 5-HT system changes can affect hippocampal neurogenesis and its functions. Overall, the neurogenic influence of these factors is primarily positive for 5-HT and norepinephrine as well as neurotrophic factors, and positive to mixed for dopamine, suggesting that further studies into endogenous regulation of neurogenesis by monoamines should investigate the complex (and potentially indirect) modulation of hippocampal neurogenesis by dopamine, including various dopaminergic receptors and receptor-specific antagonists. In contrast, the relationship between hippocampal neurogenesis and antidepressants (primarily exogenous monoaminergic signalling-related agents), as well as behavioural antidepressant effects, has been more thoroughly characterized.

4.3. Relationship between neurogenesis, antidepressants, and antidepressant effects

Chronic antidepressant treatment has been shown to increase neurogenesis (see Dranovsky and Hen, 2006 for review) and decrease anhedonia and learned helplessness behaviour (David et al., 2009; Holick et al., 2008; Jayatissa et al., 2006, 2008; Malberg and Duman, 2003; Pechnick et al., 2011; Perera et al., 2011). These effects have been observed in rodents (David et al., 2009; Jayatissa et al., 2006, 2008; Malberg and Duman, 2003), non-human primates (Perera et al., 2011), and humans (Boldrini et al., 2009, 2012). A recent report by Sahay et al. (2011) has also shown that increasing hippocampal neurogenesis through genetic manipulation in unstressed mice is not sufficient to induce some of the anxiolytic and antidepressant-like effects seen after antidepressant treatment; in addition to suggesting that an increased number of new neurons alone might not be responsible for all of the behavioural effects of antidepressants, these findings also bring to light the possibility that the involvement of increased numbers of new neurons in certain behavioural responses to antidepressants may require the presence of the monoaminergic modulation induced by these treatments, or may exist only in the presence of stress in some paradigms. It is important to note that some agents with antidepressant properties, such as nicotine, do not increase hippocampal neurogenesis (Abrous et al., 2002; Mahar et al., 2012; Mudo et al., 2007; Vazquez-Palacios et al., 2005), and in some studies chronic antidepressant treatment did not increase neurogenesis (Holick et al., 2008; Huang et al., 2008; Navailles et al., 2008).

Antidepressants can also reverse stress-induced effects on affective behaviour and neurogenesis (Li et al., 2004; Surget et al., 2008), and in some studies stress or stress hormones are required for these effects of antidepressants (Anacker et al., 2011; Dagyte et al., 2010). In fact, antidepressants may regulate neurogenesis through GRs and cyclin-dependent kinase (CDK) inhibitors. The SSRI sertraline has been found to affect glucocorticoid receptor (GR) phosphorylation via protein kinase A (PKA), and blocking PKA or GR activity blocks antidepressant-induced increases in cell proliferation (Anacker et al., 2011). Similarly, antidepressants act to differentially increase expression of the GR-dependent CDK inhibitors p27Kip1 and p57Kip2, which regulate exit from the cell cycle and increase neuronal differentiation (Lee et al., 2006; Shin et al., 2009; Ye et al., 2009), and decrease expression of p21Cip1, which prevents proliferation of neuronal progenitors (Anacker et al., 2011; Pechnick et al., 2011). The involvement of GR stimulation in proliferation is supported by the finding that

antidepressants may only increase proliferation in the presence of glucocorticoids (Anacker et al., 2011; David et al., 2009). Together, these results show that antidepressants may regulate hippocampal neurogenesis through GR phosphorylation via PKA, leading to altered expression of CDK inhibitors to increase proliferation and neuronal differentiation. However, the CDK inhibitor regulation effects may be antidepressant-specific, given that antidepressants have differing effects on proliferation and later stages of neurogenesis, corresponding to differing effects on CDK inhibitor expression changes (Anacker et al., 2011; Pechnick et al., 2011). Notably, antidepressants may also regulate hippocampal plasticity by causing the dematuration of existing granule cells to a more plastic immature state. In particular, chronic fluoxetine acting through 5-HT4 receptors causes mature granule cells in the dentate gyrus to lose calbindin expression and to display increased excitability, mirroring features of immature granule cells (Kobayashi et al., 2010).

Most importantly with respect to neurogenesis and antidepressants/antidepressant effects, neurogenesis seems to be required for antidepressant effects in some paradigms (Airan et al., 2007; Jiang et al., 2005; Perera et al., 2011; Pollak et al., 2008; Santarelli et al., 2003; Surget et al., 2008). Ablating neurogenesis appears to abolish the effects of antidepressants in the novelty-suppressed feeding task, as well as their effects on coat state in response to stress (David et al., 2009; Santarelli et al., 2003; Wang et al., 2008). Sucrose consumption is also decreased after ablation of neurogenesis (Snyder et al., 2011). The role of neurogenesis in mediating antidepressant-like behaviour in the forced swim test (FST) is somewhat controversial. David and colleagues showed that fluoxetine reduces FST immobility in the absence of neurogenesis (David et al., 2009), and Holick and colleagues showed that reduced neurogenesis did not affect response to antidepressants in the FST (Holick et al., 2008). However, other studies have provided conflicting results, in that increases in neurogenesis (but not proliferation) are associated with antidepressant-like effects in the FST at a time when the increased numbers of new neurons are especially hyperplastic (Ge et al., 2007; Mahar et al., 2011), and that ablating neurogenesis prevented an antidepressant-induced decrease in FST immobility (Airan et al., 2007; Jiang et al., 2005; Snyder et al., 2011). Overall, the evidence suggests that AD-mediated recovery from depression and depression-like phenotypes involves not only changes to 5-HT function but also changes to hippocampal neurogenesis.

Hippocampal neurogenesis also appears to be required for HPA axis regulation (Schloesser et al., 2009; Snyder et al., 2011), and is necessary for antidepressants to restore inhibition of the HPA axis by the hippocampus following chronic stress (Surget et al., 2011). To understand how this regulation of HPA axis function by neurogenesis may occur, and how neurogenic deficits could result in dysregulated responses to stress contributing to stress-induced 5-HT dysfunction and depression-related phenotypes, it is important to consider the functional anatomy of the hippocampus.

4.4. Stress and the subregional localization of neurogenic function along the septotemporal axis

CUS has repeatedly been shown to induce depressive-like behaviour (Elizalde et al., 2010; Jayatissa et al., 2009; Schmidt and Duman, 2010; Valente et al., 2012), and to negatively affect multiple stages of hippocampal neurogenesis, including proliferation (Elizalde et al., 2010; Jayatissa et al., 2009) and survival (Dagyte et al., 2011; Mineur et al., 2007) (although see Hanson et al. (2011) for a discussion of studies failing to show an effect of CUS). High doses of cortisol in vitro decrease proliferation and neuronal differentiation of human neural progenitor cells in a glucocorticoid-dependent manner, potentially via decreased TGFβ-SMAD2/3 and Hedgehog signalling and increased SGK1 activity, with increased SGK1 transcription also being observed in the blood of depressed patients and hippocampus of rats exposed to CUS, providing a putative molecular mechanism for CUS-induced decreases in hippocampal neurogenesis (Anacker et al., 2013a,b). In addition, other chronic stress paradigms have also been shown to decrease neurogenesis and induce depression-related behaviour (Brummelte and Galea, 2010; Perera et al., 2011; Veena et al., 2009; Wong and Herbert, 2004, 2006). In one study, escitalopram treatment following CUS reversed anhedonic behaviour only in animals who also displayed restored hippocampal cytogenesis; notably, this neurogenic reduction, recovery, and putative requirement for antidepressant-like effects was restricted to the ventral hippocampus (Jayatissa et al., 2006).

In fact, the relationship between neurogenesis and response to stress may be specific to particular hippocampal subregions. The hippocampus as a whole has been shown to be neither structurally nor functionally homogenous along the septotemporal axis (Bannerman et al., 2004; Fanselow and Dong, 2010; van Strien et al., 2009). The dorsal hippocampus in rodents (analogous to the posterior hippocampus in humans) appears to be more involved in learning and memory functions, whereas the ventral hippocampus (analogous to the anterior hippocampus in humans (Fanselow and Dong, 2010)) seems to be involved in emotional modulation (Bannerman et al., 2004). Lesions of the dorsal hippocampus lead to spatial memory deficits (Broadbent et al., 2010), whereas adult ventral hippocampal lesions are anxiolytic and can affect stress response (Bannerman et al., 2004; Fanselow and Dong, 2010; Hobin et al., 2006; Kjelstrup et al., 2002; Pentkowski et al., 2006). These ventral hippocampus effects may be a result of the functional connectivity of the ventral hippocampus. The ventral hippocampus has increased serotonergic, norepinephrinergic, and mesolimbic dopaminergic innervation in comparison to the dorsal hippocampus (Bjarkam et al., 2003; Gage and Thompson, 1980; Gasbarri et al., 1994; Wilson and Molliver, 1991). In addition, this structure projects to brain areas involved in emotional regulation, including the mPFC, amygdala, bed nucleus of the stria terminalis (BNST), and paraventricular nucleus of the hypothalamus (PVN) (Bannerman et al., 2004; Fanselow and Dong, 2010; van Strien et al., 2009). Notably, ventral hippocampal lesions specific to areas projecting to the neuroendocrine hypothalamus alter response to stress (Nettles et al., 2000).

The functional distinction is also reflected at the level of the DG itself, in both the temporal dynamics of neuronal maturation along the septotemporal axis (Snyder et al., 2012) and functionality, with the dorsal DG's implication in learning and memory function, and the ventral DG's implication in anxiety and depressive/antidepressant behavioural phenotypes (Deng et al., 2010; Kheirbek and Hen, 2011). More specifically, these behaviours have been associated specifically with the birth of new neurons in this structure, and many studies examining behavioural consequences of altered neurogenesis have revealed functional discrepancies between dorsal and ventral hippocampal neurogenesis. Chronic stress has been shown to cause ventral DG-specific decreases in neurogenesis (Elizalde et al., 2010; Jayatissa et al., 2006, 2008), antidepressants have been shown to increase neurogenesis selectively in the ventral DG (Banasr et al., 2006; Paizanis et al., 2010), and increases in neurogenesis restricted to the ventral DG have been associated with antidepressant effects (Mahar et al., 2011). A noteworthy recent study by Tanti et al. specifically investigating the distinction between dorsal and ventral DG consequences of stress and antidepressant effects on different neurogenic stages found that CUS reduced the number of neural progenitors specifically in the ventral DG and decreased the number of early immature neurons in the dorsal and ventral DG, with both effects reversed by fluoxetine treatment (Tanti et al., 2013).

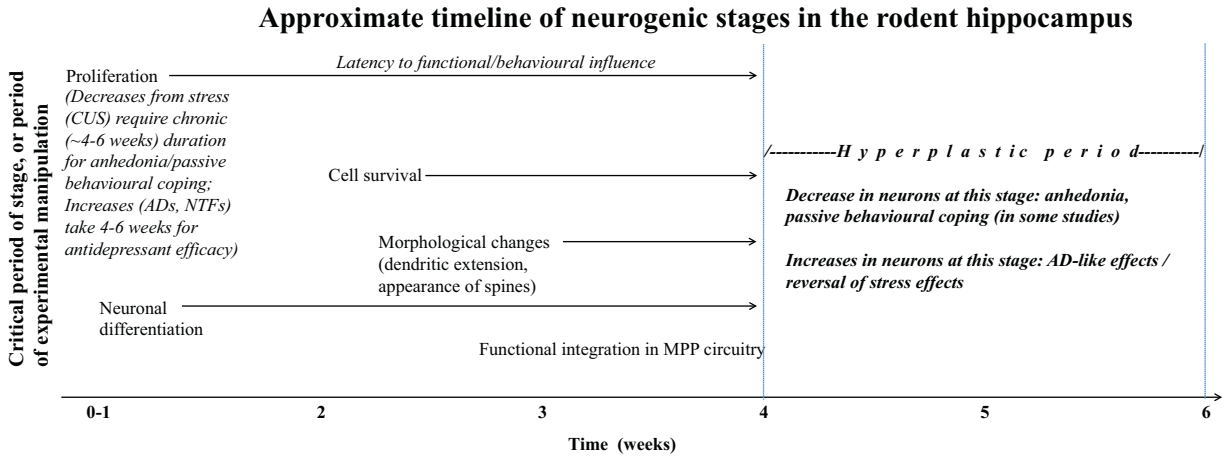

Fig. 3. Temporal dynamics of neurogenic effects. Timing of stages as shown is roughly approximated and applies particularly to rodents. We suggest that the relevant feature of hippocampal neurogenesis with respect to depression/antidepressant related behaviour is the number of hyperplastic immature functional neurons (4–6 week-old neurons in mice) present in the ventral dentate gyrus at behavioural assessment. Therefore, latency between proliferation effects and affective behaviour should be ~4–6 weeks (with potential variation by species); for changes in neuronal differentiation should be slightly sooner; and for changes in survival assessed in 2 week-old cells should be 2–4 weeks. If immature neurons can be ablated directly, or late-stage functional integration affected, effects should be apparent acutely. AD, antidepressant; CUS, chronic unpredictable stress; MPP, medial perforant path; NTF, neurotrophic factors.

