

# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

185,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index  
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?  
Contact [book.department@intechopen.com](mailto:book.department@intechopen.com)

Numbers displayed above are based on latest data collected.  
For more information visit [www.intechopen.com](http://www.intechopen.com)



---

# **Long-Term Adaptive Changes Induced by Antidepressants: From Conventional to Novel Therapies**

---

Ouissame Mnie-Filali, Erika Abrial,  
Laura Lambás-Señas and Nasser Haddjeri

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/54553>

---

## **1. Introduction**

Major depressive disorder (MDD) is a devastating disease in terms of human suffering, health costs and economic burden to society. As described in the Diagnostic and Statistical Manual of Mental Disorders, various symptoms can be observed in depressed patients including disheartened mood, loss of interest or pleasure (anhedonia), feeling of guilt or worthlessness, disturbed sleep or appetite, low energy, poor concentration and suicidal ideation. The prevalence of MDD in the general population is 4.4% to 5% with an annual incidence of 2.4% to 3.8% [1]. Regional variation in the 12-month prevalence of the major depressive episodes was also noted, ranging from 2.2% in Japan to 10.45% in Brazil with similar averages of 5.5% in developed and 5.9% in developing countries [2]. In the USA, 59% of MDD patients experience severe degree of functional impairment, making depression the largest contributor to work loss [3, 4]. Furthermore, MDD was strongly associated to self-perceived stress, childhood adversity, working status and quality of life [5-7]. According to the estimation results reported in the global burden of disease study (a study measuring disability-adjusted life-years, DALY), MDD will have become the leading cause of disability in developed countries by the year 2030 [8], indicating that the situation is not likely to improve unless something changes. A major contributor to this crisis is the lack of adequate medication to treat a large proportion of patients. Indeed, 20% do not respond to antidepressants (ADs) recommended as “first-line” drugs, 40% do so only partially, and among responders, there is a time lag of several weeks to months before a meaningful clinical effect can be observed. Failure of clinical recovery with the first AD treatment used and high risk of relapses are also common features. A common

trait of all conventional ADs is that they have a similar mode of action, which is an enhancement of synaptic transmission of the monoamines serotonin (5-HT) and/or norepinephrine (NE) [9]. In fact, development of AD medications was largely based on the monoaminergic theory of depression that links the pathophysiology of this illness to a deficiency on cerebral 5-HT and/or NE levels. Hence, first generation of ADs, monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs) inhibit the breakdown of 5-HT, NE and dopamine in presynaptic neurons and block the presynaptic uptake of 5-HT and NE through high-affinity 5-HT (SERT) or NE (NET) transporters, respectively. Although effective, the severe side effects and toxicity of MAOIs and TCAs limited their usefulness. Later, drugs with more novel approaches, including selective 5-HT reuptake inhibitors (SSRIs), NE reuptake inhibitors (NRIs) and combined-action 5-HT/NE reuptake inhibitors (SNRIs) have been introduced, but as well as the prior generation of ADs, they act through the modulation of monoamine transporters, which may explain their suboptimal therapeutic efficacy. A number of emerging ADs that target monoamine transmission attempt to act on existing targets in more synergic ways (combining 5-HT reuptake inhibition with inhibition of autoreceptors) or to broaden the spectrum of monoamine systems targeted (dopamine, melatonin) to either enhance efficacy or speed response.

Nevertheless, the complexity and heterogeneity of symptoms of MDD makes incompatible the association of a disease with a single pathophysiological disturbance. Hence, years of research and efforts gave rise to a multitude of hypotheses trying to explain the different facets of this disorder. For example, studies have associated depression with abnormalities in the hypothalamus-pituitary-adrenal axis activity including elevated concentrations of the corticotropin-releasing hormone in the cerebrospinal fluid, increased volumes of adrenal gland and pituitary and an impairment of corticosteroid receptor signaling [10, 11]. Also, extensive studies reported circadian rhythms deregulations in depressed patients, as well as an AD effect of drugs that are capable to resynchronize this biological rhythm (i.e. agomelatine) [12, 13]. Pro-inflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factors (TNF)- $\alpha$  were also implicated in depressive disorders [14, 15]. Other possible mechanisms that have been suggested to be involved in the etiology and treatment of MDD include deficit in the gamma-aminobutyric acid (GABA) transmission [16], dysfunction of glutamatergic system [17], acetylcholine imbalance [18], estrogens [19, 20] and so many others [21]. In spite of these hypotheses, one of the oldest, “the monoaminergic hypothesis of depression” which assumes that MDD is caused by an imbalance in serotonergic, norepinephrinergic and possibly dopaminergic functions, is still driving clinical development of ADs since the empirical discovery of MAOIs and TCAs. Although these monoamines are undoubtedly involved, it is now recognized that, following AD administration, changes in the levels of monoamines and subsequent adaptive processes, in particular a change in the sensitivity of some of monoamine receptors, are not sufficient on their own to explain the mechanism of action of ADs. Indeed, it is difficult to correlate the time of the delayed clinical onset of AD action (several weeks) with the increase in synaptic levels of monoamines, as this change occurs already after the initial dose of the drug. In the last decade, investigations focusing on mood disturbances have been extended to brain neuroplasticity, leading to the “neurogenic and neurotrophic hypothesis of depression”.

This latter postulates that development of MDD is, at least partially, related to a reduced neuroplasticity and/or depletion of neurotrophic factors which can lead to a structural deformity and functional impairment of the central nervous system.

The monoaminergic hypothesis of depression is still valid today, and intense research keeps focusing on the 5-HT system, its implication in the pathophysiology of depression and in the mode of action of ADs. Extensive data reported a number of cellular and molecular adaptive changes of the 5-HT system both at pre- (i.e. autoreceptor desensitization) and postsynaptic levels (i.e. stimulation of hippocampal neurogenesis and normalization of neurotrophins levels) following long-term treatment with various classes of ADs [22-24]. These neuroadaptations occurred with a time course consistent with the observation of a significant AD action. Naturally, a number of questions has to be asked; how the 5-HT system reacts in case of depression and after AD treatment? Which cellular and molecular actors are implicated in such reaction? Which brain areas are prevalent in these responses? To address these questions and others, the present chapter aims a better understanding of the biological basis of pharmacological treatments of depression. Attention will be paid to the neuroadaptive consequences of combination strategies (i.e. adjunction of antipsychotics) as well as promising targets on AD development (5-HT<sub>7</sub> receptor antagonism, 5-HT<sub>4</sub> agonism).

## 2. Neuroadaptations according to the monoaminergic hypothesis

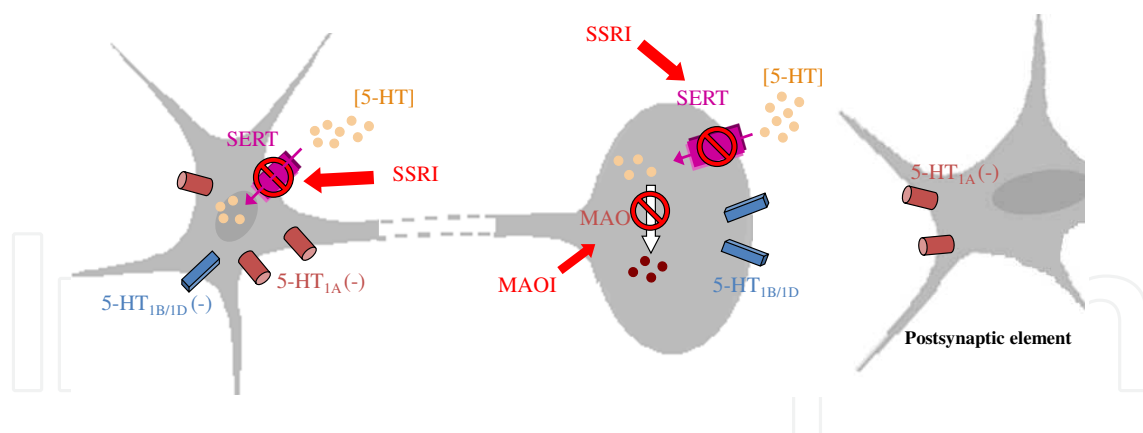
### 2.1. Chronic effects of the first generation of ADs on the 5-HT system

MAOIs and TCAs were the first ADs discovered and they have proven their efficacy for treating MDD, particularly atypical depression, anergic bipolar depression and treatment-resistant depression. However, they are not supported as first-line drugs in clinical use due to life-threatening interactions with a variety of medications and common food as well as lethal cardiac irregularities [25, 26]. Early preclinical studies showed that acute administration of MAOIs (pargyline, tranylcypromine, phenelzine and iproniazid) and TCAs (clomipramine, imipramine, amitriptyline and nortriptyline) suppresses the firing activity of 5-HT neurons in the dorsal raphe nucleus (DRN) [27-29], which is reversed by an injection of the 5-HT<sub>1A</sub> receptors antagonist, WAY-100635 [28, 30].