The influence of ventral HPC neurogenesis on affect and antidepressant activity could be related to its connection to the mPFC, in that HPC plasticity could modulate cognitive plasticity, including helplessness-related cognition (Feldmann et al., 2007), cognitive distortions, or ruminative cognition. However, the hypothalamic projection of the ventral hippocampus may be a more likely candidate, as recent research suggests that the mood-regulating actions of the ventral hippocampus (and ventral hippocampal neurogenesis) may be due to its regulation of stress. Ablation of hippocampal neurogenesis causes aberrant HPA axis activity, including increased glucocorticoid response to stress, increased HPA recovery latency following stress, and decreased HPA suppression by dexamethasone (Schloesser et al., 2009, 2013; Snyder et al., 2011). Antiglucocorticoids, which mimic the effects of increased neurogenesis with respect to HPA inhibition, have antidepressant properties (Fitzsimons et al., 2009). Thus changes in ventral hippocampal neurogenesis likely affect the HPA axis via the BNST/PVN, modulating the effects of stress on depression- and antidepressant-related behaviour. Modulation of the HPA axis by neurogenesis would thus also affect 5-HT activity, given the regulation of 5-HT systems by stress, as described earlier.

4.5. Timeline of neurogenic effects and synopsis of neurogenic role in affective modulation

Several of the aforementioned findings are best examined from a temporal perspective. Specifically: (i) antidepressants typically take several weeks to attain clinical efficacy (Jacobs et al., 2000); (ii) chronic stress can have depressogenic effects whereas acute stress often fails to (Hanson et al., 2011); (iii) neurogenesis is required for certain antidepressant-related effects (Airan et al., 2007; Jiang et al., 2005; Perera et al., 2011; Santarelli et al., 2003; Surget et al., 2008); and (iv) short-term administration of GR antagonists can produce acute antidepressant and antidepressant-like effects in humans and animal models, respectively (Belanoff et al., 2002; Flores et al., 2006; Veldhuis et al., 1985).

To understand how neurogenesis might mediate these effects, it is important to take into consideration the time course of adult hippocampal neurogenesis (Fig. 3). Proliferation of new cells proceeds rapidly in the hours following pro- or anti-proliferative stimuli. Following this stage, new cells differentiate into neuronal progenitors, extend dendrites into the molecular layer surrounding the DG and form spines, undergo apoptosis or survive to a functional state, and experience a brief period of hyperplasticity at approximately 4–6 weeks of age (Ge et al., 2007), after which these new neurons are functionally indistinguishable from older mature granule cells. Notably, the timing of this plastic window at 4–6 weeks of age may be specific to rodents, as the timing and duration of this window may differ in primates (Kohler et al., 2011; Perera et al., 2011); this possibility emphasizes the importance of increasing our understanding of the maturation of adultborn neurons in addition to their proliferation and survival. It seems that the hyperplastic stage has particular relevance to the function of hippocampal neurogenesis, as prior to this stage these cells are not functional, and immediately following this stage the loss of neurons that proliferated in the presence of a particular stimulus would represent a relatively negligible change in the function of a mature GC population that is relatively quiescent (Aimone et al., 2010; Alme et al., 2010). Thus modulation of hippocampal neurogenesis should produce changes in affective behaviour if the overall number of immature hyperplastic ventral (in rodents; anterior in humans) DG neurons is affected at the precise time of behavioural testing or clinical assessment (cf. Jayatissa et al., 2009; Mahar et al., 2011) (Fig. 3). This would explain why chronic but not acute antidepressant treatment (initially increasing proliferation of new cells that weeks later become immature neurons) has clinical efficacy, why chronic but not acute stress is depressogenic and anti-neurogenic, and why anti-GC treatments (mimicking the end result of increased neurogenesis in inhibiting HPA function) have comparatively rapid antidepressant effects.

5. Concluding remarks

Multiple theories of depression and antidepressant action have been put forward in recent years. Here we have attempted to review recent research involving two of these theories, the monoaminergic and neurogenic hypotheses, and present a view linking these theories in the context of stress and HPA axis activity. To summarize, chronic stress causes depression and depression-related behaviour through monoaminergic changes in several brain regions as well as suppression of hippocampal neurogenesis, leading to altered activity in cognition- and emotion-related brain regions, as well as HPA axis dysfunction that itself exacerbates the effects of stress, including its effects on 5-HT activity. Some of these effects are reversed by antidepressant treatment, which may act

by increasing hippocampal neurogenesis (possibly by increasing monoaminergic neurotransmission), leading to restoration of HPA activity and stress responsivity, ameliorating deleterious stress-induced 5-HT changes. Future studies involving the interaction between monoamines and neurogenesis may further elucidate this relationship. In addition, linking particular changes in brain function to particular depressive symptoms will prove useful in understanding the aetiology of depression. Finally, future clinical and post-mortem studies in human patients may further characterize this interaction in the context of depression and antidepressant effects.

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References

Aberg, M.A., Aberg, N.D., Hedbacker, H., Oscarsson, J., Eriksson, P.S., 2000. Peripheral infusion of IGF-I selectively induces neurogenesis in the adult rat hippocampus. Journal of Neuroscience: The Official Journal of the Society for Neuroscience 20, 2896–2903.

Abrous, D.N., Adriani, W., Montaron, M.F., Aurousseau, C., Rougon, G., Le Moal, M., Piazza, P.V., 2002. Nicotine self-administration impairs hippocampal plasticity. Journal of Neuroscience: The Official Journal of the Society for Neuroscience 22, 3656–3662.

Adachi, M., Barrot, M., Autry, A.E., Theobald, D., Monteggia, L.M., 2008. Selective loss of brain-derived neurotrophic factor in the dentate gyrus attenuates antidepressant efficacy. Biological Psychiatry 63, 642–649.

Ahmad, A., Rasheed, N., Banu, N., Palit, G., 2010. Alterations in monoamine levels and oxidative systems in frontal cortex, striatum, and hippocampus of the rat brain during chronic unpredictable stress. Stress 13, 355–364.

Aimone, J.B., Deng, W., Gage, F.H., 2010. Put them out to pasture? What are old granule cells good for, anyway..? Hippocampus 20, 1124–1125.

Airan, R.D., Meltzer, L.A., Roy, M., Gong, Y., Chen, H., Deisseroth, K., 2007. High-speed imaging reveals neurophysiological links to behavior in an animal model of depression. Science 317, 819–823.

Akiskal, H.S., Hirschfeld, R.M., Yerevanian, B.I., 1983. The relationship of personality to affective disorders. Archives of General Psychiatry 40, 801–810.

Albert, P.R., Benkelfat, C., Descarries, L., 2012. The neurobiology of depression – revisiting the serotonin hypothesis. I. Cellular and molecular mechanisms. Philosophical Transactions of the Royal Society of London. Series B, Biological sciences 367, 2378–2381.

Allen, N.B., Badcock, P.B., 2006. Darwinian models of depression: a review of evolutionary accounts of mood and mood disorders. Progress in Neuropsychopharmacology & Biological Psychiatry 30, 815–826.

Alme, C.B., Buzzetti, R.A., Marrone, D.F., Leutgeb, J.K., Chawla, M.K., Schaner, M.J., Bohanick, J.D., Khoboko, T., Leutgeb, S., Moser, E.I., Moser, M.B., McNaughton, B.L., Barnes, C.A., 2010. Hippocampal granule cells opt for early retirement. Hippocampus 20, 1109–1123.

Altar, C.A., Whitehead, R.E., Chen, R., Wortwein, G., Madsen, T.M., 2003. Effects of electroconvulsive seizures and antidepressant drugs on brain-derived neurotrophic factor protein in rat brain. Biological Psychiatry 54, 703–709.

Amat, J., Aleksejev, R.M., Paul, E., Watkins, L.R., Maier, S.F., 2010. Behavioral control over shock blocks behavioral and neurochemical effects of later social defeat. Neuroscience 165, 1031–1038.

Amat, J., Baratta, M.V., Paul, E., Bland, S.T., Watkins, L.R., Maier, S.F., 2005. Medial prefrontal cortex determines how stressor controllability affects behavior and dorsal raphe nucleus. Nature Neuroscience 8, 365–371.

Amat, J., Paul, E., Watkins, L.R., Maier, S.F., 2008. Activation of the ventral medial prefrontal cortex during an uncontrollable stressor reproduces both the immediate and long-term protective effects of behavioral control. Neuroscience 154, 1178–1186.

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, 5th ed. American Psychiatric Publishing, Arlington, VA.

Anacker, C., Cattaneo, A., Luoni, A., Musaelyan, K., Zunszain, P.A., Milanesi, E., Rybka, J., Berry, A., Cirulli, F., Thuret, S., Price, J., Riva, M.A., Gennarelli, M., Pariante, C.M., 2013a. Glucocorticoid-related molecular signaling pathways regulating hippocampal neurogenesis. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology 38, 872–883.

Anacker, C., Cattaneo, A., Musaelyan, K., Zunszain, P.A., Horowitz, M., Molteni, R., Luoni, A., Calabrese, F., Tansey, K., Gennarelli, M., Thuret, S., Price, J., Uher, R., Riva, M.A., Pariante, C.M., 2013b. Role for the kinase SGK1 in stress, depression, and glucocorticoid effects on hippocampal neurogenesis. Proceedings of the National Academy of Sciences of the United States of America 110, 8708–8713.

Anacker, C., Zunszain, P.A., Cattaneo, A., Carvalho, L.A., Garabedian, M.J., Thuret, S., Price, J., Pariante, C.M., 2011. Antidepressants increase human hippocampal neurogenesis by activating the glucocorticoid receptor. Molecular Psychiatry 16, 738–750.

Araneda, R., Andrade, R., 1991. 5-Hydroxytryptamine2 and 5-hydroxytryptamine 1A receptors mediate opposing responses on membrane excitability in rat association cortex. Neuroscience 40, 399–412.

Arango, V., Underwood, M.D., Boldrini, M., Tamir, H., Kassir, S.A., Hsiung, S., Chen, J.J., Mann, J.J., 2001. Serotonin 1A receptors, serotonin transporter binding and serotonin transporter mRNA expression in the brainstem of depressed suicide victims. Neuropsychopharmacology 25, 892–903.

Arborelius, L., Hawks, B.W., Owens, M.J., Plotsky, P.M., Nemeroff, C.B., 2004. Increased responsiveness of presumed 5-HT cells to citalopram in adult rats subjected to prolonged maternal separation relative to brief separation. Psychopharmacology 176, 248–255.

Ashby Jr., C.R., Edwards, E., Wang, R.Y., 1994. Electrophysiological evidence for a functional interaction between 5-HT1A and 5-HT2A receptors in the rat medial prefrontal cortex: an iontophoretic study. Synapse 17, 173–181.

Aso, E., Ozaita, A., Valdizan, E.M., Ledent, C., Pazos, A., Maldonado, R., Valverde, O., 2008. BDNF impairment in the hippocampus is related to enhanced despair behavior in CB1 knockout mice. Journal of Neurochemistry 105, 565–572.

Aso, E., Renoir, T., Mengod, G., Ledent, C., Hamon, M., Maldonado, R., Lanfumey, L., Valverde, O., 2009. Lack of CB1 receptor activity impairs serotonergic negative feedback. Journal of Neurochemistry 109, 935–944.

Avgustinovich, D.F., Kovalenko, I.L., Kudryavtseva, N.N., 2005. A model of anxious depression: persistence of behavioral pathology. Neuroscience and Behavioral Physiology 35, 917–924.

Bambico, F.R., Duranti, A., Tontini, A., Tarzia, G., Gobbi, G., 2009a. Endocannabinoids in the treatment of mood disorders: evidence from animal models. Current Pharmaceutical Design 15, 1623–1646.

Bambico, F.R., Gobbi, G., 2008. The cannabinoid CB1 receptor and the endocannabinoid anandamide: possible antidepressant targets. Expert Opinion on Therapeutic Targets 12, 1347–1366.

Bambico, F.R., Katz, N., Debonnel, G., Gobbi, G., 2007. Cannabinoids elicit antidepressant-like behavior and activate serotonergic neurons through the medial prefrontal cortex. Journal of Neuroscience: The Official Journal of the Society for Neuroscience 27, 11700–11711.

Bambico, F.R., Nguyen, N.T., Gobbi, G., 2009b. Decline in serotonergic firing activity and desensitization of 5-HT1A autoreceptors after chronic unpredictable stress. European Neuropsychopharmacology: Journal of the European College of Neuropsychopharmacology 19, 215–228.

Banasr, M., Duman, R.S., 2008. Glial loss in the prefrontal cortex is sufficient to induce depressive-like behaviors. Biological Psychiatry 64, 863–870.

Banasr, M., Hery, M., Printemps, R., Daszuta, A., 2004. Serotonin-induced increases in adult cell proliferation and neurogenesis are mediated through different and common 5-HT receptor subtypes in the dentate gyrus and the subventricular zone. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology 29, 450–460.

Banasr, M., Soumier, A., Hery, M., Mocaer, E., Daszuta, A., 2006. Agomelatine, a new antidepressant, induces regional changes in hippocampal neurogenesis. Biological Psychiatry 59, 1087–1096.

Bannerman, D.M., Rawlins, J.N., McHugh, S.B., Deacon, R.M., Yee, B.K., Bast, T., Zhang, W.N., Pothuizen, H.H., Feldon, J., 2004. Regional dissociations within the hippocampus–memory and anxiety. Neuroscience and Biobehavioral Reviews 28, 273–283.

Barr, A.M., Markou, A., Phillips, A.G., 2002. A 'crash' course on psychostimulant withdrawal as a model of depression. Trends in Pharmacological Sciences 23, 475–482.

Beck, K.D., Powell-Braxton, L., Widmer, H.R., Valverde, J., Hefti, F., 1995. Igf1 gene disruption results in reduced brain size, CNS hypomyelination, and loss of hippocampal granule and striatal parvalbumin-containing neurons. Neuron 14, 717–730.

Bekris, S., Antoniou, K., Daskas, S., Papadopoulou-Daifoti, Z., 2005. Behavioural and neurochemical effects induced by chronic mild stress applied to two different rat strains. Behavioural Brain Research 161, 45–59.

Belanoff, J.K., Rothschild, A.J., Cassidy, F., DeBattista, C., Baulieu, E.E., Schold, C., Schatzberg, A.F., 2002. An open label trial of C-1073 (mifepristone) for psychotic major depression. Biological Psychiatry 52, 386–392.

Bell, C., Abrams, J., Nutt, D., 2001. Tryptophan depletion and its implications for psychiatry. British Journal of Psychiatry: Journal of Mental Science 178, 399–405.

Belmaker, R.H., Agam, G., 2008. Major depressive disorder. New England Journal of Medicine 358, 55–68.

Benkelfat, C., Ellenbogen, M.A., Dean, P., Palmour, R.M., Young, S.N., 1994. Mood-lowering effect of tryptophan depletion. Enhanced susceptibility in young men at genetic risk for major affective disorders. Archives of General Psychiatry 51, 687–697.

Bergstrom, A., Jayatissa, M.N., Mork, A., Wiborg, O., 2008. Stress sensitivity and resilience in the chronic mild stress rat model of depression; an in situ hybridization study. Brain Research 1196, 41–52.

Bhagwagar, Z., Rabiner, E.A., Sargent, P.A., Grasby, P.M., Cowen, P.J., 2004. Persistent reduction in brain serotonin1A receptor binding in recovered depressed men measured by positron emission tomography with [11C]WAY-100635. Molecular Psychiatry 9, 386–392.

Bhutani, M.K., Bishnoi, M., Kulkarni, S.K., 2009. Anti-depressant like effect of curcumin and its combination with piperine in unpredictable chronic stress-induced behavioral, biochemical and neurochemical changes. Pharmacology, Biochemistry, and Behavior 92, 39–43.
Bijak, M., Tokarski, K., Czyrak, A., Mackowiak, M., Wedzony, K., 1996. Imipramine increases the 5-HT1A receptor-mediated inhibition of hippocampal neurons without changing the 5-HT1A receptor binding. European Journal of Pharmacology 305, 79–85.
Billings, A.G., Cronkite, R.C., Moos, R.H., 1983. Social-environmental factors in unipolar depression: comparisons of depressed patients and nondepressed controls. Journal of Abnormal Psychology 92, 119–133.
Bjarkam, C.R., Sorensen, J.C., Geneser, F.A., 2003. Distribution and morphology of serotonin-immunoreactive axons in the hippocampal region of the New Zealand white rabbit. I. Area dentata and hippocampus. Hippocampus 13, 21–37.
Blier, P., de Montigny, C., 1999. Serotonin and drug-induced therapeutic responses in major depression, obsessive–compulsive and panic disorders. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology 21, 91S–98S.
Blier, P., Pineyro, G., el Mansari, M., Bergeron, R., de Montigny, C., 1998. Role of somatodendritic 5-HT autoreceptors in modulating 5-HT neurotransmission. Annals of the New York Academy of Sciences 861, 204–216.
Boldrini, M., Hen, R., Underwood, M.D., Rosoklija, G.B., Dwork, A.J., Mann, J.J., Arango, V., 2012. Hippocampal angiogenesis and progenitor cell proliferation are increased with antidepressant use in major depression. Biological Psychiatry 72, 562–571, http://dx.doi.org/10.1016/j.biopsych.2012.04.024.
Boldrini, M., Santiago, A.N., Hen, R., Dwork, A.J., Rosoklija, G.B., Tamir, H., Arango, V., Mann, J.J., 2013. Hippocampal granule neuron number and dentate gyrus volume in antidepressant-treated and untreated major depression. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology 38, 1068–1077, http://dx.doi.org/10.1038/npp.2013.5.
Boldrini, M., Underwood, M.D., Hen, R., Rosoklija, G.B., Dwork, A.J., John Mann, J., Arango, V., 2009. Antidepressants increase neural progenitor cells in the human hippocampus. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology 34, 2376–2389.
Borsini, F., Ceci, A., Bietti, G., Donetti, A., 1995. BIMT 17, a 5-HT1A receptor agonist/5-HT2A receptor antagonist, directly activates postsynaptic 5-HT inhibitory responses in the rat cerebral cortex. Naunyn-Schmiedeberg's Archives of Pharmacology 352, 283–290.
Bosker, F.J., Klompmakers, A., Westenberg, H.G., 1997. Postsynaptic 5-HT1A receptors mediate 5-hydroxytryptamine release in the amygdala through a feedback to the caudal linear raphe. European Journal of Pharmacology 333, 147–157.
Branchi, I., Santarelli, S., Capoccia, S., Poggini, S., D'Andrea, I., Cirulli, F., Alleva, E., 2013. Antidepressant treatment outcome depends on the quality of the living environment: a pre-clinical investigation in mice. PLoS ONE 8, e62226.
Brenes Saenz, J.C., Villagra, O.R., Fornaguera Trias, J., 2006. Factor analysis of forced swimming test, sucrose preference test and open field test on enriched, social and isolated reared rats. Behavioural Brain Research 169, 57–65.
Brezun, J.M., Daszuta, A., 2000a. Serotonergic reinnervation reverses lesion-induced decreases in PSA-NCAM labeling and proliferation of hippocampal cells in adult rats. Hippocampus 10, 37–46.
Brezun, J.M., Daszuta, A., 2000b. Serotonin may stimulate granule cell proliferation in the adult hippocampus, as observed in rats grafted with foetal raphe neurons. European Journal of Neuroscience 12, 391–396.
Broadbent, N.J., Gaskin, S., Squire, L.R., Clark, R.E., 2010. Object recognition memory and the rodent hippocampus. Learning & Memory 17, 5–11.
Brown, E.S., Varghese, F.P., McEwen, B.S., 2004. Association of depression with medical illness: does cortisol play a role? Biological Psychiatry 55, 1–9.
Brummelte, S., Galea, L.A., 2010. Chronic high corticosterone reduces neurogenesis in the dentate gyrus of adult male and female rats. Neuroscience 168, 680–690.
Cai, X., Gu, Z., Zhong, P., Ren, Y., Yan, Z., 2002. Serotonin 5-HT1A receptors regulate AMPA receptor channels through inhibiting Ca2+/calmodulin-dependent kinase II in prefrontal cortical pyramidal neurons. Journal of Biological Chemistry 277, 36553–36562.
Carlsson, T., Schindler, F.R., Hollerhage, M., Depboylu, C., Arias-Carrion, O., Schnurrbusch, S., Rosler, T.W., Wozny, W., Schwall, G.P., Groebe, K., Oertel, W.H., Brundin, P., Schrattenholz, A., Hoglinger, G.U., 2011. Systemic administration of neuregulin-1beta1 protects dopaminergic neurons in a mouse model of Parkinson's disease. Journal of Neurochemistry 117, 1066–1074.
Caspi, A., Hariri, A.R., Holmes, A., Uher, R., Moffitt, T.E., 2010. Genetic sensitivity to the environment: the case of the serotonin transporter gene and its implications for studying complex diseases and traits. American Journal of Psychiatry 167, 509–527.
Caspi, A., Sugden, K., Moffitt, T.E., Taylor, A., Craig, I.W., Harrington, H., McClay, J., Mill, J., Martin, J., Braithwaite, A., Poulton, R., 2003. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 301, 386–389.
Celada, P., Puig, M.V., Casanovas, J.M., Guillazo, G., Artigas, F., 2001. Control of dorsal raphe serotonergic neurons by the medial prefrontal cortex: Involvement of serotonin-1A, GABA(A), and glutamate receptors. Journal of Neuroscience: The Official Journal of the Society for Neuroscience 21, 9917–9929.
Chiba, S., Numakawa, T., Ninomiya, M., Richards, M.C., Wakabayashi, C., Kunugi, H., 2012. Chronic restraint stress causes anxiety- and depression-like behaviors, downregulates glucocorticoid receptor expression, and attenuates glutamate release induced by brain-derived neurotrophic factor in the prefrontal cortex. Progress in Neuropsychopharmacology & Biological Psychiatry 39, 112–119.
Christiansen, S., Bouzinova, E.V., Palme, R., Wiborg, O., 2012. Circadian activity of the hypothalamic–pituitary–adrenal axis is differentially affected in the rat chronic mild stress model of depression. Stress 15, 647–657.
Commons, K.G., 2008. Evidence for topographically organized endogenous 5-HT-1A receptor-dependent feedback inhibition of the ascending serotonin system. European Journal of Neuroscience 27, 2611–2618.
Cowen, P.J., Power, A.C., Ware, C.J., Anderson, I.M., 1994. 5-HT1A receptor sensitivity in major depression. A neuroendocrine study with buspirone. British Journal of Psychiatry 164, 372–379.
Crawford, L.K., Craige, C.P., Beck, S.G., 2010. Increased intrinsic excitability of lateral wing serotonin neurons of the dorsal raphe: a mechanism for selective activation in stress circuits. Journal of Neurophysiology 103, 2652–2663.
Crespi, F., 2009. Apamin increases 5-HT cell firing in raphe dorsalis and extracellular 5-HT levels in amygdala: a concomitant in vivo study in anesthetized rats. Brain Research 1281, 35–46.
Crespi, F., 2010. SK channel blocker apamin attenuates the effect of SSRI fluoxetine upon cell firing in dorsal raphe nucleus: a concomitant electrophysiological and electrochemical in vivo study reveals implications for modulating extracellular 5-HT. Brain Research 1334, 1–11.
Cryan, J.F., Holmes, A., 2005. The ascent of mouse: advances in modelling human depression and anxiety. Nature Reviews. Drug Discovery 4, 775–790.
Czubak, A., Nowakowska, E., Kus, K., Burda, K., Metelska, J., Baer-Dubowska, W., Cichocki, M., 2009. Influences of chronic venlafaxine, olanzapine and nicotine on the hippocampal and cortical concentrations of brain-derived neurotrophic factor (BDNF). Pharmacological Reports 61, 1017–1023.
Dagyte, G., Crescente, I., Postema, F., Seguin, L., Gabriel, C., Mocaer, E., Boer, J.A., Koolhaas, J.M., 2011. Agomelatine reverses the decrease in hippocampal cell survival induced by chronic mild stress. Behavioural Brain Research 218, 121–128.
Dagyte, G., Trentani, A., Postema, F., Luiten, P.G., Den Boer, J.A., Gabriel, C., Mocaer, E., Meerlo, P., Van der Zee, E.A., 2010. The novel antidepressant agomelatine normalizes hippocampal neuronal activity and promotes neurogenesis in chronically stressed rats. CNS Neuroscience & Therapeutics 16, 195–207.
Dahlstroem, A., Fuxe, K., 1964. Evidence for the existence of monoamine-containing neurons in the central nervous system. I. Demonstration of monoamines in the cell bodies of brain stem neurons. Acta Physiologica Scandinavica. Supplementum (Suppl. 232), 231–255.
Dang, H., Chen, Y., Liu, X., Wang, Q., Wang, L., Jia, W., Wang, Y., 2009a. Antidepressant effects of ginseng total saponins in the forced swimming test and chronic mild stress models of depression. Progress in Neuropsychopharmacology & Biological Psychiatry 33, 1417–1424.
Dang, H., Sun, L., Liu, X., Peng, B., Wang, Q., Jia, W., Chen, Y., Pan, A., Xiao, P., 2009b. Preventive action of Kai Xin San aqueous extract on depressive-like symptoms and cognition deficit induced by chronic mild stress. Experimental Biology and Medicine 234, 785–793.
David, D.J., Samuels, B.A., Rainer, Q., Wang, J.W., Marsteller, D., Mendez, I., Drew, M., Craig, D.A., Guiard, B.P., Guilloux, J.P., Artymyshyn, R.P., Gardier, A.M., Gerald, C., Antonijevic, I.A., Leonardo, E.D., Hen, R., 2009. Neurogenesis-dependent and -independent effects of fluoxetine in an animal model of anxiety/depression. Neuron 62, 479–493.
De Montigny, C., 1981. Enhancement of the 5-HT neurotransmission by antidepressant treatments. Journal de Physiologie 77, 455–461.
Delgado, P.L., Miller, H.L., Salomon, R.M., Licinio, J., Krystal, J.H., Moreno, F.A., Heninger, G.R., Charney, D.S., 1999. Tryptophan-depletion challenge in depressed patients treated with desipramine or fluoxetine: implications for the role of serotonin in the mechanism of antidepressant action. Biological Psychiatry 46, 212–220.
Deng, W., Aimone, J.B., Gage, F.H., 2010. New neurons and new memories: how does adult hippocampal neurogenesis affect learning and memory? Nature Reviews. Neuroscience 11, 339–350.
Descarries, L., Watkins, K.C., Garcia, S., Beaudet, A., 1982. The serotonin neurons in nucleus raphe dorsalis of adult rat: a light and electron microscope radioautographic study. Journal of Comparative Neurology 207, 239–254.
Diaz, S.L., Doly, S., Narboux-Neme, N., Fernandez, S., Mazot, P., Banas, S.M., Boutourlinsky, K., Moutkine, I., Belmer, A., Roumier, A., Maroteaux, L., 2012. 5-HT2B receptors are required for serotonin-selective antidepressant actions. Molecular Psychiatry 17, 154–163.
Dranovsky, A., Hen, R., 2006. Hippocampal neurogenesis: regulation by stress and antidepressants. Biological Psychiatry 59, 1136–1143.
Drevets, W.C., Thase, M.E., Moses-Kolko, E.L., Price, J., Frank, E., Kupfer, D.J., Mathis, C., 2007. Serotonin-1A receptor imaging in recurrent depression: replication and literature review. Nuclear Medicine and Biology 34, 865–877.
Dulawa, S.C., Hen, R., 2005. Recent advances in animal models of chronic antidepressant effects: the novelty-induced hypophagia test. Neuroscience and Biobehavioral Reviews 29, 771–783.
Duman, C.H., Schlesinger, L., Terwilliger, R., Russell, D.S., Newton, S.S., Duman, R.S., 2009. Peripheral insulin-like growth factor-I produces antidepressant-like behavior and contributes to the effect of exercise. Behavioural Brain Research 198, 366–371.
Duric, V., Banasr, M., Stockmeier, C.A., Simen, A.A., Newton, S.S., Overholser, J.C., Jurjus, G.J., Dieter, L., Duman, R.S., 2013. Altered expression of synapse and glutamate related genes in post-mortem hippocampus of depressed subjects. The International Journal of Neuropsychopharmacology/Official Scientific Journal of the Collegium Internationale Neuropsychopharmacologicum 16, 69–82.