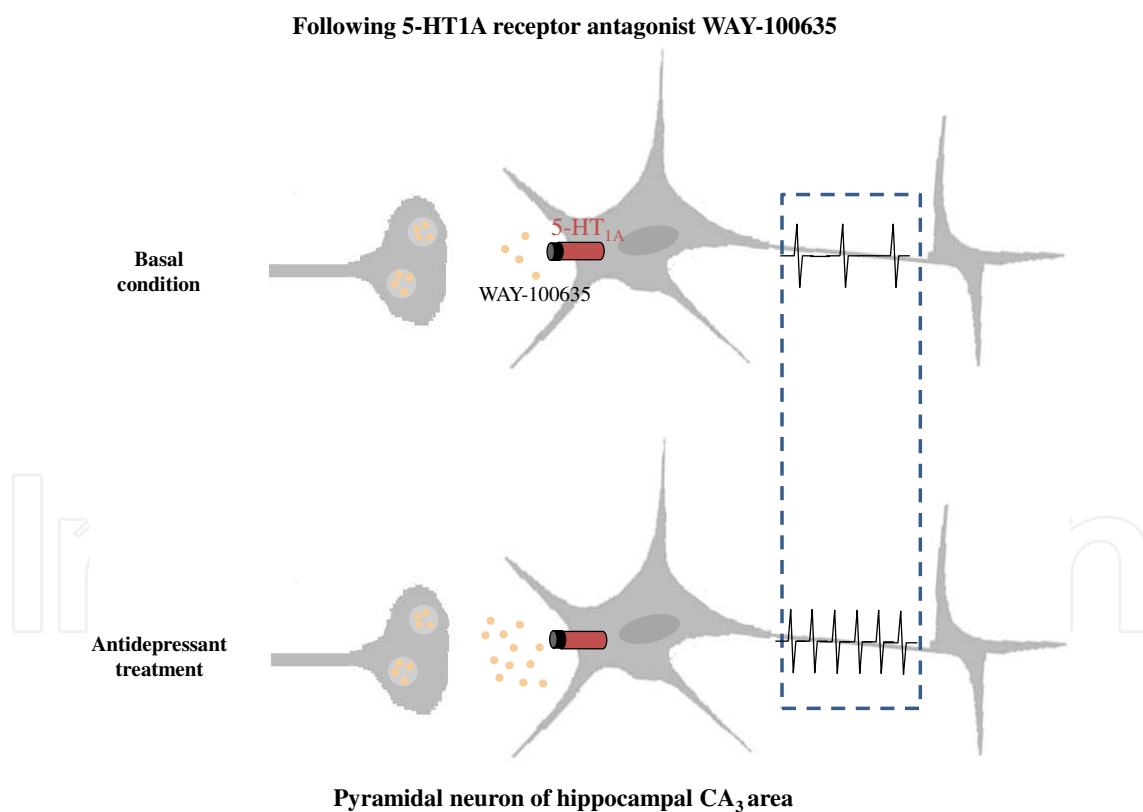
A prolonged administration of MAOIs induces a complete recovery of the firing activity of DRN 5-HT neurons, an effect attributable to a desensitization of the somatodendritic 5-HT<sub>1A</sub> autoreceptors since the reducing effect of 5-HT<sub>1A</sub> receptors agonists is completely abolished (Figure 1) [31-33]. Accordingly, a reduction of the ability of 8-OH-DPAT to inhibit forskolin-stimulated adenylate cyclase activity [34] and an increase of the ED<sub>50</sub> for 8-OH-DPAT induced lower lip retraction [35] were reported after chronic treatment with MAOIs (MDL 72394, clorgyline or tranylcypromine) in rats. This desensitization of 5-HT<sub>1A</sub> autoreceptors seems to occur at the level of receptor-G protein interactions rather than their simple downregulation. In fact, an autoradiographic study showed that the 5-HT<sub>1A</sub> agonist-stimulated [<sup>35</sup>S]-GTPγS binding is reduced in rats treated for 21 days with clorgyline [36]. Importantly, such chronic treatment with MAOIs was shown to increase the extracellular

concentrations of 5-HT, an effect greater in raphe nuclei than in their projection areas [37]. A microdialysis study measuring the extracellular levels of 5-HT in the frontal cortex of rats reported that chronic administration of the reversible MAOI MDL72394 significantly increased 5-HT amounts, without having any effect on the ability of the 5-HT<sub>1A</sub> and 5-HT<sub>1B</sub> agonist RU24969 to reduce these levels [38], suggesting that the sensitivity of these autoreceptors are not affected by chronic treatment with MAOIs. This is supported by data from an electrophysiological study demonstrating that long-term administration of clorgyline increased the efficacy of the stimulation of the 5-HT pathway to suppress the firing activity of CA3 pyramidal neurons of the dorsal hippocampus, whereas the enhancing effect of the antagonist of the terminal 5-HT autoreceptors methiothepin remained unchanged [39]. However, it is of high interest to note that long-term treatment with the reversible MAO-A inhibitor befloxatone resulted in a tonic activation of postsynaptic 5-HT<sub>1A</sub> receptors located on the dorsal hippocampus CA3 pyramidal neurons since the highly potent and selective antagonist, WAY-100635, markedly increased the firing activity of these neurons (Figure 2) [40]. It is also noteworthy that MAO-A knock-out mice exhibit high extracellular amounts of 5-HT and an overall decrease of 5-HT<sub>1A</sub> receptors density, including raphe autoreceptors as well as hippocampus and spinal cord postsynaptic receptors [41, 42]. In summary, chronic treatment with MAOIs does desensitize inhibitory 5-HT<sub>1A</sub> autoreceptors, keep sensitivity of terminal 5-HT autoreceptors unaltered and enhance the tonic activation of postsynaptic 5-HT<sub>1A</sub> receptors. Similarly to MAOIs, chronic treatment with TCAs (imipramine, iprindole, desipramine and femoxetine) did not change the mean firing rate of the DRN 5-HT neurons in comparison to controls [31]. However, the responsiveness to intravenous injection of the 5-HT agonist LSD or the effectiveness of microiontophoretic application of 5-HT and LSD were not altered by such treatment [31], suggesting that the sensitivity of the 5-HT autoreceptors is not modified. The 5-HT<sub>1A</sub>/G-protein coupling is usually assessed by measuring [<sup>35</sup>S]-GTPγS binding induced by 5-HT<sub>1A</sub> receptor activation [43]. It was reported that chronic treatment with the TCA amitriptyline did not alter the 5-HT<sub>1A</sub> agonist-stimulated [<sup>35</sup>S]-GTPγS binding in dorsal and median raphe nuclei [44, 45], further confirming an absence of desensitization of the somatodendritic 5-HT<sub>1A</sub> autoreceptor following chronic TCAs. In contrast, the same treatments have different effects on postsynaptic levels. Indeed, long-term application of imipramine increased the responsiveness of postsynaptic CA3 hippocampus pyramidal neurons to the microiontophoretic application of 5-HT or 8-OH-DPAT [46]. In accordance, Rossi et al. [45] showed that chronic administration of amitriptyline increased the 5-HT<sub>1A</sub> receptor-stimulated [<sup>35</sup>S]-GTPγS binding in the hippocampus, without affecting the binding of [<sup>3</sup>H]8-OH-DPAT (indicating the number of 5-HT<sub>1A</sub> receptors in the coupled high-affinity agonist state). These authors suggest that, in absence of an increase in the binding of [<sup>3</sup>H]8-OH-DPAT, the increased capacity of 5-HT<sub>1A</sub> receptors to activate G proteins in CA1 and dentate gyrus of the hippocampus may be due to regulatory changes at the level of the G protein, e.g. phosphorylation [45]. In summary, chronic TCA treatment does not desensitize inhibitory 5-HT<sub>1A</sub> autoreceptors and enhance the sensitivity of postsynaptic 5-HT<sub>1A</sub> receptors in the hippocampus.





**Figure 1.** Representation of the effects of the serotonergic antidepressants on 5-HT neurotransmission. Monoamine oxidase inhibitors (MAOIs) and selective serotonin reuptake inhibitors (SSRIs) act on the 5-HT system, respectively, by inhibiting the 5-HT degradation and by blocking the 5-HT transporter (SERT). Their administration induces the raise of extracellular levels of 5-HT which activate 5-HT receptors. In the raphe nuclei, the somatodendritic 5-HT<sub>1A</sub> autoreceptors negatively control the firing activity of the 5-HT neurons, while the 5-HT<sub>1B/1C</sub> autoreceptors control the 5-HT release. Long-term administration of both classes of antidepressants desensitize 5-HT<sub>1A</sub> autoreceptors. Modified from Faure et al. [22].



**Figure 2.** Representation of the effect of antidepressant treatments on hippocampal neurons. The raise of extracellular 5-HT levels decreases the firing activity of hippocampus CA3 pyramidal neuron and this is mediated by postsynaptic 5-HT<sub>1A</sub> receptors. In control animals, no or low firing activity increase is observed after administration of the antagonist WAY-100635. However, in antidepressant-treated animals, WAY-100635 disinhibits pyramidal cells, suggesting that antidepressants increase 5-HT tone in the hippocampus. Modified from Blier and de Montigny [201].

## 2.2. Chronic effects of the SSRIs on the 5-HT system

SSRIs represent the first-line ADs in clinical use nowadays, mainly due to their relatively lower burden of adverse effects and safety in overdose. SSRIs include fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, escitalopram and more recently vilazodone [47, 48]. These drugs are believed to exert their effects by blocking SERT, which induces an increase of 5-HT synaptic levels. In turn, the chronic enhancement of 5-HT bioavailability produces numerous neuroadaptive changes leading to an enhancement of the 5-HT neurotransmission (Figure 1) [22, 40, 49]. In particular, it was widely reported that acute administration of SSRIs inhibits the firing activity of the 5-HT neurons in DRN, resulting from an enhancement of somatodendritic 5-HT release which activates the 5-HT<sub>1A</sub> autoreceptors [50-55]. However, immunoelectron microscopy studies using specific antibodies showed a significant decrease of the 5-HT<sub>1A</sub> immunogold labeling of the plasma membrane of the DRN dendrites and an increase in their cytoplasmic labeling after a single injection of the SSRI fluoxetine in animals, indicating an internalization of these autoreceptors under acute conditions [56, 57]. Importantly, a very recent double-blind positron emission tomography study investigated the binding of the 5-HT<sub>1A</sub> radioligand [<sup>18</sup>F]MPPF in human volunteers after taking a single tablet of fluoxetine or placebo. This study clearly demonstrated that in DRN, and nowhere else in the brain, a significant decrease in [<sup>18</sup>F]MPPF binding potential between fluoxetine and placebo [58]. In animals, this autoreceptor internalization seems to be very transient since a microdialysis study reported that administration of a 5-HT<sub>1A</sub> receptor agonist a few hours after single injection of fluoxetine reverses the SSRI-induced increase in the 5-HT levels [59]. Short-term treatment with SSRIs also reduced the firing activity of the DRN 5-HT neurons [50]. Only chronic (2 to 3 weeks) treatments with these drugs completely recover the 5-HT firing activity, and this is accompanied with a desensitization of the somatodendritic 5-HT<sub>1A</sub> autoreceptors [50, 51, 60, 61]. Interestingly, when rats chronically treated with fluoxetine were challenged with a single dose of 8-OH-DPAT, there was no internalization of the 5-HT<sub>1A</sub> autoreceptors in keeping with their desensitized form [62]. In fact, after such treatment, neither the density of the 5-HT<sub>1A</sub> autoreceptors on the plasma membrane of DRN neurons nor the [<sup>18</sup>F]MPPF binding were changed [56, 58, 62, 63]. One explanation is that, after repeated internalization and retargeting, functional 5-HT<sub>1A</sub> autoreceptors are replaced by receptors uncoupled from their G proteins (inactivated form of the receptor) on the plasma membrane of DRN 5-HT neurons [62]. However, controversial results have been reported about the effects of chronic SSRI treatment on the functional status of the 5-HT<sub>1A</sub> autoreceptors. An attenuation of 8-OH-DPAT-mediated [<sup>35</sup>S]-GTPγS stimulation has been consistently observed in the DRN by certain groups after chronic fluoxetine [36, 44, 49, 64, 65], while others reported no change in this parameter after chronic sertraline or citalopram [63, 66]. These findings raised the possibility that SSRIs may not be a homogenous class of AD drugs with regard to the mechanism by which the function of somatodendritic 5-HT<sub>1A</sub> autoreceptors is regulated. Thus, at least in the case of fluoxetine, acute and chronic treatments seem to induce two distinct types of 5-HT<sub>1A</sub> autoreceptor desensitization: one rapid and reversible (associated with the internalization of the functional pool of membrane-bound receptors), the other being progressive and long-lasting, no longer accompanied with receptor sequestration, but which probably resulted from the reiteration of this process throughout the course of chronic fluoxetine treatment [58]. Another

picture can be drawn for the postsynaptic 5-HT<sub>1A</sub> heteroreceptors. In fact, neither acute nor chronic treatment with SSRIs induced a change in the subcellular distribution of the 5-HT<sub>1A</sub> receptors in dendrites or in the *in vivo* binding of the 5-HT<sub>1A</sub> radioligand [18F]MPPF in projection areas, particularly hippocampus and frontal cortex [56, 62, 63]. Such differences between 5-HT<sub>1A</sub> receptors in DRN and projection areas were explained by a differential coupling, the autoreceptors being coupled to Gα<sub>i3</sub> while heteroreceptors are coupled to Gα<sub>o</sub> protein [67]. However, agonist-induced [<sup>35</sup>S]-GTPγS binding data showed an increase [36, 63, 64] or no change [44, 49, 68] after long-term SSRI treatment, further adding complexity to the whole picture. Importantly, long-term application of SSRIs produced an increase in tonic activation of pyramidal neurons, indicated by the disinhibition of firing rate in response to the antagonist WAY-100635 (Figure 2) [40, 51]. This further supports the increase of the efficacy of the 5-HT neurotransmission seen *in vivo* (enhancing the effectiveness of the stimulation of the 5-HT pathway to suppress the firing activity of CA3 pyramidal neurons) and *in vitro* (increasing the electrically-evoked release of tritiated 5-HT from preloaded hippocampal slices) [46, 69]. More recent studies noted a decrease in the density of the 5-HT<sub>4</sub> receptor binding in the CA1 field of hippocampus of rats as well as in several areas of the striatum after a 21-day treatment with the SSRI fluoxetine [70]. The activity of these postsynaptic receptors in the hippocampus, measured as the excitatory action of the 5-HT<sub>4</sub> agonist zacopride in pyramidal cells of CA1 evoked by Schaffer collateral stimulation, was attenuated also after such chronic treatment [70]. This suggests a net decrease in the signalisation pathway of 5-HT<sub>4</sub> receptors after chronic SSRI treatment. In addition, desensitization of the 5-HT<sub>7</sub> receptors [71] and downregulation in the 5-HT<sub>7</sub> binding site in the hypothalamus [72] were reported following chronic treatment with fluoxetine.

Another interesting consequence of chronic, but not acute, treatment with SSRIs is a reduction of the surface expression of SERT. In fact, electron microscopy studies reported that long-term administration of fluoxetine induced an internalization of SERT in both cell bodies and axon terminals of 5-HT neurons [58]. Moreover, the total amounts of SERT immunoreactivity is also reduced, suggesting that, rather than a simple internalization, a long-term degradation of this protein happened in the course of the treatment [58].

### 2.3. Chronic effects of new antidepressant strategies

The suboptimal efficacy and the delayed onset of action of different classes of ADs raises the necessity to find new strategies to treat depression, especially treatment-resistant depression and depressive episodes associated with bipolar disorders. For example, a number of second-generation antipsychotics have been investigated and approved for use as augmentation agents in combination with currently approved first-line ADs such as adjunctive aripiprazole, olanzapine or quetiapine to standard doses of SSRIs [73-75]. The effect of such combination on the 5-HT system is yet not well described in the literature, and only very recent preclinical studies began to investigate their mechanisms of action. For example, Chernoloz et al. [76] showed in rats that long-term administration (14 days) of quetiapine alone or in combination with the SSRI escitalopram led to significant inhibition of the spontaneous firing activity of the DRN 5-HT neurons, while escitalopram alone (as previously described for SSRIs) induced a



recovery of this neuronal activity at this time point. Co-administration of quetiapine and escitalopram for 14 days produced an increase in tonic activation of postsynaptic 5-HT<sub>1A</sub> receptors located on the dorsal hippocampus CA3 pyramidal neurons, but in the same range as that obtained with chronic escitalopram alone [76]. The enhancement in 5-HT transmission produced by this combination was attributable to the attenuated inhibitory function of  $\alpha_2$ -adrenergic receptors on 5-HT terminals and possibly to direct 5-HT<sub>1A</sub> receptor agonism by quetiapine [76]. Similarly, risperidone co-administered with escitalopram for 14 days was shown to prevent the restoration of the 5-HT neuronal firing rate, obtained with the SSRI alone [77]. Therefore, it might be suggested that risperidone co-administrated with the SSRIs increases 5-HT neurotransmission by indirect action on the 5-HT system. Indeed, Marcus et al. [78] reported that adjunctive low-dose of risperidone to escitalopram significantly enhanced both dopamine outflow and NMDA receptor-mediated transmission in the medial prefrontal cortex (PFC) of rats. Taken together, these results pointed out the possibility that, rather than a direct action on the 5-HT system, combining an SSRI and an antipsychotic of second-generation implicate multiple neurotransmitter systems to exert their beneficial effects.

Among novel targets to develop more efficacious and fast-acting ADs, 5-HT<sub>4</sub> and 5-HT<sub>7</sub> receptors are promising candidates [71, 79]. For example, brain regional changes in the binding of the 5-HT<sub>4</sub> receptors were found in murine models of depression-related states including olfactory bulbectomy model, glucocorticoid receptor heterozygous mice and Flinders sensitive line depression model [80, 81]. Lucas et al. [79] showed in rats that a 3-day treatment with the 5-HT<sub>4</sub> receptor agonist RS67333 modifies several rat brain parameters considered as key markers of AD action, which are changed only after 2 to 3 weeks with classical ADs. These changes include desensitization of the 5-HT<sub>1A</sub> autoreceptors and increased tonus on hippocampal postsynaptic 5-HT<sub>1A</sub> receptors [79]. Accordingly, subchronic (3 days) administration of RS67333, but not acute, increased basal 5-HT levels and decreased its metabolite levels 5-HIAA in the rat ventral hippocampus [82]. Furthermore, a 3-day co-administration of the SSRI citalopram and a 5-HT<sub>4</sub> receptor agonist, RS67333 or prucalopride, resulted in an increase of DRN 5-HT neuron mean firing activity, displaying a similar, or even slightly superior, firing amplitude obtained with each agonist alone [83]. At the postsynaptic level, this translated into the manifestation of a tonus on hippocampal postsynaptic 5-HT<sub>1A</sub> receptors, which was two to three times stronger when the 5-HT<sub>4</sub> receptor agonist was combined with citalopram [83]. This suggests an important increase on the 5-HT neurotransmission following adjunction of an SSRI to a 5-HT<sub>4</sub> receptor agonist, clearly indicating a rapid AD-like potential of these agonists.

Moreover, antipsychotics (lurasidone, amisulpride), as well as a novel AD-like multimodal 5-HT agent (Lu-AA21004), have been proved to be potent 5-HT<sub>7</sub> antagonists [84-88]. Furthermore, genetic deletion of this receptor confers to mice AD-like behaviors including decreased immobility in the forced swim and tail suspension tests as well as shorter and less frequent episodes of rapid eye movement sleep [89], indicating that antagonists might have therapeutic value as ADs. In this context, we showed that a 1-week treatment with the selective 5-HT<sub>7</sub> receptor antagonist, SB-269970, did not alter 5-HT firing activity but desensitized somatodendritic 5-HT<sub>1A</sub> autoreceptors and enhanced the tonic activation of

postsynaptic 5-HT<sub>1A</sub> receptors in the hippocampus [71]. Taken together, these findings show that new AD strategies targeting 5-HT receptor manipulation resulted in similar adaptive changes of the 5-HT system than those produced by classical ADs, except that they took place faster in both pre- and postsynaptic levels.

In summary, a change of 5-HT receptor sensitivity that occurs only after chronic treatment seems to be a common mechanism of AD action, which takes place depending on the delay onset of action of each 5-HT AD. This represents the major argument supporting the 5-HT hypothesis of depression. However, it became obvious that depression involves further modifications besides those at the 5-HT system. Several studies emerged to assess new pharmacological models that may help to better understand the mechanisms and pathophysiological changes leading to a depressive behaviour.

### **3. Neurogenic and neurotrophic adaptations induced by 5-HT antidepressants**

Recent studies indicate that an impairment of cellular and synaptic plasticity in specific areas of the brain, especially the hippocampus and PFC, may be a core factor in the pathophysiology of depression. The abnormal neuronal plasticity including neurogenesis, axon branching, dendritogenesis and synaptogenesis was suggested to be related to alterations in the level of neurotrophic factors, particularly brain-derived neurotrophic factor (BDNF) which plays a central role in the adaptation of neural networks. Numerous studies reported that AD treatments may act by normalizing neurotrophic levels in the brain and enhancing neurogenesis and synaptogenesis, leading to a gain of function in neuronal networks altered by depressive states. In the following paragraphs, we enumerate the chronic effects of the previously cited AD strategies on the cellular and synaptic plasticity, as well as neurotrophin expression. A critical view of the role of each parameter on the etiology of depression and AD action is also described.