Egeland, M., Zhang, X., Millan, M.J., Mocaer, E., Svenningsson, P., 2012. Pharmacological or genetic blockade of the dopamine D3 receptor increases cell proliferation in the hippocampus of adult mice. Journal of Neurochemistry 123, 811–823.
Eisch, A.J., Petrik, D., 2012. Depression and hippocampal neurogenesis: a road to remission? Science 338, 72–75.
El Hage, W., Powell, J.F., Surguladze, S.A., 2009. Vulnerability to depression: what is the role of stress genes in gene × environment interaction? Psychological Medicine 39, 1407–1411.
Elizalde, N., Garcia-Garcia, A.L., Totterdell, S., Gendive, N., Venzala, E., Ramirez, M.J., Del Rio, J., Tordera, R.M., 2010. Sustained stress-induced changes in mice as a model for chronic depression. Psychopharmacology 210, 393–406.
Eriksson, P.S., Perfilieva, E., Bjork-Eriksson, T., Alborn, A.M., Nordborg, C., Peterson, D.A., Gage, F.H., 1998. Neurogenesis in the adult human hippocampus. Nature Medicine 4, 1313–1317.
Fabre, V., Beaufour, C., Evrard, A., Rioux, A., Hanoun, N., Lesch, K.P., Murphy, D.L., Lanfumey, L., Hamon, M., Martres, M.P., 2000. Altered expression and functions of serotonin 5-HT1A and 5-HT1B receptors in knock-out mice lacking the 5-HT transporter. European Journal of Neuroscience 12, 2299–2310.
Fairbank, J.A., Hansen, D.J., Fitterling, J.M., 1991. Patterns of appraisal and coping across different stressor conditions among former prisoners of war with and without posttraumatic stress disorder. Journal of Consulting and Clinical Psychology 59, 274–281.
Fanselow, M.S., Dong, H.W., 2010. Are the dorsal and ventral hippocampus functionally distinct structures? Neuron 65, 7–19.
Feldmann Jr., R.E., Sawa, A., Seidler, G.H., 2007. Causality of stem cell based neurogenesis and depression – to be or not to be, is that the question? Journal of Psychiatric Research 41, 713–723.
Ferland, C.L., Schrader, L.A., 2011. Regulation of histone acetylation in the hippocampus of chronically stressed rats: a potential role of sirtuins. Neuroscience 174, 104–114.
Ferres-Coy, A., Pilar-Cuellar, F., Vidal, R., Paz, V., Masana, M., Cortes, R., Carmona, M.C., Campa, L., Pazos, A., Montefeltro, A., Valdizan, E.M., Artigas, F., Bortolozzi, A., 2013. RNAi-mediated serotonin transporter suppression rapidly increases serotonergic neurotransmission and hippocampal neurogenesis. Translational Psychiatry 3, e211.
Firk, C., Markus, C.R., 2007. Review: serotonin by stress interaction: a susceptibility factor for the development of depression? Journal of Psychopharmacology 21, 538–544.
Fitzsimons, C.P., van Hooijdonk, L.W., Morrow, J.A., Peeters, B.W., Hamilton, N., Craighead, M., Vreugdenhil, E., 2009. Antiglucocorticoids, neurogenesis and depression. Mini Reviews in Medicinal Chemistry 9, 249–264.
Flores, B.H., Kenna, H., Keller, J., Solvason, H.B., Schatzberg, A.F., 2006. Clinical and biological effects of mifepristone treatment for psychotic depression. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology 31, 628–636.
Froger, N., Palazzo, E., Boni, C., Hanoun, N., Saurini, F., Joubert, C., Dutriez-Casteloot, I., Enache, M., Maccari, S., Barden, N., Cohen-Salmon, C., Hamon, M., Lanfumey, L., 2004. Neurochemical and behavioral alterations in glucocorticoid receptor-impaired transgenic mice after chronic mild stress. Journal of Neuroscience: The Official Journal of the Society for Neuroscience 24, 2787–2796.
Gabbott, P.L.A., Warner, T.A., Jays, P.R.L., Salway, P., Busby, S.J., 2005. Prefrontal cortex in the rat: projections to subcortical autonomic, motor, and limbic centers. Journal of Comparative Neurology 492, 145–177.
Gage, F.H., Thompson, R.G., 1980. Differential distribution of norepinephrine and serotonin along the dorsal–ventral axis of the hippocampal formation. Brain Research Bulletin 5, 771–773.
Gartside, S.E., Hajos-Korcsok, E., Bagdy, E., Harsing Jr., L.G., Sharp, T., Hajos, M., 2000. Neurochemical and electrophysiological studies on the functional significance of burst firing in serotonergic neurons. Neuroscience 98, 295–300.
Gartside, S.E., Leitch, M.M., Young, A.H., 2003. Altered glucocorticoid rhythm attenuates the ability of a chronic SSRI to elevate forebrain 5-HT: implications for the treatment of depression. Neuropsychopharmacology 28, 1572–1578.
Gasbarri, A., Verney, C., Innocenzi, R., Campana, E., Pacitti, C., 1994. Mesolimbic dopaminergic neurons innervating the hippocampal formation in the rat: a combined retrograde tracing and immunohistochemical study. Brain Research 668, 71–79.
Ge, S., Yang, C.H., Hsu, K.S., Ming, G.L., Song, H., 2007. A critical period for enhanced synaptic plasticity in newly generated neurons of the adult brain. Neuron 54, 559–566.
Gersner, R., Toth, E., Isserles, M., Zangen, A., 2010. Site-specific antidepressant effects of repeated subconvulsive electrical stimulation: potential role of brain-derived neurotrophic factor. Biological Psychiatry 67, 125–132.
Glasper, E.R., Llorens-Martin, M.V., Leuner, B., Gould, E., Trejo, J.L., 2010. Blockade of insulin-like growth factor-I has complex effects on structural plasticity in the hippocampus. Hippocampus 20, 706–712.
Gobbi, G., Murphy, D.L., Lesch, K., Blier, P., 2001. Modifications of the serotonergic system in mice lacking serotonin transporters: an in vivo electrophysiological study. Journal of Pharmacology and Experimental Therapeutics 296, 987–995.
Goldstein, G., Fava, M., Culler, M., Fisher, A., Rickels, K., Lydiard, R.B., Rosenbaum, J., 2000. Elevated plasma thymopoietin associated with therapeutic nonresponsiveness in major depression. Biological Psychiatry 48, 65–69.
Grahn, R.E., Will, M.J., Hammack, S.E., Maswood, S., McQueen, M.B., Watkins, L.R., Maier, S.F., 1999. Activation of serotonin-immunoreactive cells in the dorsal raphe nucleus in rats exposed to an uncontrollable stressor. Brain Research 826, 35–43.
Gray, N.A., Milak, M.S., DeLorenzo, C., Ogden, R.T., Huang, Y.Y., Mann, J.J., Parsey, R.V., 2013. Antidepressant treatment reduces serotonin-1A autoreceptor binding in major depressive disorder. Biological Psychiatry 74, 26–31.
Grippo, A.J., Beltz, T.G., Weiss, R.M., Johnson, A.K., 2006. The effects of chronic fluoxetine treatment on chronic mild stress-induced cardiovascular changes and anhedonia. Biological Psychiatry 59, 309–316.
Grippo, A.J., Sullivan, N.R., Damjanoska, K.J., Crane, J.W., Carrasco, G.A., Shi, J., Chen, Z., Garcia, F., Muma, N.A., Van de Kar, L.D., 2005. Chronic mild stress induces behavioral and physiological changes, and may alter serotonin 1A receptor function, in male and cycling female rats. Psychopharmacology 179, 769–780.
Guiard, B.P., El Mansari, M., Blier, P., 2008a. Cross-talk between dopaminergic and noradrenergic systems in the rat ventral tegmental area, locus ceruleus, and dorsal hippocampus. Molecular Pharmacology 74, 1463–1475.
Guiard, B.P., El Mansari, M., Merali, Z., Blier, P., 2008b. Functional interactions between dopamine, serotonin and norepinephrine neurons: an in-vivo electrophysiological study in rats with monoaminergic lesions. The International Journal of Neuropsychopharmacology/Official Scientific Journal of the Collegium Internationale Neuropsychopharmacologicum 11, 625–639.
Hajos, M., Hajos-Korcsok, E., Sharp, T., 1999. Role of the medial prefrontal cortex in 5-HT1A receptor-induced inhibition of 5-HT neuronal activity in the rat. British Journal of Pharmacology 126, 1741–1750.
Hale, M.W., Hay-Schmidt, A., Mikkelsen, J.D., Poulsen, B., Bouwknecht, J.A., Evans, A.K., Stamper, C.E., Shekhar, A., Lowry, C.A., 2008. Exposure to an open-field arena increases c-Fos expression in a subpopulation of neurons in the dorsal raphe nucleus, including neurons projecting to the basolateral amygdaloid complex. Neuroscience 157, 733–748.
Hall, H., Lundkvist, C., Halldin, C., Farde, L., Pike, V.W., McCarron, J.A., Fletcher, A., Cliffe, I.A., Barf, T., Wikstrom, H., Sedvall, G., 1997. Autoradiographic localization of 5-HT1A receptors in the post-mortem human brain using [3H]WAY-100635 and [11C]way-100635. Brain Research 745, 96–108.
Hamani, C., Diwan, M., Isabella, S., Lozano, A.M., Nobrega, J.N., 2010a. Effects of different stimulation parameters on the antidepressant-like response of medial prefrontal cortex deep brain stimulation in rats. Journal of Psychiatric Research 44, 683–687.
Hamani, C., Diwan, M., Macedo, C.E., Brandao, M.L., Shumake, J., Gonzalez-Lima, F., Raymond, R., Lozano, A.M., Fletcher, P.J., Nobrega, J.N., 2010b. Antidepressant-like effects of medial prefrontal cortex deep brain stimulation in rats. Biological Psychiatry 67, 117–124.
Hanson, N.D., Owens, M.J., Nemeroff, C.B., 2011. Depression, antidepressants, and neurogenesis: a critical reappraisal. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology 36, 2589–2602.
Harkin, A., Kelly, J.P., Leonard, B.E., 2003. A review of the relevance and validity of olfactory bulbectomy as a model of depression. Clinical Neuroscience Research 3, 253–262.
Hasler, G., 2010. Pathophysiology of depression: do we have any solid evidence of interest to clinicians? World Psychiatry 9, 155–161.
Henningsen, K., Palmfeldt, J., Christiansen, S., Baiges, I., Bak, S., Jensen, O.N., Gregersen, N., Wiborg, O., 2012. Candidate hippocampal biomarkers of susceptibility and resilience to stress in a rat model of depression. Molecular & Cellular Proteomics MCP 11, M111 016428.
Hervas, I., Artigas, F., 1998. Effect of fluoxetine on extracellular 5-hydroxytryptamine in rat brain. Role of 5-HT autoreceptors. European Journal of Pharmacology 358, 9–18.
Heym, J., Trulson, M.E., Jacobs, B.L., 1982. Raphe unit activity in freely moving cats: effects of phasic auditory and visual stimuli. Brain Research 232, 29–39.
Hill, M.N., Hillard, C.J., Bambico, F.R., Patel, S., Gorzalka, B.B., Gobbi, G., 2009. The therapeutic potential of the endocannabinoid system for the development of a novel class of antidepressants. Trends in Pharmacological Sciences 30, 484–493.
Hirvonen, J., Karlsson, H., Kajander, J., Lepola, A., Markkula, J., Rasi-Hakala, H., Nagren, K., Salminen, J.K., Hietala, J., 2008. Decreased brain serotonin 5-HT1A receptor availability in medication-naive patients with major depressive disorder: an in-vivo imaging study using PET and [carbonyl-11C]WAY-100635. International Journal of Neuropsychopharmacology 11, 465–476.
Hobin, J.A., Ji, J., Maren, S., 2006. Ventral hippocampal muscimol disrupts context-specific fear memory retrieval after extinction in rats. Hippocampus 16, 174–182.
Hoglinger, G.U., Rizk, P., Muriel, M.P., Duyckaerts, C., Oertel, W.H., Caille, I., Hirsch, E.C., 2004. Dopamine depletion impairs precursor cell proliferation in Parkinson disease. Nature Neuroscience 7, 726–735.
Holderbach, R., Clark, K., Moreau, J.-L., Bischofberger, J., Normann, C., 2007. Enhanced long-term synaptic depression in an animal model of depression. Biological Psychiatry 62, 92–9100.
Holick, K.A., Lee, D.C., Hen, R., Dulawa, S.C., 2008. Behavioral effects of chronic fluoxetine in BALB/cJ mice do not require adult hippocampal neurogenesis or the serotonin 1A receptor. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology 33, 406–417.
Holmes, A., 2008. Genetic variation in cortico-amygdala serotonin function and risk for stress-related disease. Neuroscience and Biobehavioral Reviews 32, 1293–1314.
Huang, G.J., Bannerman, D., Flint, J., 2008. Chronic fluoxetine treatment alters behavior, but not adult hippocampal neurogenesis, in BALB/cJ mice. Molecular Psychiatry 13, 119–121.
Jacobs, B.L., van Praag, H., Gage, F.H., 2000. Adult brain neurogenesis and psychiatry: a novel theory of depression. Molecular Psychiatry 5, 262–269.
Jacobs, N., Kenis, G., Peeters, F., Derom, C., Vlietinck, R., van Os, J., 2006. Stress-related negative affectivity and genetically altered serotonin transporter function:

evidence of synergism in shaping risk of depression. Archives of General Psychiatry 63, 989–996.
Jans, L.A., Riedel, W.J., Markus, C.R., Blokland, A., 2007. Serotonergic vulnerability and depression: assumptions, experimental evidence and implications. Molecular Psychiatry 12, 522–543.
Jayatissa, M.N., Bisgaard, C., Tingstrom, A., Papp, M., Wiborg, O., 2006. Hippocampal cytogenesis correlates to escitalopram-mediated recovery in a chronic mild stress rat model of depression. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology 31, 2395–2404.
Jayatissa, M.N., Bisgaard, C.F., West, M.J., Wiborg, O., 2008. The number of granule cells in rat hippocampus is reduced after chronic mild stress and re-established after chronic escitalopram treatment. Neuropharmacology 54, 530–541.
Jayatissa, M.N., Henningsen, K., West, M.J., Wiborg, O., 2009. Decreased cell proliferation in the dentate gyrus does not associate with development of anhedonic-like symptoms in rats. Brain Research 1290, 133–141.
Jhaveri, D.J., Mackay, E.W., Hamlin, A.S., Marathe, S.V., Nandam, L.S., Vaidya, V.A., Bartlett, P.F., 2010. Norepinephrine directly activates adult hippocampal precursors via beta3-adrenergic receptors. Journal of Neuroscience: The Official Journal of the Society for Neuroscience 30, 2795–2806.
Jiang, W., Zhang, Y., Xiao, L., Van Cleemput, J., Ji, S.P., Bai, G., Zhang, X., 2005. Cannabinoids promote embryonic and adult hippocampus neurogenesis and produce anxiolytic- and antidepressant-like effects. Journal of Clinical Investigation 115, 3104–3116.
Jin, K., Zhu, Y., Sun, Y., Mao, X.O., Xie, L., Greenberg, D.A., 2002. Vascular endothelial growth factor (VEGF) stimulates neurogenesis in vitro and in vivo. Proceedings of the National Academy of Sciences of the United States of America 99, 11946–11950.
Juckel, G., Mendlin, A., Jacobs, B.L., 1999. Electrical stimulation of rat medial prefrontal cortex enhances forebrain serotonin output: implications for electroconvulsive therapy and transcranial magnetic stimulation in depression. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology 21, 391–398.
Judd, L.L., Akiskal, H.S., Maser, J.D., Zeller, P.J., Endicott, J., Coryell, W., Paulus, M.P., Kunovac, J.L., Leon, A.C., Mueller, T.I., Rice, J.A., Keller, M.B., 1998. Major depressive disorder: a prospective study of residual subthreshold depressive symptoms as predictor of rapid relapse. Journal of Affective Disorders 50, 97–108.
Kang, M., Pyun, K.H., Jang, C.G., Kim, H., Bae, H., Shim, I., 2005. Nelumbinis Semen reverses a decrease in hippocampal 5-HT release induced by chronic mild stress in rats. Journal of Pharmacy and Pharmacology 57, 651–656.
Karg, K., Burmeister, M., Shedden, K., Sen, S., 2011. The serotonin transporter promoter variant (5-HTTLPR), stress, and depression meta-analysis revisited: evidence of genetic moderation. Archives of General Psychiatry 68, 444–454.
Kastin, A.J., Akerstrom, V., Pan, W., 2004. Neuregulin-1-beta1 enters brain and spinal cord by receptor-mediated transport. Journal of Neurochemistry 88, 965–970.
Kaufman, J., Yang, B.Z., Douglas-Palumberi, H., Houshyar, S., Lipschitz, D., Krystal, J.H., Gelernter, J., 2004. Social supports and serotonin transporter gene moderate depression in maltreated children. Proceedings of the National Academy of Sciences of the United States of America 101, 17316–17321.
Keller, M.C., Neale, M.C., Kendler, K.S., 2007. Association of different adverse life events with distinct patterns of depressive symptoms. American Journal of Psychiatry 164, 1521–1529.
Kempermann, G., 2002. Regulation of adult hippocampal neurogenesis – implications for novel theories of major depression. Bipolar Disorders 4, 17–33.
Kempermann, G., 2011. Adult Neurogenesis 2, 2nd ed. Oxford University Press, New York, NY.
Kempermann, G., Kronenberg, G., 2003. Depressed new neurons – adult hippocampal neurogenesis and a cellular plasticity hypothesis of major depression. Biological Psychiatry 54, 499–503.
Kendler, K.S., Gardner, C.O., Prescott, C.A., 2002. Toward a comprehensive developmental model for major depression in women. American Journal of Psychiatry 159, 1133–1145.
Kendler, K.S., Gardner, C.O., Prescott, C.A., 2006. Toward a comprehensive developmental model for major depression in men. American Journal of Psychiatry 163, 115–124.
Kendler, K.S., Kessler, R.C., Walters, E.E., MacLean, C., Neale, M.C., Heath, A.C., Eaves, L.J., 1995. Stressful life events, genetic liability, and onset of an episode of major depression in women. American Journal of Psychiatry 152, 833–842.
Kendler, K.S., Kuhn, J.W., Prescott, C.A., 2004. Childhood sexual abuse, stressful life events and risk for major depression in women. Psychological Medicine 34, 1475–1482.
Kendler, K.S., Kuhn, J.W., Vittum, J., Prescott, C.A., Riley, B., 2005. The interaction of stressful life events and a serotonin transporter polymorphism in the prediction of episodes of major depression: a replication. Archives of General Psychiatry 62, 529–535.
Kessler, R.C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K.R., Rush, A.J., Walters, E.E., Wang, P.S., National Comorbidity Survey, R., 2003. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA: Journal of the American Medical Association 289, 3095–3105.
Kheirbek, M.A., Hen, R., 2011. Dorsal vs ventral hippocampal neurogenesis: implications for cognition and mood. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology 36, 373–374.
Kim, H., Whang, W.W., Kim, H.T., Pyun, K.H., Cho, S.Y., Hahm, D.H., Lee, H.J., Shim, I., 2003. Expression of neuropeptide Y and cholecystokinin in the rat brain by chronic mild stress. Brain Research 983, 201–208.
Kinney, G.G., Vogel, G.W., Feng, P., 1997. Decreased dorsal raphe nucleus neuronal activity in adult chloral hydrate anesthetized rats following neonatal clomipramine treatment: implications for endogenous depression. Brain Research 756, 68–75.
Kiuchi, T., Lee, H., Mikami, T., 2012. Regular exercise cures depression-like behavior via VEGF-Flk-1 signaling in chronically stressed mice. Neuroscience 207, 208–217.
Kiyasova, V., Bonnavion, P., Scotto-Lomassese, S., Fabre, V., Sahly, I., Tronche, F., Deneris, E., Gaspar, P., Fernandez, S.P., 2013. A subpopulation of serotonergic neurons that do not express the 5-HT1A autoreceptor. ACS Chemical Neuroscience 4, 89–95.
Kjelstrup, K.G., Tuvnes, F.A., Steffenach, H.A., Murison, R., Moser, E.I., Moser, M.B., 2002. Reduced fear expression after lesions of the ventral hippocampus. Proceedings of the National Academy of Sciences of the United States of America 99, 10825–10830.
Klaassen, T., Riedel, W.J., Deutz, N.E., van Someren, A., van Praag, H.M., 1999a. Specificity of the tryptophan depletion method. Psychopharmacology 141, 279–286.
Klaassen, T., Riedel, W.J., van Someren, A., Deutz, N.E., Honig, A., van Praag, H.M., 1999b. Mood effects of 24-hour tryptophan depletion in healthy first-degree relatives of patients with affective disorders. Biological Psychiatry 46, 489–497.
Kobayashi, K., Ikeda, Y., Sakai, A., Yamasaki, N., Haneda, E., Miyakawa, T., Suzuki, H., 2010. Reversal of hippocampal neuronal maturation by serotonergic antidepressants. Proceedings of the National Academy of Sciences of the United States of America 107, 8434–8439.
Kohler, S.J., Williams, N.I., Stanton, G.B., Cameron, J.L., Greenough, W.T., 2011. Maturation time of new granule cells in the dentate gyrus of adult macaque monkeys exceeds six months. Proceedings of the National Academy of Sciences of the United States of America 108, 10326–10331.
Kulkarni, V.A., Jha, S., Vaidya, V.A., 2002. Depletion of norepinephrine decreases the proliferation, but does not influence the survival and differentiation, of granule cell progenitors in the adult rat hippocampus. European Journal of Neuroscience 16, 2008–2012.
Laaris, N., Le Poul, E., Hamon, M., Lanfumey, L., 1997. Stress-induced alterations of somatodendritic 5-HT1A autoreceptor sensitivity in the rat dorsal raphe nucleus – in vitro electrophysiological evidence. Fundamental & Clinical Pharmacology 11, 206–214.
Lan, M.J., Hesselgrave, N., Ciarleglio, A., Ogden, R.T., Sullivan, G.M., Mann, J.J., Parsey, R.V., 2013. Higher pretreatment 5-HT1A receptor binding potential in bipolar disorder depression is associated with treatment remission: a naturalistic treatment pilot PET study. Synapse 67, 773–778.
Lanfumey, L., Mongeau, R., Cohen-Salmon, C., Hamon, M., 2008. Corticosteroid-serotonin interactions in the neurobiological mechanisms of stress-related disorders. Neuroscience and Biobehavioral Reviews 32, 1174–1184.
Lanfumey, L., Pardon, M.C., Laaris, N., Joubert, C., Hanoun, N., Hamon, M., Cohen-Salmon, C., 1999. 5-HT1A autoreceptor desensitization by chronic ultramild stress in mice. Neuroreport 10, 3369–3374.
Larsen, M.H., Mikkelsen, J.D., Hay-Schmidt, A., Sandi, C., 2010. Regulation of brain-derived neurotrophic factor (BDNF) in the chronic unpredictable stress rat model and the effects of chronic antidepressant treatment. Journal of Psychiatric Research 44, 808–816.
Le Francois, B., Czesak, M., Steubl, D., Albert, P.R., 2008. Transcriptional regulation at a HTR1A polymorphism associated with mental illness. Neuropharmacology 55, 977–985.
Le Poul, E., Laaris, N., Hamon, M., Lanfumey, L., 1997. Fluoxetine-induced desensitization of somatodendritic 5-HT1A autoreceptors is independent of glucocorticoid(s). Synapse 27, 303–312.
Lee, Y.S., Liu, F., Segil, N., 2006. A morphogenetic wave of p27Kip1 transcription directs cell cycle exit during organ of Corti development. Development 133, 2817–2826.
Lesch, K.P., 2004. Gene-environment interaction and the genetics of depression. Journal of Psychiatry & Neuroscience 29, 174–184.
Lesch, K.P., Bengel, D., Heils, A., Sabol, S.Z., Greenberg, B.D., Petri, S., Benjamin, J., Muller, C.R., Hamer, D.H., Murphy, D.L., 1996. Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. Science 274, 1527–1531.
Leussis, M.P., Freund, N., Brenhouse, H.C., Thompson, B.S., Andersen, S.L., 2012. Depressive-like behavior in adolescents after maternal separation: sex differences, controllability, and GABA. Developmental Neuroscience 34, 210–217.
Levinson, D.F., 2006. The genetics of depression: a review. Biological Psychiatry 60, 84–92.
Leyton, M., Ghadirian, A.M., Young, S.N., Palmour, R.M., Blier, P., Helmers, K.F., Benkelfat, C., 2000. Depressive relapse following acute tryptophan depletion in patients with major depressive disorder. Journal of Psychopharmacology 14, 284–287.
Li, Q., Wichems, C., Heils, A., Lesch, K.P., Murphy, D.L., 2000. Reduction in the density and expression, but not G-protein coupling, of serotonin receptors (5-HT1A) in 5-HT transporter knock-out mice: gender and brain region differences. Journal of Neuroscience: The Official Journal of the Society for Neuroscience 20, 7888–7895.
Li, Y.F., Zhang, Y.Z., Liu, Y.Q., Wang, H.L., Yuan, L., Luo, Z.P., 2004. Moclobemide upregulates proliferation of hippocampal progenitor cells in chronically stressed mice. Acta Pharmacologica Sinica 25, 1408–1412.
Lira, A., Zhou, M., Castanon, N., Ansorge, M.S., Gordon, J.A., Francis, J.H., Bradley-Moore, M., Lira, J., Underwood, M.D., Arango, V., Kung, H.F., Hofer, M.A., Hen, R., Gingrich, J.A., 2003. Altered depression-related behaviors and functional