#### **3.1. Neurogenesis**

The first evidence of newly generated neurons in the adult central nervous system was reported in 1965 when Altman and Das [90] used <sup>3</sup>H-thymidine to label proliferating cells in the rat dentate gyrus (DG) of the hippocampus. Subsequent studies confirmed the existence of this hippocampal neurogenesis in adulthood in several species including humans [91, 92], using the new tool bromodeoxyuridine (BrdU), a thymidine analog that labels dividing cells in S-phase [93]. In the hippocampus, progenitor cells are located in the subgranular zone (SGZ) where they divide and a subset of the new cells survive, migrate into granule cell layer and differentiates into neurons. An excellent review of Hanson et al. [94] described the timeline of cell division and maturation as well as markers of cells from different stages of neurogenesis in the SGZ. The subventricular zone (SVZ) was also identified as a highly neurogenic area of the adult brain [95], although other regions retain the potential to generate new neurons [96-98].

The hippocampal neurogenesis was shown to be implicated in the pathophysiology of depression (Table 1). Clinical studies showed that patients suffering from MDD had lower hippocampal volume than healthy subjects [99, 100], that may be linked to increased neuronal atrophy. Only patients who remitted after 8 weeks of AD treatment present larger hippocampal volume in comparison to subjects who did not remit [101]. A more evident correlation came firstly from the preclinical study of Santarelli et al. [102]. In this study, mice treated 28 days with the SSRI fluoxetine exhibited an increase in the number of BrdU-positive cells in the SGZ of DG with a concomitant decrease in the latency to feed in the novelty suppressed-feeding (NSF) paradigm. However, ablation of cell proliferation in the SGZ, but not the SVZ, following X-ray treatment suppressed behavioral responses to chronic fluoxetine [102]. The requirement of hippocampal neurogenesis for therapeutic efficacy of ADs was subsequently confirmed in non-human primates [103]. Consistent with the time course of their therapeutic action, only chronic treatment regimen with MAOIs [104, 105], TCAs [106, 107], SSRIs [61, 102, 105, 108], putative fast-acting AD drugs including 5-HT<sub>4</sub> agonists [79] and 5-HT<sub>7</sub> antagonists [71] and finally adjunctive strategies (olanzapine plus fluoxetine) [108] increased the cell proliferation in the SGZ of the hippocampus at comparable extent. This indicates that upregulation of hippocampal neurogenesis may be a common denominator of the mechanism of action of ADs. Although the function of these newly generated cells in the adult brain is still unclear, it has been suggested that young granule cells constitute a distinct population exhibiting a greater degree of plasticity than mature neurons. In particular, they display a reduced threshold to induction of long-term potentiation (LTP) [109], and can be tonically activated by ambient GABA before being sequentially innervated by GABA- and glutamate-mediated synaptic inputs, leading to marked defects in their synapse formation and dendritic development *in vivo* [110].

Given the emergence of new data, the initial research cited above suggesting a model of hippocampal degeneration as basis of depression and reversal by ADs through neurogenesis seems to be uncertain. In fact, as chronic ADs, mood stabilizers (lithium) and atypical antipsychotics induce hippocampal cell proliferation [108, 111-113], but whether these drugs can be used as monotherapy in depression is an area of debate and clinical data failed to support it. It is also noteworthy that, even in the famous study of Santarelli et al. [102], X-ray of hippocampus suppressing neurogenesis in non-treated rats failed to induce a depressive-like behavior. Accordingly, cyclin D2 (a protein involved in the cell cycle regulation) knock-out mice, specifically lacking adult brain neurogenesis, showed normal anxiety levels in the open-field and elevated plus maze [114]. In contrast, increasing hippocampal neurogenesis in mice was not reported to produce anxiolytic or AD-like behavioral effects [115]. These latter reports add complexity to the understanding of the role of altered neurogenesis in the pathology of depression. That is why, some neuroscientists postulate that, beyond a simple increase of hippocampal neurogenesis in response to ADs, insertion of the newly generated neurons (even a small number) in functional neural networks especially through synaptogenesis, may be more relevant for the explanation of their mechanism of action.

In this context, an elegant theory in which neurogenesis is seen as an epiphenomenon of a more widespread alteration in dendritic length and spine number was already proposed [116].

According to this theory, exposure to chronic stress and stressful life events increases excitotoxic glutamatergic neurotransmission in multiple brain areas. To protect neurons from consequent apoptosis, dendrites retract and spine number decreases thus limiting the number of exposed glutamate receptors.

### 3.2. Synaptic plasticity and synaptogenesis

The regulation of synapse formation or synaptogenesis is a subcellular neuronal alteration that contributes to synaptic plasticity [117, 118], which defines the ability to integrate informations from different neuronal inputs and make the appropriate adaptive responses. An increase in functional synaptogenesis is typically accompanied by an increase in the number of dendritic spines, the physical site of synaptic connections [118, 119]. In recent years, it has become clear that spines are dynamic structures that undergo rapid remodeling important for synapse formation, function and plasticity [120, 121]. In the adulthood, spines continue to remodel in response to a variety of physiological stimuli. For example, synaptic activity that induces LTP, a long-lasting enhancement of synaptic strength, promotes spine enlargement and new spine formation [122], whereas activity that induces long-term depression (LTD), a persistent weakening of synaptic strength, causes spine shrinkage or retraction [123]. The potential role of spines and dendrites in MDD (Table 1) is supported by preclinical studies demonstrating that exposure to chronic stress negatively influence dendritic spine density and morphology in brain areas such as DG, CA1 and CA3 subfields of the hippocampus and PFC [124-126]. This includes a decrease in spine density, dendritic length and branch number [127, 128]. These effects could contribute to the reduction in volume of PFC and hippocampus determined by imaging the brains of depressed patients [100, 101, 129]. In accordance, a recent study revealed lower expression of synaptic function-related genes in the dorsolateral PFC of MDD subjects and a corresponding lower number of synapses [130].

As for neurogenesis, ADs regulate these different forms of synaptic plasticity. Synaptic communication is altered by chronic stress which impairs LTP and facilitates LTD induction in the CA1 of the hippocampus [131-133]. It has been reported that repeated application of the SSRI fluvoxamine (21 days) increased the extent of LTP induction in the CA1 region of rats that experienced chronic mild stress [131]. Using rats neonatally-exposed to clomipramine as an animal model of depression, Bhagya et al. [134] found that these animals displayed a decreased LTP in the hippocampal CA1 and a 14-day treatment with the SSRI escitalopram restored this LTP. Similarly, retrieval of LTP in the CA1 field of hippocampus was obtained in stressed animals after repeated application of other classes of ADs including the SNRI milnacipran and electroconvulsive stimulation (ECS) [132, 135]. In contrast, other groups described an impairment of LTP after chronic SSRI fluoxetine, TCA imipramine, SNRI venlafaxine or ECS, but in non-stressed animals [136-138], indicating a stress-dependent action of the ADs on hippocampal LTP. In the same way, chronic fluoxetine was reported to increase dendritic spine density and arborization of granule cells in the mouse hippocampus [139, 140]. Daily administration of fluoxetine to ovariectomized rats for 5 days was shown to induce a robust increase in pyramidal cell dendritic spine synapse density in the hippocampal CA1 field, with similar changes appearing in CA3 after 2 weeks of treatment [141]. This rapid



synaptic remodelling might represent an early step in the fluoxetine-induced cascade of responses that spread across the entire hippocampal circuitry, leading to the restoration of normal function in the hippocampus [141]. In accordance, a recent study using ovariectomized hamsters exposed to diminished light at night displayed depressive-like behaviors and reduced hippocampal CA1 dendritic spine density, but a 2-week treatment with citalopram rescued this behavior and moderately improved the spine density in the CA1 but not fully restored it [142]. Also, chronic treatment with the TCA amitriptyline reversed the bullectomy-induced reduction in dendritic spine density in CA1, CA3 and dentate gyrus of hippocampus [143]. It has to be noted that single injection of the 5-HT<sub>4</sub> receptor partial agonist SL65.0155 does not promote spine growth in the naive mouse hippocampus [144], and the 5-HT<sub>7</sub> receptor agonist AS-19 increased neurite length and number in primary embryonic hippocampal neurons [145], still the characterization of the *in vivo* effects of their chronic manipulation is missing. It is obvious that the effects on synaptic plasticity of chronic treatment with different AD strategies will be an important area of further research.

Significant evidence suggests that ADs regulate synaptic plasticity and reorganization through the modulation of cell adhesion protein and synaptic function/structure related genes. In particular, the neural cell adhesion molecule NCAM is necessary for activity-dependent LTP in the hippocampus [146]. Its highly sialylated isoform PSA-NCAM promotes plasticity through the negatively charged PSA, postulated to be a spacer that reduces adhesion forces between cells allowing their dynamic changes [147]. It was reported that chronic treatment with the selective MAO-B inhibitor deprenyl, the TCA imipramine or the SSRI fluoxetine increased the expression of PSA-NCAM in the hippocampus and medial PFC [148-151]. Interestingly, chronic exposure to second-generation antipsychotics olanzapine or risperidone enhances PSA-NCAM expression in the PFC, but not in the hippocampus, suggesting that modulation of cell adhesion protein in the hippocampus may be specific to the mechanism of action of ADs [152, 153]. Moreover, an increased expression of synaptophysin, a glycoprotein localized in presynaptic vesicle membranes required for docking and fusion of neurotransmitter-containing synaptic vesicles as well as endocytosis [154], was observed in hippocampus and/or cerebral cortex of rats chronically treated with the MAOI tranylcypromine, the TCA amitriptyline or the SSRI fluoxetine [148, 155, 156]. Also, Arc (Activity-regulated, cytoskeletal-associated protein), a highly expressed protein in dendrites and postsynaptic densities [157] is implicated in LTP and spine size and type [158-160]. Repeated administration (14 days) of the SSRI paroxetine, the TCA desipramine or the MAOI tranylcypromine increased Arc mRNA and the number of Arc-immunoreactive cells in frontal and parietal cortex as well as in the CA1 region of the hippocampus, while acute injection had no effect [161].