changes in the dorsal raphe nucleus of serotonin transporter-deficient mice. Biological Psychiatry 54, 960–971.
Lucki, I., 1997. The forced swimming test as a model for core and component behavioral effects of antidepressant drugs. Behavioural Pharmacology 8, 523–532.
Luo, D.D., An, S.C., Zhang, X., 2008. Involvement of hippocampal serotonin and neuropeptide Y in depression induced by chronic unpredicted mild stress. Brain Research Bulletin 77, 8–12.
Lupien, S.J., McEwen, B.S., Gunnar, M.R., Heim, C., 2009. Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nature Reviews. Neuroscience 10, 434–445.
Mahar, I., Bagot, R.C., Davoli, M.A., Miksys, S., Tyndale, R.F., Walker, C.D., Maheu, M., Huang, S.H., Wong, T.P., Mechawar, N., 2012. Developmental hippocampal neuroplasticity in a model of nicotine replacement therapy during pregnancy and breastfeeding. PLoS ONE 7, e37219.
Mahar, I., Tan, S., Davoli, M.A., Dominguez-Lopez, S., Qiang, C., Rachalski, A., Turecki, G., Mechawar, N., 2011. Subchronic peripheral neuregulin-1 increases ventral hippocampal neurogenesis and induces antidepressant-like effects. PLoS ONE 6, e26610.
Maier, S.F., Amat, J., Baratta, M.V., Paul, E., Watkins, L.R., 2006. Behavioral control, the medial prefrontal cortex, and resilience. Dialogues in Clinical Neuroscience 8, 397–406.
Maier, S.F., Watkins, L.R., 2005. Stressor controllability and learned helplessness: the roles of the dorsal raphe nucleus, serotonin, and corticotropin-releasing factor. Neuroscience and Biobehavioral Reviews 29, 829–841.
Malberg, J.E., Duman, R.S., 2003. Cell proliferation in adult hippocampus is decreased by inescapable stress: reversal by fluoxetine treatment. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology 28, 1562–1571.
Malberg, J.E., Eisch, A.J., Nestler, E.J., Duman, R.S., 2000. Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. Journal of Neuroscience: The Official Journal of the Society for Neuroscience 20, 9104–9110.
Mann, J.J., Huang, Y.Y., Underwood, M.D., Kassir, S.A., Oppenheim, S., Kelly, T.M., Dwork, A.J., Arango, V., 2000. A serotonin transporter gene promoter polymorphism (5-HTTLPR) and prefrontal cortical binding in major depression and suicide. Archives of General Psychiatry 57, 729–738.
Martin-Ruiz, R., Puig, M.V., Celada, P., Shapiro, D.A., Roth, B.L., Mengod, G., Artigas, F., 2001. Control of serotonergic function in medial prefrontal cortex by serotonin-2A receptors through a glutamate-dependent mechanism. Journal of Neuroscience: The Official Journal of the Society for Neuroscience 21, 9856–9866.
Martin-Ruiz, R., Ugedo, L., 2001. Electrophysiological evidence for postsynaptic 5-HT(1A) receptor control of dorsal raphe 5-HT neurones. Neuropharmacology 41, 72–78.
Masuda, T., Nakagawa, S., Boku, S., Nishikawa, H., Takamura, N., Kato, A., Inoue, T., Koyama, T., 2012. Noradrenaline increases neural precursor cells derived from adult rat dentate gyrus through beta2 receptor. Progress in Neuropsychopharmacology & Biological Psychiatry 36, 44–51.
Maudhuit, C., Hamon, M., Adrien, J., 1995. Electrophysiological activity of raphe dorsalis serotoninergic neurones in a possible model of endogenous depression. Neuroreport 6, 681–684.
Maudhuit, C., Hamon, M., Adrien, J., 1996. Effects of chronic treatment with zimelidine and REM sleep deprivation on the regulation of raphe neuronal activity in a rat model of depression. Psychopharmacology 124, 267–274.
Mayberg, H.S., Lozano, A.M., Voon, V., McNeely, H.E., Seminowicz, D., Hamani, C., Schwalb, J.M., Kennedy, S.H., 2005. Deep brain stimulation for treatment-resistant depression. Neuron 45, 651–660.
McArthur, R., Borsini, F., 2006. Animal models of depression in drug discovery: a historical perspective. Pharmacology, Biochemistry, and Behavior 84, 436–452.
McGrath, P.J., Khan, A.Y., Trivedi, M.H., Stewart, J.W., Morris, D.W., Wisniewski, S.R., Miyahara, S., Nierenberg, A.A., Fava, M., Rush, A.J., 2008. Response to a selective serotonin reuptake inhibitor (citalopram) in major depressive disorder with melancholic features: a STAR*D report. Journal of Clinical Psychiatry 69, 1847–1855.
Meltzer, C.C., Price, J.C., Mathis, C.A., Butters, M.A., Ziolko, S.K., Moses-Kolko, E., Mazumdar, S., Mulsant, B.H., Houck, P.R., Lopresti, B.J., Weissfeld, L.A., Reynolds, C.F., 2004. Serotonin 1A receptor binding and treatment response in late-life depression. Neuropsychopharmacology 29, 2258–2265.
Menke, A., Klengel, T., Binder, E.B., 2012. Epigenetics, depression and antidepressant treatment. Current Pharmaceutical Design 18, 5879–5889.
Miller, J.M., Hesselgrave, N., Ogden, R.T., Zanderigo, F., Oquendo, M.A., Mann, J.J., Parsey, R.V., 2013. Brain serotonin 1A receptor binding as a predictor of treatment outcome in major depressive disorder. Biological Psychiatry 74, 760–767.
Mineur, Y.S., Belzung, C., Crusio, W.E., 2007. Functional implications of decreases in neurogenesis following chronic mild stress in mice. Neuroscience 150, 251–259.
Mo, B., Feng, N., Renner, K., Forster, G., 2008. Restraint stress increases serotonin release in the central nucleus of the amygdala via activation of corticotropin-releasing factor receptors. Brain Research Bulletin 76, 493–498.
Monroe, S.M., Simons, A.D., 1991. Diathesis-stress theories in the context of life stress research: implications for the depressive disorders. Psychological Bulletin 110, 406–425.
Moreau, J.L., Jenck, F., Martin, J.R., Mortas, P., Haefely, W.E., 1992. Antidepressant treatment prevents chronic unpredictable mild stress-induced anhedonia as assessed by ventral tegmentum self-stimulation behavior in rats. European Neuropsychopharmacology: Journal of the European College of Neuropsychopharmacology 2, 43–49.
Moreau, J.L., Scherschlicht, R., Jenck, F., Martin, J.R., 1995. Chronic mild stress-induced anhedonia model of depression; sleep abnormalities and curative effects of electroshock treatment. Behavioural Pharmacology 6, 682–687.
Mosko, S.S., Jacobs, B.L., 1974. Midbrain raphe neurons: spontaneous activity and response to light. Physiology & Behavior 13, 589–593.
Mudo, G., Belluardo, N., Mauro, A., Fuxe, K., 2007. Acute intermittent nicotine treatment induces fibroblast growth factor-2 in the subventricular zone of the adult rat brain and enhances neuronal precursor cell proliferation. Neuroscience 145, 470–483.
Musazzi, L., Cattaneo, A., Tardito, D., Barbon, A., Gennarelli, M., Barlati, S., Racagni, G., Popoli, M., 2009. Early raise of BDNF in hippocampus suggests induction of posttranscriptional mechanisms by antidepressants. BMC Neuroscience 10, 48.
Navailles, S., Hof, P.R., Schmauss, C., 2008. Antidepressant drug-induced stimulation of mouse hippocampal neurogenesis is age-dependent and altered by early life stress. Journal of Comparative Neurology 509, 372–381.
Nestler, E.J., Barrot, M., DiLeone, R.J., Eisch, A.J., Gold, S.J., Monteggia, L.M., 2002. Neurobiology of depression. Neuron 34, 13–25.
Nettles, K.W., Pesold, C., Goldman, M.B., 2000. Influence of the ventral hippocampal formation on plasma vasopressin, hypothalamic–pituitary–adrenal axis, and behavioral responses to novel acoustic stress. Brain Research 858, 181–190.
Neumaier, J.F., Edwards, E., Plotsky, P.M., 2002. 5-HT(1B) mrna regulation in two animal models of altered stress reactivity. Biological Psychiatry 51, 902–908.
Neumeister, A., Bain, E., Nugent, A.C., Carson, R.E., Bonne, O., Luckenbaugh, D.A., Eckelman, W., Herscovitch, P., Charney, D.S., Drevets, W.C., 2004. Reduced serotonin type 1A receptor binding in panic disorder. Journal of Neuroscience: The Official Journal of the Society for Neuroscience 24, 589–591.
Neumeister, A., Konstantinidis, A., Stastny, J., Schwarz, M.J., Vitouch, O., Willeit, M., Praschak-Rieder, N., Zach, J., de Zwaan, M., Bondy, B., Ackenheil, M., Kasper, S., 2002. Association between serotonin transporter gene promoter polymorphism (5HTTLPR) and behavioral responses to tryptophan depletion in healthy women with and without family history of depression. Archives of General Psychiatry 59, 613–620.
Nibuya, M., Morinobu, S., Duman, R.S., 1995. Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. Journal of Neuroscience: The Official Journal of the Society for Neuroscience 15, 7539–7547.
Olivier, J.D., Van Der Hart, M.G., Van Swelm, R.P., Dederen, P.J., Homberg, J.R., Cremers, T., Deen, P.M., Cuppen, E., Cools, A.R., Ellenbroek, B.A., 2008. A study in male and female 5-HT transporter knockout rats: an animal model for anxiety and depression disorders. Neuroscience 152, 573–584.
Overstreet, D.H., 1993. The flinders sensitive line rats: a genetic animal model of depression. Neuroscience and Biobehavioral Reviews 17, 51–68.
Paizanis, E., Renoir, T., Lelievre, V., Saurini, F., Melfort, M., Gabriel, C., Barden, N., Mocaer, E., Hamon, M., Lanfumey, L., 2010. Behavioural and neuroplastic effects of the new-generation antidepressant agomelatine compared to fluoxetine in glucocorticoid receptor-impaired mice. The International Journal of Neuropsychopharmacology/Official Scientific Journal of the Collegium Internationale Neuropsychopharmacologicum 13, 759–774.
Parihar, V.K., Hattiangady, B., Kuruba, R., Shuai, B., Shetty, A.K., 2011. Predictable chronic mild stress improves mood, hippocampal neurogenesis and memory. Molecular Psychiatry 16, 171–183.
Park, J.H., Enikolopov, G., 2010. Transient elevation of adult hippocampal neurogenesis after dopamine depletion. Experimental Neurology 222, 267–276.
Pazos, A., Probst, A., Palacios, J.M., 1987. Serotonin receptors in the human brain – IV. Autoradiographic mapping of serotonin-2 receptors. Neuroscience 21, 123–139.
Pechnick, R.N., Zonis, S., Wawrowsky, K., Cosgayon, R., Farrokhi, C., Lacayo, L., Chesnokova, V., 2011. Antidepressants stimulate hippocampal neurogenesis by inhibiting p21 expression in the subgranular zone of the hipppocampus. PLoS ONE 6, e27290.
Pentkowski, N.S., Blanchard, D.C., Lever, C., Litvin, Y., Blanchard, R.J., 2006. Effects of lesions to the dorsal and ventral hippocampus on defensive behaviors in rats. European Journal of Neuroscience 23, 2185–2196.
Perera, T.D., Coplan, J.D., Lisanby, S.H., Lipira, C.M., Arif, M., Carpio, C., Spitzer, G., Santarelli, L., Scharf, B., Hen, R., Rosoklija, G., Sackeim, H.A., Dwork, A.J., 2007. Antidepressant-induced neurogenesis in the hippocampus of adult nonhuman primates. Journal of Neuroscience: The Official Journal of the Society for Neuroscience 27, 4894–4901.
Perera, T.D., Dwork, A.J., Keegan, K.A., Thirumangalakudi, L., Lipira, C.M., Joyce, N., Lange, C., Higley, J.D., Rosoklija, G., Hen, R., Sackeim, H.A., Coplan, J.D., 2011. Necessity of hippocampal neurogenesis for the therapeutic action of antidepressants in adult nonhuman primates. PLoS ONE 6, e17600.
Petrik, D., Lagace, D.C., Eisch, A.J., 2012. The neurogenesis hypothesis of affective and anxiety disorders: are we mistaking the scaffolding for the building? Neuropharmacology 62, 21–34.
Peyron, C., Petit, J.M., Rampon, C., Jouvet, M., Luppi, P.H., 1998. Forebrain afferents to the rat dorsal raphe nucleus demonstrated by retrograde and anterograde tracing methods. Neuroscience 82, 443–468.
Pitchot, W., Hansenne, M., Pinto, E., Reggers, J., Fuchs, S., Ansseau, M., 2005. 5-Hydroxytryptamine 1A receptors, major depression, and suicidal behavior. Biological Psychiatry 58, 854–858.
Pitychoutis, P.M., Griva, E., Ioannou, K., Tsitsilonis, O.E., Papadopoulou-Daifoti, Z., 2009. Chronic antidepressant treatment exerts sexually dimorphic immunomodulatory effects in an experimental model of major depression: do females lack an advantage? The International Journal of Neuropsychopharmacology/official Scientific Journal of the Collegium Internationale Neuropsychopharmacologicum 12, 1157–1163.