How do ADs exert their effect on synaptic plasticity is a matter of discussion. Several putative mechanisms have been proposed in this context. However, the observation that antidepressants increased anti-apoptotic factors and the synthesis of neurotrophic factors raises the possibility that these drugs act via a mechanism of neuroprotection rather than a neuroregeneration [23]. Particular attention was given to neurotrophins such as brain-derived neurotrophic factor (BDNF).



3.3. Neurotrophins modulation by 5-HT antidepressants

Neurotrophins are growth factors with crucial roles in the formation and plasticity of neuronal networks [162], and BDNF is the most studied in this context. The dystrophic action of stress was reported in animal models of depression (Table 1). Animals exposed to chronic stress such as chronic mild stress or social deprivation displayed a decrease in the protein levels of BDNF and an increase of its receptor tyrosine-kinase TrkB in several brain regions including hippocampus (DG, CA1 and CA3), frontal cortex and midbrain [163-168]. BDNF-deficient mice or with specific knockdown of BDNF in the DG also displayed depressive-like behaviors [169, 170]. Accordingly, drug-free MDD patients showed lower serum or plasma BDNF levels in comparison to healthy subjects [171-174]. Moreover, human BDNF gene polymorphism Val66Met was suggested to be related to the pathophysiology of MDD and affect clinical response to AD treatment [175-177].

Studies	Stress type	Neuroplasticity consequence	References
Preclinical			
	Repeated restraint stress paradigm in rats	Reduction on the number and length of apical dendritic branches in mPFC	[127] [126]
		Atrophy of apical dendrites of CA3 pyramidal neurons	[201]
		LTP suppression in DG and CA3 in a site-specific manner	[202]
	Chronic unpredictable stress paradigm in rats	Dendritic atrophy in CA3 region	[125]
		Atrophy in granule and CA1 pyramidal neurons	
		LTP impairment in CA1 area and decrease of synaptophysin density in CA3 region	[131]
		Decrease in BDNF mRNA level in hippocampus and cerebral cortex	[203,204]
	Chronic corticosterone administration in rats	Atrophy in granule and CA1 pyramidal neurons	[125]
		Dendritic atrophy in CA3 area	
		Retraction of apical dendrites in mPFC	[205]
Decrease in BDNF mRNA level in hippocampus and cerebral cortex		[204]	
Chronic sleep deprivation in rats	Decrease in hippocampal volume	[207]	
	Suppression of cell proliferation in the hippocampus	[208]	
	Impairment of LTP in the CA1 region	[209]	
Clinical			
	Unipolar depression	Lower hippocampal volume	[99, 210]
		Volume reduction in orbitofrontal cortex, frontal cortex, hippocampus, striatum, and cingulate cortex	[128]

Studies	Stress type	Neuroplasticity consequence	References
	Recurrent MDD	Lower hippocampal volume	[211, 212]
		Reduced volume in dorsolateral prefrontal cortex	[213]
		Lower plasma BDNF	[172]
	First-episode depression	Lower hippocampal volume	[214, 215]
		Smaller left hippocampal volume only in males	[216]
		Lower plasma BDNF	[172]
	Late-life depression	Reduction in hippocampal volume	[217, 218]
		Specific reduction in left hippocampus	[219]
		Volume reduction in orbitofrontal cortex, putamen and thalamus	[217]
		Lower plasma BDNF	[220]
	Familial recurrent MDD	Smaller volume of the right hippocampus	[221, 222]
	Cumulative adversity (recurrent stressful life events)	Smaller volume in medial prefrontal cortex, insular cortex and subgenual anterior cingulate regions)	[223]

**Table 1.** Effects of chronic stress and depression on different neuroplasticity actors in the brain. mPFC: median prefrontal cortex. DG: dentate gyrus. LTP: long-term potentiation. BDNF: Brain-derived neurotrophic factor. MDD: major depressive disorder.

Intracortical infusion of BDNF in the adult rat was shown to produce a robust sprouting of 5-HT nerve terminals and accelerated the regrowth of 5-HT axons in basal conditions or following their destruction [178, 179]. AD treatments could oppose or reverse the actions of stress on the 5-HT system via a positive action on cerebral BDNF. Indeed, several studies showed that long-term AD treatments including SSRIs (fluoxetine) and MAOIs (tranylcypromine, phenelzine) increase BDNF levels in the brain [168, 180-182], although a time-dependent modulation seems to occur. Indeed, De Foubert et al. [182] demonstrated in rat hippocampus that a 4-day administration of the SSRI fluoxetine decreased BDNF mRNA levels, a 7-day treatment had no effect, but a 14-day treatment increased it. One explanation of this biphasic change in BDNF gene expression could be a differential transcript regulation, since the rat BDNF gene expresses four mRNA isoforms which can be modulated by different signaling cascades. In fact, a recent study demonstrated that acute injection of fluoxetine or tranylcypromine decreased total BDNF mRNA (exon V) as well as exon IV mRNA with no significant changes on exon I or III mRNAs [183]. In contrast, chronic administration of these two drugs enhanced expression of exon V and exon I mRNAs with no changes for exon III or IV [183]. It is of high interest to note that ADs, besides regulating BDNF levels in naive animals, normalize it under stress conditions. Hence, chronic treatment with fluoxetine increased the BDNF protein till control levels in the hippocampus of rats experiencing chronic mild stress [184], indicating that AD treatment can oppose the dystrophic actions of stress. Accordingly, clinical studies reported that untreated depressed patients showed a decrease of serum or platelet

BDNF levels before treatment, and a normalization of this parameter following several weeks of SSRI (escitalopram or paroxetine) administration accompanied with an improvement in depressive symptoms [185, 186]. Unfortunately, very few studies were conducted in this field using novel ADs targeting the 5-HT system. For example, subchronic administration (3 injections in 24h) of the 5-HT<sub>4</sub> receptor partial agonist SL65.0155, but not citalopram or clomipramine, was reported to enhance hippocampal BDNF protein levels in rats, further supporting a fast-acting AD profile of 5-HT<sub>4</sub> receptor agonists [187]. Also, Agostinho et al. [188] reported that combinatory treatment for 28 days with olanzapine and fluoxetine had no effect on BDNF protein levels but enhanced specifically in the PFC the protein levels of NT-3, a neurotrophin implicated in the pathophysiology of MDD [189]. However, these authors reported also that 28 days of fluoxetine administration did not increase BDNF proteins levels neither in the hippocampus nor in the PFC, even at high doses [188], raising some concern about this study. Obviously, more investigations are needed to characterize the exact effects on BDNF of these new treatment strategies.

#### 4. Conclusion

The study of MDD is a real challenge for those who want to reveal the pathophysiological basis of this disease. The monoaminergic and neurotrophic/neurogenic hypotheses cited in this review give only a partial explanation of this basis. In the former, the function of a number of 5-HT receptors is still not yet elucidated and growing data implicate each receptor in a different way in the AD mechanism of action. In the latter, the role of new-added neurons in the hippocampus is still under investigation, although their integration in functional networks may confer additional plasticity to rescue stress effects. These hypotheses can be considered complementary as the activation of monoamine receptors may modulate the expression of intracellular proteins and neurotrophic factors, permitting the re-organization of complex neuronal networks involved in depression. Hence, ADs, particularly those targeting the 5-HT system, were shown to induce changes at the level of 5-HT autoreceptors localized in the raphe nuclei as well as the activation of neurotrophic factors expression and induction of cellular proliferation within projecting areas such as the hippocampus. Yet, combining these two hypotheses is not sufficient to fully explain the pathophysiology of depression, since conventional ADs were shown to modulate each factor (5-HT sensitivity, hippocampal cell proliferation, neurotrophic expression), but still displaying moderate efficacy to alleviate depression symptoms. Thus, the re-construction of a new and more convincing model is an urgent necessity.

While there has been a major emphasis on the co-incidental changes in neurotransmitters and the related receptors, neurogenesis and neurotrophic factors, less attention has been paid to changes in glia. These non-neuronal cells, particularly astrocytes, were long considered to have simple supportive role for neurons providing structure and adequate environmental conditions for neuronal functions. However, recent discoveries changed this view and led to a reconceptualization of neuronal signaling with astrocytes forming an integral part of the “tripartite synapse” along with the pre- and postsynaptic neurons [190]. In fact, glia was shown

to use variations in cytoplasmic calcium as a form of cellular excitability allowing signaling to other glia, neurons and blood vessels [191]. The astrocytes excitability can be triggered by various neurotransmitters receptors expressed on glia and, in turn, these cells can release a wide variety of gliotransmitters including glutamate, adenosine triphosphate and D-serine, which regulate synaptic transmission and plasticity [191] [192]. Strikingly, reductions in the density and ultrastructure of glial cells were detected in fronto-limbic regions in major depression [193, 194], indicating the relevance of studying these cells in the pathophysiological basis of MDD. Also, glial cells seem to play a central role in inflammation that contributes to the main symptom of depression [195, 196], while fluoxetine requires microglia to exert its neuroprotective action [184].

Being a heterogeneous condition, depression is unlikely to be explained by a single pathophysiological disturbance, hence, it is not expected that a single mechanism of drug action can be uniformly effective. A new vision in which neurons and glial cells are involved side by side will be more adequate to explain the heterogeneity of MDD. In the basis of very recent researches, a “network hypothesis”, in which information processing implicating neurons and glia within particular brain networks is altered in MDD and can be improved by AD treatment, can be proposed. Hence, Sheline et al. [197] reported, in depressed subjects, a dramatic increase in connectivity of three different brain networks: the cognitive control network, default mode network and affective network, with the “dorsal nexus”, a bilateral region of the dorsal medial PFC. Recent reports using subpsychomimetic doses of ketamine, an ionotropic glutamatergic N-methyl-D-aspartate (NMDA) receptor antagonist, showed a rapid AD response in MDD subjects [198], which is hypothesized to be mediated by i) lower Glx/glutamate ratio in the PFC associated with reductions in glial cells in the same region [199] and, ii) decreased functional connectivity of the default mode network to the dorsal nexus [200]. More investigations are needed to define how brain networks can respond faster to this novel antidepressant, how neurons and glia are implicating in such process and how the involved mechanism can be used to the discovery of new treatment strategies in MDD.