Pollak, D.D., Monje, F.J., Zuckerman, L., Denny, C.A., Drew, M.R., Kandel, E.R., 2008. An animal model of a behavioral intervention for depression. Neuron 60, 149–161.
Possel, P., 2011. Can Beck's theory of depression and the response style theory be integrated? Journal of Counseling Psychology 58, 618–629.
Price, J.L., Drevets, W.C., 2010. Neurocircuitry of mood disorders. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology 35, 192–216.
Pruessner, M., Hellhammer, D.H., Pruessner, J.C., Lupien, S.J., 2003. Self-reported depressive symptoms and stress levels in healthy young men: associations with the cortisol response to awakening. Psychosomatic Medicine 65, 92–99.
Pucilowski, O., Overstreet, D.H., Rezvani, A.H., Janowsky, D.S., 1993. Chronic mild stress-induced anhedonia: greater effect in a genetic rat model of depression. Physiology & Behavior 54, 1215–1220.
Qi, X., Lin, W., Li, J., Pan, Y., Wang, W., 2006. The depressive-like behaviors are correlated with decreased phosphorylation of mitogen-activated protein kinases in rat brain following chronic forced swim stress. Behavioural Brain Research 175, 233–240.
Rabiner, E.A., Bhagwagar, Z., Gunn, R.N., Cowen, P.J., Grasby, P.M., 2004. Preferential 5-HT1A autoreceptor occupancy by pindolol is attenuated in depressed patients: effect of treatment or an endophenotype of depression? Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology 29, 1688–1698.
Rainer, Q., Xia, L., Guilloux, J.P., Gabriel, C., Mocaer, E., Hen, R., Enhamre, E., Gardier, A.M., David, D.J., 2011. Beneficial behavioural and neurogenic effects of agomelatine in a model of depression/anxiety. International Journal of Neuropsychopharmacology, 1–15.
Raison, C.L., Miller, A.H., 2003. When not enough is too much: the role of insufficient glucocorticoid signaling in the pathophysiology of stress-related disorders. American Journal of Psychiatry 160, 1554–1565.
Rasheed, N., Tyagi, E., Ahmad, A., Siripurapu, K.B., Lahiri, S., Shukla, R., Palit, G., 2008. Involvement of monoamines and proinflammatory cytokines in mediating the anti-stress effects of Panax quinquefolium. Journal of Ethnopharmacology 117, 257–262.
Renthal, W., Maze, I., Krishnan, V., Covington, H.E., Xiao, G., Kumar, A., Russo, S.J., Graham, A., Tsankova, N., Kippin, T.E., Kerstetter, K.A., Neve, R.L., Haggarty, S.J., McKinsey, T.A., Bassel-Duby, R., Olson, E.N., Nestler, E.J., 2007. Histone deacetylase 5 epigenetically controls behavioral adaptations to chronic emotional stimuli. Neuron 56, 517–529.
Ressler, K.J., Nemeroff, C.B., 2000. Role of serotonergic and noradrenergic systems in the pathophysiology of depression and anxiety disorders. Depress Anxiety 12 (Suppl. 1), 2–19.
Riad, M., Rbah, L., Verdurand, M., Aznavour, N., Zimmer, L., Descarries, L., 2008. Unchanged density of 5-HT(1A) autoreceptors on the plasma membrane of nucleus raphe dorsalis neurons in rats chronically treated with fluoxetine. Neuroscience 151, 692–700.
Riad, M., Zimmer, L., Rbah, L., Watkins, K.C., Hamon, M., Descarries, L., 2004. Acute treatment with the antidepressant fluoxetine internalizes 5-HT1A autoreceptors and reduces the in vivo binding of the PET radioligand [18F]MPPF in the nucleus raphe dorsalis of rat. Journal of Neuroscience: The Official Journal of the Society for Neuroscience 24, 5420–5426.
Richardson-Jones, J.W., Craige, C.P., Guiard, B.P., Stephen, A., Metzger, K.L., Kung, H.F., Gardier, A.M., Dranovsky, A., David, D.J., Beck, S.G., Hen, R., Leonardo, E.D., 2010. 5-HT1A autoreceptor levels determine vulnerability to stress and response to antidepressants. Neuron 65, 40–52.
Richell, R.A., Deakin, J.F., Anderson, I.M., 2005. Effect of acute tryptophan depletion on the response to controllable and uncontrollable noise stress. Biological Psychiatry 57, 295–300.
Rizk, P., Salazar, J., Raisman-Vozari, R., Marien, M., Ruberg, M., Colpaert, F., Debeir, T., 2006. The alpha2-adrenoceptor antagonist dexefaroxan enhances hippocampal neurogenesis by increasing the survival and differentiation of new granule cells. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology 31, 1146–1157.
Roman, O., Seres, J., Pometlova, M., Jurcovicova, J., 2004. Neuroendocrine or behavioral effects of acute or chronic emotional stress in Wistar Kyoto (WKY) and spontaneously hypertensive (SHR) rats. Endocrine Regulations 38, 151–155.
Rosa-Neto, P., Diksic, M., Okazawa, H., Leyton, M., Ghadirian, N., Mzengeza, S., Nakai, A., Debonnel, G., Blier, P., Benkelfat, C., 2004. Measurement of brain regional alpha-[11C]methyl-L-tryptophan trapping as a measure of serotonin synthesis in medication-free patients with major depression. Archives of General Psychiatry 61, 556–563.
Rossi, C., Angelucci, A., Costantin, L., Braschi, C., Mazzantini, M., Babbini, F., Fabbri, M.E., Tessarollo, L., Maffei, L., Berardi, N., Caleo, M., 2006. Brain-derived neurotrophic factor (BDNF) is required for the enhancement of hippocampal neurogenesis following environmental enrichment. European Journal of Neuroscience 24, 1850–1856.
Rouchet, N., Waroux, O., Lamy, C., Massotte, L., Scuvee-Moreau, J., Liegeois, J.-F., Seutin, V., 2008. SK channel blockade promotes burst firing in dorsal raphe serotonergic neurons. European Journal of Neuroscience 28, 1108–1115.
Russo, S.J., Murrough, J.W., Han, M.-H., Charney, D.S., Nestler, E.J., 2012. Neurobiology of resilience. Nature Neuroscience 15, 1475–1484.
Sahay, A., Scobie, K.N., Hill, A.S., O'Carroll, C.M., Kheirbek, M.A., Burghardt, N.S., Fenton, A.A., Dranovsky, A., Hen, R., 2011. Increasing adult hippocampal neurogenesis is sufficient to improve pattern separation. Nature 472, U466–U539.
Sairanen, M., Lucas, G., Ernfors, P., Castren, M., Castren, E., 2005. Brain-derived neurotrophic factor and antidepressant drugs have different but coordinated effects on neuronal turnover, proliferation, and survival in the adult dentate gyrus. Journal of Neuroscience: The Official Journal of the Society for Neuroscience 25, 1089–1094.
Santarelli, L., Saxe, M., Gross, C., Surget, A., Battaglia, F., Dulawa, S., Weisstaub, N., Lee, J., Duman, R., Arancio, O., Belzung, C., Hen, R., 2003. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. Science 301, 805–809.
Sapolsky, R., 2003. Taming stress. Scientific American 289, 86–95.
Sargent, P.A., Kjaer, K.H., Bench, C.J., Rabiner, E.A., Messa, C., Meyer, J., Gunn, R.N., Grasby, P.M., Cowen, P.J., 2000. Brain serotonin1A receptor binding measured by positron emission tomography with [11C]WAY-100635: effects of depression and antidepressant treatment. Archives of General Psychiatry 57, 174–180.
Scharfman, H., Goodman, J., Macleod, A., Phani, S., Antonelli, C., Croll, S., 2005. Increased neurogenesis and the ectopic granule cells after intrahippocampal BDNF infusion in adult rats. Experimental Neurology 192, 348–356.
Schloesser, R.J., Jimenez, D.V., Hardy, N.F., Paredes, D., Catlow, B.J., Manji, H.K., McKay, R.D., Martinowich, K., 2013. Atrophy of pyramidal neurons and increased stress-induced glutamate levels in CA3 following chronic suppression of adult neurogenesis. Brain Structure & Function http://www.ncbi.nlm.nih.gov/pubmed/23483239
Schloesser, R.J., Manji, H.K., Martinowich, K., 2009. Suppression of adult neurogenesis leads to an increased hypothalamo-pituitary–adrenal axis response. Neuroreport 20, 553–557.
Schmidt, H.D., Duman, R.S., 2010. Peripheral BDNF produces antidepressant-like effects in cellular and behavioral models. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology 35, 2378–2391.
Schultz, W., 2007. Multiple dopamine functions at different time courses. Annual review of neuroscience 30, 259–288.
Schweimer, J.V., Ungless, M.A., 2010. Phasic responses in dorsal raphe serotonin neurons to noxious stimuli. Neuroscience 171, 1209–1215.
Sharp, T., Boothman, L., Raley, J., Queree, P., 2007. Important messages in the 'post': recent discoveries in 5-HT neurone feedback control. Trends in Pharmacological Sciences 28, 629–636.
Sheikh, N., Ahmad, A., Siripurapu, K.B., Kuchibhotla, V.K., Singh, S., Palit, G., 2007. Effect of Bacopa monniera on stress induced changes in plasma corticosterone and brain monoamines in rats. Journal of Ethnopharmacology 111, 671–676.
Shi, S.S., Shao, S.H., Yuan, B.P., Pan, F., Li, Z.L., 2010. Acute stress and chronic stress change brain-derived neurotrophic factor (BDNF) and tyrosine kinase-coupled receptor (TrkB) expression in both young and aged rat hippocampus. Yonsei Medical Journal 51, 661–671.
Shima, K., Nakahama, H., Yamamoto, M., 1986. Firing properties of two types of nucleus raphe dorsalis neurons during the sleep-waking cycle and their responses to sensory stimuli. Brain Research 399, 317–326.
Shin, M.H., Mavila, N., Wang, W.H., Vega Alvarez, S., Hall, M.C., Andrisani, O.M., 2009. Time-dependent activation of Phox2a by the cyclic AMP pathway modulates onset and duration of p27Kip1 transcription. Molecular and Cellular Biology 29, 4878–4890.
Shirayama, Y., Chen, A.C., Nakagawa, S., Russell, D.S., Duman, R.S., 2002. Brain-derived neurotrophic factor produces antidepressant effects in behavioral models of depression. Journal of Neuroscience: The Official Journal of the Society for Neuroscience 22, 3251–3261.
Silberg, J., Pickles, A., Rutter, M., Hewitt, J., Simonoff, E., Maes, H., Carbonneau, R., Murrelle, L., Foley, D., Eaves, L., 1999. The influence of genetic factors and life stress on depression among adolescent girls. Archives of General Psychiatry 56, 225–232.
Silverman, L.H., 1976. Psychoanalytic theory "the reports of my death are greatly exaggerated". American Psychologist 31, 621–637.
Smith, M.A., Makino, S., Kim, S.Y., Kvetnansky, R., 1995a. Stress increases brain-derived neurotropic factor messenger ribonucleic acid in the hypothalamus and pituitary. Endocrinology 136, 3743–3750.
Smith, M.A., Makino, S., Kvetnansky, R., Post, R.M., 1995b. Stress and glucocorticoids affect the expression of brain-derived neurotrophic factor and neurotrophin-3 mRNAs in the hippocampus. Journal of Neuroscience: The Official Journal of the Society for Neuroscience 15, 1768–1777.
Snyder, J.S., Ferrante, S.C., Cameron, H.A., 2012. Late maturation of adult-born neurons in the temporal dentate gyrus. PLoS ONE 7, e48757.
Snyder, J.S., Soumier, A., Brewer, M., Pickel, J., Cameron, H.A., 2011. Adult hippocampal neurogenesis buffers stress responses and depressive behaviour. Nature 476, 458–461.
Song, C., Leonard, B.E., 2005. The olfactory bulbectomised rat as a model of depression. Neuroscience and Biobehavioral Reviews 29, 627–647.
Spalding, K.L., Bergmann, O., Alkass, K., Bernard, S., Salehpour, M., Huttner, H.B., Bostrom, E., Westerlund, I., Vial, C., Buchholz, B.A., Possnert, G., Mash, D.C., Druid, H., Frisen, J., 2013. Dynamics of hippocampal neurogenesis in adult humans. Cell 153, 1219–1227.
Steciuk, M., Kram, M., Kramer, G.L., Petty, F., 2000. Acute stress does not alter 5-HT1A receptor density. Progress in Neuropsychopharmacology & Biological Psychiatry 24,155–161.
Steinbusch, H.W., 1981. Distribution of serotonin-immunoreactivity in the central nervous system of the rat-cell bodies and terminals. Neuroscience 6, 557–618.
Steiner, M.A., Wanisch, K., Monory, K., Marsicano, G., Borroni, E., Bachli, H., Holsboer, F., Lutz, B., Wotjak, C.T., 2008. Impaired cannabinoid receptor type 1 signaling interferes with stress-coping behavior in mice. Pharmacogenomics Journal 8, 196–208.