## Author details

Ouissame Mnie-Filali<sup>1</sup>, Erika Abrial<sup>2,3</sup>, Laura Lambás-Señas<sup>2,3</sup> and Nasser Haddjeri<sup>2,3\*</sup>

\*Address all correspondence to: nasser.haddjeri@univ-lyon1.fr

1 Département de Pathologie et Biologie cellulaire, Université de Montréal, Montréal, Québec, Canada

2 Institut Cellule Souche et Cerveau, INSERM U, Université de Lyon, F-69373, Lyon, France

3 Université Lyon , Equipe Neuropsychopharmacologie des troubles affectifs, Lyon, France

## References

- [1] Ferrari AJ, Somerville AJ, Baxter AJ, Norman R, Patten SB, Vos T, et al. Global variation in the prevalence and incidence of major depressive disorder: a systematic review of the epidemiological literature. *Psychological medicine*. 2012;1-11. Epub 2012/07/27.
- [2] Bromet E, Andrade LH, Hwang I, Sampson NA, Alonso J, de Girolamo G, et al. Cross-national epidemiology of DSM-IV major depressive episode. *BMC medicine*. 2011;9:90. Epub 2011/07/28.
- [3] Kessler RC, Akiskal HS, Ames M, Birnbaum H, Greenberg P, Hirschfeld RM, et al. Prevalence and effects of mood disorders on work performance in a nationally representative sample of U.S. workers. *The American journal of psychiatry*. 2006;163(9):1561-8. Epub 2006/09/02.
- [4] Wang PS, Beck A, Berglund P, Leutzinger JA, Pronk N, Richling D, et al. Chronic medical conditions and work performance in the health and work performance questionnaire calibration surveys. *Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine*. 2003;45(12):1303-11. Epub 2003/12/11.
- [5] Fisher HL, Cohen-Woods S, Hosang GM, Korszun A, Owen M, Craddock N, et al. Interaction between specific forms of childhood maltreatment and the serotonin transporter gene (5-HTT) in recurrent depressive disorder. *Journal of affective disorders*. 2012. Epub 2012/07/31.
- [6] McIntyre RS, Soczynska JK, Liauw SS, Woldeyohannes HO, Brietzke E, Nathanson J, et al. The association between childhood adversity and components of metabolic syndrome in adults with mood disorders: results from the international mood disorders collaborative project. *International journal of psychiatry in medicine*. 2012;43(2):165-77. Epub 2012/08/02.
- [7] Rusli BN, Edimansyah BA, Naing L. Working conditions, self-perceived stress, anxiety, depression and quality of life: a structural equation modelling approach. *BMC public health*. 2008;8:48. Epub 2008/02/08.
- [8] Organization WH. The Global Burden of Disease: 2004 Update. WHO Press [Internet]. 2008; Geneva, Switzerland 2008.
- [9] Jayanthi LD, Ramamoorthy S. Regulation of monoamine transporters: influence of psychostimulants and therapeutic antidepressants. *The AAPS journal*. 2005;7(3):E728-38. Epub 2005/12/16.
- [10] Holsboer F. The corticosteroid receptor hypothesis of depression. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 2000;23(5):477-501. Epub 2000/10/12.



- [11] Kunugi H, Hori H, Adachi N, Numakawa T. Interface between hypothalamic-pituitary-adrenal axis and brain-derived neurotrophic factor in depression. *Psychiatry and clinical neurosciences*. 2010;64(5):447-59. Epub 2010/10/07.
- [12] Carney RM, Shelton RC. Agomelatine for the treatment of major depressive disorder. *Expert opinion on pharmacotherapy*. 2011;12(15):2411-9. Epub 2011/09/16.
- [13] Kasper S, Hamon M. Beyond the monoaminergic hypothesis: agomelatine, a new antidepressant with an innovative mechanism of action. *The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry*. 2009;10(2):117-26. Epub 2009/03/04.
- [14] Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nature reviews Neuroscience*. 2008;9(1):46-56. Epub 2007/12/13.
- [15] Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, et al. A meta-analysis of cytokines in major depression. *Biological psychiatry*. 2010;67(5):446-57. Epub 2009/12/18.
- [16] Luscher B, Shen Q, Sahir N. The GABAergic deficit hypothesis of major depressive disorder. *Molecular psychiatry*. 2011;16(4):383-406. Epub 2010/11/17.
- [17] Sanacora G, Treccani G, Popoli M. Towards a glutamate hypothesis of depression: an emerging frontier of neuropsychopharmacology for mood disorders. *Neuropharmacology*. 2012;62(1):63-77. Epub 2011/08/11.
- [18] Mineur YS, Picciotto MR. Nicotine receptors and depression: revisiting and revising the cholinergic hypothesis. *Trends in pharmacological sciences*. 2010;31(12):580-6. Epub 2010/10/23.
- [19] Craig MC, Murphy DG. Estrogen: effects on normal brain function and neuropsychiatric disorders. *Climacteric : the journal of the International Menopause Society*. 2007;10 Suppl 2:97-104. Epub 2007/10/27.
- [20] Estrada-Camarena E, Lopez-Rubalcava C, Vega-Rivera N, Recamier-Carballo S, Fernandez-Guasti A. Antidepressant effects of estrogens: a basic approximation. *Behavioural pharmacology*. 2010;21(5-6):451-64. Epub 2010/08/12.
- [21] Maes M, Fisar Z, Medina M, Scapagnini G, Nowak G, Berk M. New drug targets in depression: inflammatory, cell-mediated immune, oxidative and nitrosative stress, mitochondrial, antioxidant, and neuroprogressive pathways. And new drug candidates--Nrf2 activators and GSK-3 inhibitors. *Inflammopharmacology*. 2012;20(3):127-50. Epub 2012/01/25.
- [22] Faure C, Mnie-Filali O, Haddjeri N. Long-term adaptive changes induced by serotonergic antidepressant drugs. *Expert review of neurotherapeutics*. 2006;6(2):235-45. Epub 2006/02/10.

- [23] Neto FL, Borges G, Torres-Sanchez S, Mico JA, Berrocoso E. Neurotrophins role in depression neurobiology: a review of basic and clinical evidence. *Current neuropharmacology*. 2011;9(4):530-52. Epub 2012/06/02.
- [24] Paizanis E, Hamon M, Lanfumey L. Hippocampal neurogenesis, depressive disorders, and antidepressant therapy. *Neural plasticity*. 2007;2007:73754. Epub 2007/07/21.
- [25] Grady MM, Stahl SM. Practical guide for prescribing MAOIs: debunking myths and removing barriers. *CNS spectrums*. 2012;17(1):2-10. Epub 2012/07/14.
- [26] Miller J. Managing antidepressant overdoses. *Emergency medical services*. 2004;33(10):113-9. Epub 2004/11/24.
- [27] Aghajanian GK, Graham AW, Sheard MH. Serotonin-containing neurons in brain: depression of firing by monoamine oxidase inhibitors. *Science*. 1970;169(3950):1100-2. Epub 1970/09/11.
- [28] Gartside SE, Umbers V, Sharp T. Inhibition of 5-HT cell firing in the DRN by non-selective 5-HT reuptake inhibitors: studies on the role of 5-HT<sub>1A</sub> autoreceptors and noradrenergic mechanisms. *Psychopharmacology*. 1997;130(3):261-8. Epub 1997/04/01.
- [29] Scuvée-Moreau JJ, Dresse AE. Effect of various antidepressant drugs on the spontaneous firing rate of locus coeruleus and dorsal raphe neurons of the rat. *European journal of pharmacology*. 1979;57(2-3):219-25. Epub 1979/08/01.
- [30] Sharp T, Gartside SE, Umbers V. Effects of co-administration of a monoamine oxidase inhibitor and a 5-HT<sub>1A</sub> receptor antagonist on 5-hydroxytryptamine cell firing and release. *European journal of pharmacology*. 1997;320(1):15-9. Epub 1997/02/05.
- [31] Blier P, de Montigny C. Effect of chronic tricyclic antidepressant treatment on the serotonergic autoreceptor: a microiontophoretic study in the rat. *Naunyn-Schmiedeberg's archives of pharmacology*. 1980;314(2):123-8. Epub 1980/11/01.
- [32] Blier P, de Montigny C. Serotonergic but not noradrenergic neurons in rat central nervous system adapt to long-term treatment with monoamine oxidase inhibitors. *Neuroscience*. 1985;16(4):949-55. Epub 1985/12/01.
- [33] Blier P, de Montigny C. Current advances and trends in the treatment of depression. *Trends in pharmacological sciences*. 1994;15(7):220-6. Epub 1994/07/01.
- [34] Sleight AJ, Marsden CA, Palfreyman MG, Mir AK, Lovenberg W. Chronic MAO A and MAO B inhibition decreases the 5-HT<sub>1A</sub> receptor-mediated inhibition of forskolin-stimulated adenylate cyclase. *European journal of pharmacology*. 1988;154(3):255-61. Epub 1988/09/23.
- [35] Berendsen HH, Broekkamp CL. Attenuation of 5-HT<sub>1A</sub> and 5-HT<sub>2</sub> but not 5-HT<sub>1C</sub> receptor mediated behaviour in rats following chronic treatment with 5-HT receptor agonists, antagonists or anti-depressants. *Psychopharmacology*. 1991;105(2):219-24. Epub 1991/01/01.

- [36] Shen C, Li H, Meller E. Repeated treatment with antidepressants differentially alters 5-HT<sub>1A</sub> agonist-stimulated [<sup>35</sup>S]GTP gamma S binding in rat brain regions. *Neuropharmacology*. 2002;42(8):1031-8. Epub 2002/07/20.
- [37] Celada P, Artigas F. Monoamine oxidase inhibitors increase preferentially extracellular 5-hydroxytryptamine in the midbrain raphe nuclei. A brain microdialysis study in the awake rat. *Naunyn-Schmiedeberg's archives of pharmacology*. 1993;347(6):583-90. Epub 1993/06/01.
- [38] Sleight AJ, Smith RJ, Marsden CA, Palfreyman MG. The effects of chronic treatment with amitriptyline and MDL 72394 on the control of 5-HT release in vivo. *Neuropharmacology*. 1989;28(5):477-80. Epub 1989/05/01.
- [39] Blier P, Chaput Y, de Montigny C. Long-term 5-HT reuptake blockade, but not monoamine oxidase inhibition, decreases the function of terminal 5-HT autoreceptors: an electrophysiological study in the rat brain. *Naunyn-Schmiedeberg's archives of pharmacology*. 1988;337(3):246-54. Epub 1988/03/01.
- [40] Haddjeri N, Blier P, de Montigny C. Long-term antidepressant treatments result in a tonic activation of forebrain 5-HT<sub>1A</sub> receptors. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 1998;18(23):10150-6. Epub 1998/11/21.
- [41] Evrard A, Malagie I, Laporte AM, Boni C, Hanoun N, Trillat AC, et al. Altered regulation of the 5-HT system in the brain of MAO-A knock-out mice. *The European journal of neuroscience*. 2002;15(5):841-51. Epub 2002/03/22.
- [42] Lanoir J, Hilaire G, Seif I. Reduced density of functional 5-HT<sub>1A</sub> receptors in the brain, medulla and spinal cord of monoamine oxidase-A knockout mouse neonates. *The Journal of comparative neurology*. 2006;495(5):607-23. Epub 2006/02/25.
- [43] Fabre V, Beaufour C, Evrard A, Rioux A, Hanoun N, Lesch KP, et al. Altered expression and functions of serotonin 5-HT<sub>1A</sub> and 5-HT<sub>1B</sub> receptors in knock-out mice lacking the 5-HT transporter. *The European journal of neuroscience*. 2000;12(7):2299-310. Epub 2000/08/18.
- [44] Hensler JG. Differential regulation of 5-HT<sub>1A</sub> receptor-G protein interactions in brain following chronic antidepressant administration. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 2002;26(5):565-73. Epub 2002/04/03.
- [45] Rossi DV, Valdez M, Gould GG, Hensler JG. Chronic administration of venlafaxine fails to attenuate 5-HT<sub>1A</sub> receptor function at the level of receptor-G protein interaction. *The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum*. 2006;9(4):393-406. Epub 2005/07/23.
- [46] Chaput Y, de Montigny C, Blier P. Presynaptic and postsynaptic modifications of the serotonin system by long-term administration of antidepressant treatments. An in vivo electrophysiologic study in the rat. *Neuropsychopharmacology : official publication of*

the American College of Neuropsychopharmacology. 1991;5(4):219-29. Epub 1991/12/01.

- [47] Mandrioli R, Mercolini L, Saracino MA, Raggi MA. Selective serotonin reuptake inhibitors (SSRIs): therapeutic drug monitoring and pharmacological interactions. *Current medicinal chemistry*. 2012;19(12):1846-63. Epub 2012/03/15.
- [48] Reed CR, Kajdasz DK, Whalen H, Athanasiou MC, Gallipoli S, Thase ME. The efficacy profile of vilazodone, a novel antidepressant for the treatment of major depressive disorder. *Current medical research and opinion*. 2012;28(1):27-39. Epub 2011/11/24.
- [49] Pejchal T, Foley MA, Kosofsky BE, Waeber C. Chronic fluoxetine treatment selectively uncouples raphe 5-HT(1A) receptors as measured by [(35)S]-GTP gamma S autoradiography. *British journal of pharmacology*. 2002;135(5):1115-22. Epub 2002/03/06.
- [50] Czachura JF, Rasmussen K. Effects of acute and chronic administration of fluoxetine on the activity of serotonergic neurons in the dorsal raphe nucleus of the rat. *Naunyn-Schmiedeberg's archives of pharmacology*. 2000;362(3):266-75. Epub 2000/09/21.
- [51] El Mansari M, Sanchez C, Chouvet G, Renaud B, Haddjeri N. Effects of acute and long-term administration of escitalopram and citalopram on serotonin neurotransmission: an in vivo electrophysiological study in rat brain. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 2005;30(7):1269-77. Epub 2005/02/11.
- [52] Invernizzi R, Belli S, Samanin R. Citalopram's ability to increase the extracellular concentrations of serotonin in the dorsal raphe prevents the drug's effect in the frontal cortex. *Brain research*. 1992;584(1-2):322-4. Epub 1992/07/03.
- [53] Mansari ME, Wiborg O, Mnie-Filali O, Benturquia N, Sanchez C, Haddjeri N. Allosteric modulation of the effect of escitalopram, paroxetine and fluoxetine: in-vitro and in-vivo studies. *The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum*. 2007;10(1):31-40. Epub 2006/02/02.
- [54] Mnie-Filali O, El Mansari M, Espana A, Sanchez C, Haddjeri N. Allosteric modulation of the effects of the 5-HT reuptake inhibitor escitalopram on the rat hippocampal synaptic plasticity. *Neuroscience letters*. 2006;395(1):23-7. Epub 2005/12/07.
- [55] Smith JE, Lakoski JM. Electrophysiological effects of fluoxetine and duloxetine in the dorsal raphe nucleus and hippocampus. *European journal of pharmacology*. 1997;323(1):69-73. Epub 1997/03/26.
- [56] Aznavour N, Rbah L, Riad M, Reilhac A, Costes N, Descarries L, et al. A PET imaging study of 5-HT(1A) receptors in cat brain after acute and chronic fluoxetine treatment. *NeuroImage*. 2006;33(3):834-42. Epub 2006/09/26.
- [57] Riad M, Zimmer L, Rbah L, Watkins KC, Hamon M, Descarries L. 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. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2004;24(23):5420-6. Epub 2004/06/11.
- [58] Descarries L, Riad M. Effects of the antidepressant fluoxetine on the subcellular localization of 5-HT<sub>1A</sub> receptors and SERT. *Philosophical transactions of the Royal Society of London Series B, Biological sciences*. 2012;367(1601):2416-25. Epub 2012/07/25.
- [59] Rutter JJ, Auerbach SB. Acute uptake inhibition increases extracellular serotonin in the rat forebrain. *The Journal of pharmacology and experimental therapeutics*. 1993;265(3):1319-24. Epub 1993/06/01.
- [60] Le Poul E, Laaris N, Doucet E, Laporte AM, Hamon M, Lanfumey L. Early desensitization of somato-dendritic 5-HT<sub>1A</sub> autoreceptors in rats treated with fluoxetine or paroxetine. *Naunyn-Schmiedeberg's archives of pharmacology*. 1995;352(2):141-8. Epub 1995/08/01.
- [61] Mnie-Filali O, Faure C, Mansari ME, Lambas-Senas L, Berod A, Zimmer L, et al. R-citalopram prevents the neuronal adaptive changes induced by escitalopram. *Neuroreport*. 2007;18(15):1553-6. Epub 2007/09/22.
- [62] Riad M, Rbah L, Verdurand M, Aznavour N, Zimmer L, Descarries L. Unchanged density of 5-HT<sub>1A</sub> autoreceptors on the plasma membrane of nucleus raphe dorsalis neurons in rats chronically treated with fluoxetine. *Neuroscience*. 2008;151(3):692-700. Epub 2008/01/02.
- [63] Moulin-Sallanon M, Charnay Y, Ginovart N, Perret P, Lanfumey L, Hamon M, et al. Acute and chronic effects of citalopram on 5-HT<sub>1A</sub> receptor-labeling by [18F]MPPF and -coupling to receptors-G proteins. *Synapse*. 2009;63(2):106-16. Epub 2008/11/20.
- [64] Castro ME, Diaz A, del Olmo E, Pazos A. Chronic fluoxetine induces opposite changes in G protein coupling at pre and postsynaptic 5-HT<sub>1A</sub> receptors in rat brain. *Neuropharmacology*. 2003;44(1):93-101. Epub 2003/02/01.
- [65] Hanoun N, Mocaer E, Boyer PA, Hamon M, Lanfumey L. Differential effects of the novel antidepressant agomelatine (S 20098) versus fluoxetine on 5-HT<sub>1A</sub> receptors in the rat brain. *Neuropharmacology*. 2004;47(4):515-26. Epub 2004/09/24.
- [66] Rossi DV, Burke TF, McCasland M, Hensler JG. Serotonin-1A receptor function in the dorsal raphe nucleus following chronic administration of the selective serotonin reuptake inhibitor sertraline. *Journal of neurochemistry*. 2008;105(4):1091-9. Epub 2008/01/10.
- [67] Mannoury la Cour C, El Mestikawy S, Hanoun N, Hamon M, Lanfumey L. Regional differences in the coupling of 5-hydroxytryptamine-1A receptors to G proteins in the rat brain. *Molecular pharmacology*. 2006;70(3):1013-21. Epub 2006/06/15.