Stockmeier, C.A., Shapiro, L.A., Dilley, G.E., Kolli, T.N., Friedman, L., Rajkowska, G., 1998. Increase in serotonin-1A autoreceptors in the midbrain of suicide victims with major depression-postmortem evidence for decreased serotonin activity. Journal of Neuroscience: The Official Journal of the Society for Neuroscience 18, 7394–7401.

Sun, Y., Jin, K., Childs, J.T., Xie, L., Mao, X.O., Greenberg, D.A., 2006. Vascular endothelial growth factor-B (VEGFB) stimulates neurogenesis: evidence from knockout mice and growth factor administration. Developmental Biology 289, 329–335.

Surget, A., Saxe, M., Leman, S., Ibarguen-Vargas, Y., Chalon, S., Griebel, G., Hen, R., Belzung, C., 2008. Drug-dependent requirement of hippocampal neurogenesis in a model of depression and of antidepressant reversal. Biological Psychiatry 64, 293–301.

Surget, A., Tanti, A., Leonardo, E.D., Laugeray, A., Rainer, Q., Touma, C., Palme, R., Griebel, G., Ibarguen-Vargas, Y., Hen, R., Belzung, C., 2011. Antidepressants recruit new neurons to improve stress response regulation. Molecular Psychiatry 16, 1177–1188.

Swiergiel, A.H., Leskov, I.L., Dunn, A.J., 2008. Effects of chronic and acute stressors and CRF on depression-like behavior in mice. Behavioural Brain Research 186, 32–40.

Takase, L.F., Nogueira, M.I., Baratta, M., Bland, S.T., Watkins, L.R., Maier, S.F., Fornal, C.A., Jacobs, B.L., 2004. Inescapable shock activates serotonergic neurons in all raphe nuclei of rat. Behavioural Brain Research 153, 233–239.

Taliaz, D., Stall, N., Dar, D.E., Zangen, A., 2010. Knockdown of brain-derived neurotrophic factor in specific brain sites precipitates behaviors associated with depression and reduces neurogenesis. Molecular Psychiatry 15, 80–92.

Tanti, A., Westphal, W.P., Girault, V., Brizard, B., Devers, S., Leguisquet, A.M., Surget, A., Belzung, C., 2013. Region-dependent and stage-specific effects of stress, environmental enrichment, and antidepressant treatment on hippocampal neurogenesis. Hippocampus.

Trulson, M.E., Jacobs, B.L., 1979. Raphe unit activity in freely moving cats: correlation with level of behavioral arousal. Brain Research 163, 135–150.

Trulson, M.E., Preussler, D.W., 1984. Dopamine-containing ventral tegmental area neurons in freely moving cats: activity during the sleep-waking cycle and effects of stress. Experimental Neurology 83, 367–377.

Tsankova, N., Renthal, W., Kumar, A., Nestler, E.J., 2007. Epigenetic regulation in psychiatric disorders. Nature reviews. Neuroscience 8, 355–367.

Ueyama, E., Ukai, S., Ogawa, A., Yamamoto, M., Kawaguchi, S., Ishii, R., Shinosaki, K., 2011. Chronic repetitive transcranial magnetic stimulation increases hippocampal neurogenesis in rats. Psychiatry and Clinical Neurosciences 65, 77–81.

Valente, M.M., Bortolotto, V., Cuccurazzu, B., Ubezio, F., Meneghini, V., Francese, M.T., Canonico, P.L., Grilli, M., 2012. alpha2delta ligands act as positive modulators of adult hippocampal neurogenesis and prevent depression-like behavior induced by chronic restraint stress. Molecular Pharmacology 82, 271–280.

Valverde, O., Torrens, M., 2012. CB1 receptor-deficient mice as a model for depression. Neuroscience 204, 193–206.

van Praag, H., 1996. Serotonin-related, anxiety/aggression-driven, stressor-precipitated depression. A psycho-biological hypothesis. European Psychiatry: Journal of the Association of European Psychiatrists 11, 57–67.

van Praag, H.M., 2004. Can stress cause depression? Progress in Neuropsychopharmacology & Biological Psychiatry 28, 891–907.

van Strien, N.M., Cappaert, N.L., Witter, M.P., 2009. The anatomy of memory: an interactive overview of the parahippocampal–hippocampal network. Nature reviews. Neuroscience 10, 272–282.

Vazquez-Palacios, G., Bonilla-Jaime, H., Velazquez-Moctezuma, J., 2005. Antidepressant effects of nicotine and fluoxetine in an animal model of depression induced by neonatal treatment with clomipramine. Progress in Neuropsychopharmacology & Biological Psychiatry 29, 39–46.

Veena, J., Rao, B.S., Srikumar, B.N., 2011. Regulation of adult neurogenesis in the hippocampus by stress, acetylcholine and dopamine. Journal of Natural Science, Biology, and Medicine 2, 26–37.

Veena, J., Srikumar, B.N., Mahati, K., Bhagya, V., Raju, T.R., Shankaranarayana Rao, B.S., 2009. Enriched environment restores hippocampal cell proliferation and ameliorates cognitive deficits in chronically stressed rats. Journal of Neuroscience Research 87, 831–843.

Veldhuis, H.D., De Korte, C.C., De Kloet, E.R., 1985. Glucocorticoids facilitate the retention of acquired immobility during forced swimming. European Journal of Pharmacology 115, 211–217.

Vicentic, A., Francis, D., Moffett, M., Lakatos, A., Rogge, G., Hubert, G.W., Harley, J., Kuhar, M.J., 2006. Maternal separation alters serotonergic transporter densities and serotonergic 1A receptors in rat brain. Neuroscience 140, 355–365.

Vogel, G., Neill, D., Hagler, M., Kors, D., 1990. A new animal model of endogenous depression: a summary of present findings. Neuroscience and Biobehavioral Reviews 14, 85–91.

Vollmayr, B., Simonis, C., Weber, S., Gass, P., Henn, F., 2003. Reduced cell proliferation in the dentate gyrus is not correlated with the development of learned helplessness. Biological Psychiatry 54, 1035–1040.

Walletschek, H., Raab, A., 1982. Spontaneous activity of dorsal raphe neurons during defensive and offensive encounters in the tree-shrew. Physiology & Behavior 28, 697–705.

Wang, J.W., David, D.J., Monckton, J.E., Battaglia, F., Hen, R., 2008. Chronic fluoxetine stimulates maturation and synaptic plasticity of adult-born hippocampal granule cells. Journal of Neuroscience: The Official Journal of the Society for Neuroscience 28, 1374–1384.

Warner-Schmidt, J.L., Duman, R.S., 2007. VEGF is an essential mediator of the neurogenic and behavioral actions of antidepressants. Proceedings of the National Academy of Sciences of the United States of America 104, 4647–4652.

Waterhouse, E.G., An, J.J., Orefice, L.L., Baydyuk, M., Liao, G.Y., Zheng, K., Lu, B., Xu, B., 2012. BDNF promotes differentiation and maturation of adult-born neurons through GABAergic transmission. Journal of Neuroscience: The Official Journal of the Society for Neuroscience 32, 14318–14330.

Weiss, J.M., Cierpial, M.A., West, C.H., 1998. Selective breeding of rats for high and low motor activity in a swim test: toward a new animal model of depression. Pharmacology, Biochemistry, and Behavior 61, 49–66.

Wilber, A.A., Walker, A.G., Southwood, C.J., Farrell, M.R., Lin, G.L., Rebec, G.V., Wellman, C.L., 2011. Chronic stress alters neural activity in medial prefrontal cortex during retrieval of extinction. Neuroscience 174, 115–131.

Wilkinson, L.O., Jacobs, B.L., 1988. Lack of response of serotonergic neurons in the dorsal raphe nucleus of freely moving cats to stressful stimuli. Experimental Neurology 101, 445–457.

Willner, P., 1990. Animal models of depression: an overview. Pharmacology & Therapeutics 45, 425–455.

Willner, P., 1997. Validity, reliability and utility of the chronic mild stress model of depression: a 10-year review and evaluation. Psychopharmacology 134, 319–329.

Willner, P., 2005. Chronic mild stress (CMS) revisited: consistency and behavioural–neurobiological concordance in the effects of CMS. Neuropsychobiology 52, 90–110.

Willner, P., Muscat, R., Papp, M., 1992. Chronic mild stress-induced anhedonia: a realistic animal model of depression. Neuroscience and Biobehavioral Reviews 16, 525–534.

Willner, P., Towell, A., Sampson, D., Sophokleous, S., Muscat, R., 1987. Reduction of sucrose preference by chronic unpredictable mild stress, and its restoration by a tricyclic antidepressant. Psychopharmacology 93, 358–364.

Wilson, M.A., Molliver, M.E., 1991. The organization of serotonergic projections to cerebral cortex in primates: retrograde transport studies. Neuroscience 44, 555–570.

Wong, E.Y., Herbert, J., 2004. The corticoid environment: a determining factor for neural progenitors' survival in the adult hippocampus. European Journal of Neuroscience 20, 2491–2498.

Wong, E.Y., Herbert, J., 2006. Raised circulating corticosterone inhibits neuronal differentiation of progenitor cells in the adult hippocampus. Neuroscience 137, 83–92.

Yang, P., Arnold, S.A., Habas, A., Hetman, M., Hagg, T., 2008. Ciliary neurotrophic factor mediates dopamine D2 receptor-induced CNS neurogenesis in adult mice. Journal of Neuroscience: The Official Journal of the Society for Neuroscience 28, 2231–2241.

Ye, W., Mairet-Coello, G., Pasoreck, E., Dicicco-Bloom, E., 2009. Patterns of p57Kip2 expression in embryonic rat brain suggest roles in progenitor cell cycle exit and neuronal differentiation. Developmental neurobiology 69, 1–21.

Yi, L.T., Li, J.M., Li, Y.C., Pan, Y., Xu, Q., Kong, L.D., 2008. Antidepressant-like behavioral and neurochemical effects of the citrus-associated chemical apigenin. Life Sciences 82, 741–751.

Zalsman, G., Huang, Y.Y., Oquendo, M.A., Burke, A.K., Hu, X.Z., Brent, D.A., Ellis, S.P., Goldman, D., Mann, J.J., 2006. Association of a triallelic serotonin transporter gene promoter region (5-HTTLPR) polymorphism with stressful life events and severity of depression. American Journal of Psychiatry 163, 1588–1593.

Zhang, T.Y., Meaney, M.J., 2010. Epigenetics and the environmental regulation of the genome and its function. Annual Review of Psychology 61, 439–466, C431–433.

Ziabreva, I., Poeggel, G., Schnabel, R., Braun, K., 2003. Separation-induced receptor changes in the hippocampus and amygdala of Octodon degus: influence of maternal vocalizations. Journal of Neuroscience: The Official Journal of the Society for Neuroscience 23, 5329–5336.