- [68] Castro E, Diaz A, Rodriguez-Gaztelumendi A, Del Olmo E, Pazos A. WAY100635 prevents the changes induced by fluoxetine upon the 5-HT<sub>1A</sub> receptor functionality. *Neuropharmacology*. 2008;55(8):1391-6. Epub 2008/09/24.
- [69] Blier P, Bouchard C. Modulation of 5-HT release in the guinea-pig brain following long-term administration of antidepressant drugs. *British journal of pharmacology*. 1994;113(2):485-95. Epub 1994/10/01.
- [70] Vidal R, Valdizan EM, Mostany R, Pazos A, Castro E. Long-term treatment with fluoxetine induces desensitization of 5-HT<sub>4</sub> receptor-dependent signalling and functionality in rat brain. *Journal of neurochemistry*. 2009;110(3):1120-7. Epub 2009/06/16.
- [71] Mnie-Filali O, Faure C, Lambas-Senas L, El Mansari M, Belblidia H, Gondard E, et al. Pharmacological blockade of 5-HT<sub>7</sub> receptors as a putative fast acting antidepressant strategy. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 2011;36(6):1275-88. Epub 2011/02/18.
- [72] Sleight AJ, Carolo C, Petit N, Zwingelstein C, Bourson A. Identification of 5-hydroxytryptamine<sub>7</sub> receptor binding sites in rat hypothalamus: sensitivity to chronic antidepressant treatment. *Molecular pharmacology*. 1995;47(1):99-103. Epub 1995/01/01.
- [73] Jing Y, Kalsekar I, Curkendall SM, Carls GS, Bagalman E, Forbes RA, et al. Intent-to-treat analysis of health care expenditures of patients treated with atypical antipsychotics as adjunctive therapy in depression. *Clinical therapeutics*. 2011;33(9):1246-57. Epub 2011/08/16.
- [74] Lin CH, Lin SH, Jang FL. Adjunctive low-dose aripiprazole with standard-dose sertraline in treating fresh major depressive disorder: a randomized, double-blind, controlled study. *Journal of clinical psychopharmacology*. 2011;31(5):563-8. Epub 2011/08/27.
- [75] Trivedi MH, Thase ME, Fava M, Nelson CJ, Yang H, Qi Y, et al. Adjunctive aripiprazole in major depressive disorder: analysis of efficacy and safety in patients with anxious and atypical features. *The Journal of clinical psychiatry*. 2008;69(12):1928-36. Epub 2009/02/05.
- [76] Cherneloz O, El Mansari M, Blier P. Effects of sustained administration of quetiapine alone and in combination with a serotonin reuptake inhibitor on norepinephrine and serotonin transmission. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 2012;37(7):1717-28. Epub 2012/03/01.
- [77] Dremencov E, El Mansari M, Blier P. Distinct electrophysiological effects of paliperidone and risperidone on the firing activity of rat serotonin and norepinephrine neurons. *Psychopharmacology*. 2007;194(1):63-72. Epub 2007/05/29.
- [78] Marcus MM, Jardemark K, Malmerfelt A, Gertow J, Konradsson-Geuken A, Svensson TH. Augmentation by escitalopram, but not citalopram or R-citalopram, of the effects

- of low-dose risperidone: behavioral, biochemical, and electrophysiological evidence. *Synapse*. 2012;66(4):277-90. Epub 2011/11/29.
- [79] Lucas G, Rymar VV, Du J, Mnie-Filali O, Bisgaard C, Manta S, et al. Serotonin(4) (5-HT<sub>4</sub>) receptor agonists are putative antidepressants with a rapid onset of action. *Neuron*. 2007;55(5):712-25. Epub 2007/09/06.
- [80] Licht CL, Kirkegaard L, Zueger M, Chourbaji S, Gass P, Aznar S, et al. Changes in 5-HT<sub>4</sub> receptor and 5-HT transporter binding in olfactory bulbectomized and glucocorticoid receptor heterozygous mice. *Neurochemistry international*. 2010;56(4):603-10. Epub 2010/01/12.
- [81] Licht CL, Marcussen AB, Wegener G, Overstreet DH, Aznar S, Knudsen GM. The brain 5-HT<sub>4</sub> receptor binding is down-regulated in the Flinders Sensitive Line depression model and in response to paroxetine administration. *Journal of neurochemistry*. 2009;109(5):1363-74. Epub 2009/05/30.
- [82] Licht CL, Knudsen GM, Sharp T. Effects of the 5-HT<sub>4</sub> receptor agonist RS67333 and paroxetine on hippocampal extracellular 5-HT levels. *Neuroscience letters*. 2010b;476(2):58-61. Epub 2010/04/13.
- [83] Lucas G, Du J, Romeas T, Mnie-Filali O, Haddjeri N, Pineyro G, et al. Selective serotonin reuptake inhibitors potentiate the rapid antidepressant-like effects of serotonin<sub>4</sub> receptor agonists in the rat. *PloS one*. 2010;5(2):e9253. Epub 2010/02/20.
- [84] Abbas AI, Hedlund PB, Huang XP, Tran TB, Meltzer HY, Roth BL. Amisulpride is a potent 5-HT<sub>7</sub> antagonist: relevance for antidepressant actions in vivo. *Psychopharmacology*. 2009;205(1):119-28. Epub 2009/04/02.
- [85] Adell A. Lu-AA21004, a multimodal serotonergic agent, for the potential treatment of depression and anxiety. *IDrugs : the investigational drugs journal*. 2010;13(12):900-10. Epub 2010/12/15.
- [86] Baldwin DS, Hansen T, Florea I. Vortioxetine (Lu AA21004) in the long-term open-label treatment of major depressive disorder. *Current medical research and opinion*. 2012;28(10):1717-24. Epub 2012/09/18.
- [87] Bang-Andersen B, Ruhland T, Jorgensen M, Smith G, Frederiksen K, Jensen KG, et al. Discovery of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine (Lu AA21004): a novel multimodal compound for the treatment of major depressive disorder. *Journal of medicinal chemistry*. 2011;54(9):3206-21. Epub 2011/04/14.
- [88] Ishibashi T, Horisawa T, Tokuda K, Ishiyama T, Ogasa M, Tagashira R, et al. Pharmacological profile of lurasidone, a novel antipsychotic agent with potent 5-hydroxytryptamine 7 (5-HT<sub>7</sub>) and 5-HT<sub>1A</sub> receptor activity. *The Journal of pharmacology and experimental therapeutics*. 2010;334(1):171-81. Epub 2010/04/21.
- [89] Hedlund PB, Huitron-Resendiz S, Henriksen SJ, Sutcliffe JG. 5-HT<sub>7</sub> receptor inhibition and inactivation induce antidepressantlike behavior and sleep pattern. *Biological psychiatry*. 2005;58(10):831-7. Epub 2005/07/16.

- [90] Altman J, Das GD. Autoradiographic and histological evidence of postnatal hippocampal neurogenesis in rats. *The Journal of comparative neurology*. 1965;124(3):319-35. Epub 1965/06/01.
- [91] Eriksson PS, Perfilieva E, Bjork-Eriksson T, Alborn AM, Nordborg C, Peterson DA, et al. Neurogenesis in the adult human hippocampus. *Nature medicine*. 1998;4(11):1313-7. Epub 1998/11/11.
- [92] Murrell W, Bushell GR, Livesey J, McGrath J, MacDonald KP, Bates PR, et al. Neurogenesis in adult human. *Neuroreport*. 1996;7(6):1189-94. Epub 1996/04/26.
- [93] Takahashi T, Nowakowski RS, Caviness VS, Jr. BUdR as an S-phase marker for quantitative studies of cytokinetic behaviour in the murine cerebral ventricular zone. *Journal of neurocytology*. 1992;21(3):185-97. Epub 1992/03/11.
- [94] Hanson ND, Owens MJ, Nemeroff CB. Depression, antidepressants, and neurogenesis: a critical reappraisal. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 2011;36(13):2589-602. Epub 2011/09/23.
- [95] Garcia-Verdugo JM, Doetsch F, Wichterle H, Lim DA, Alvarez-Buylla A. Architecture and cell types of the adult subventricular zone: in search of the stem cells. *Journal of neurobiology*. 1998;36(2):234-48. Epub 1998/08/26.
- [96] Benraiss A, Chmielnicki E, Lerner K, Roh D, Goldman SA. Adenoviral brain-derived neurotrophic factor induces both neostriatal and olfactory neuronal recruitment from endogenous progenitor cells in the adult forebrain. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2001;21(17):6718-31. Epub 2001/08/23.
- [97] Magavi SS, Leavitt BR, Macklis JD. Induction of neurogenesis in the neocortex of adult mice. *Nature*. 2000;405(6789):951-5. Epub 2000/07/06.
- [98] Pencea V, Bingaman KD, Wiegand SJ, Luskin MB. Infusion of brain-derived neurotrophic factor into the lateral ventricle of the adult rat leads to new neurons in the parenchyma of the striatum, septum, thalamus, and hypothalamus. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2001;21(17):6706-17. Epub 2001/08/23.
- [99] Campbell S, Marriott M, Nahmias C, MacQueen GM. Lower hippocampal volume in patients suffering from depression: a meta-analysis. *The American journal of psychiatry*. 2004;161(4):598-607. Epub 2004/04/02.
- [100] Videbech P, Ravnkilde B. Hippocampal volume and depression: a meta-analysis of MRI studies. *The American journal of psychiatry*. 2004;161(11):1957-66. Epub 2004/10/30.
- [101] MacQueen GM, Yucel K, Taylor VH, Macdonald K, Joffe R. Posterior hippocampal volumes are associated with remission rates in patients with major depressive disorder. *Biological psychiatry*. 2008;64(10):880-3. Epub 2008/08/30.

- [102] Santarelli L, Saxe M, Gross C, Surget A, Battaglia F, Dulawa S, et al. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science*. 2003;301(5634):805-9. Epub 2003/08/09.
- [103] Perera TD, Dwork AJ, Keegan KA, Thirumangalakudi L, Lipira CM, Joyce N, et al. Necessity of hippocampal neurogenesis for the therapeutic action of antidepressants in adult nonhuman primates. *PloS one*. 2011;6(4):e17600. Epub 2011/04/29.
- [104] Li YF, Zhang YZ, Liu YQ, Wang HL, Yuan L, Luo ZP. Moclobemide up-regulates proliferation of hippocampal progenitor cells in chronically stressed mice. *Acta pharmacologica Sinica*. 2004;25(11):1408-12. Epub 2004/11/05.
- [105] Malberg JE, Eisch AJ, Nestler EJ, Duman RS. Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2000;20(24):9104-10. Epub 2000/01/11.
- [106] Chen F, Madsen TM, Wegener G, Nyengaard JR. Imipramine treatment increases the number of hippocampal synapses and neurons in a genetic animal model of depression. *Hippocampus*. 2010;20(12):1376-84. Epub 2009/11/19.
- [107] Pechnick RN, Zonis S, Wawrowsky K, Cosgayon R, Farrokhi C, Lacayo L, et al. Antidepressants stimulate hippocampal neurogenesis by inhibiting p21 expression in the subgranular zone of the hippocampus. *PloS one*. 2011;6(11):e27290. Epub 2011/11/15.
- [108] Kodama M, Fujioka T, Duman RS. Chronic olanzapine or fluoxetine administration increases cell proliferation in hippocampus and prefrontal cortex of adult rat. *Biological psychiatry*. 2004;56(8):570-80. Epub 2004/10/13.
- [109] Snyder JS, Kee N, Wojtowicz JM. Effects of adult neurogenesis on synaptic plasticity in the rat dentate gyrus. *Journal of neurophysiology*. 2001;85(6):2423-31. Epub 2001/06/02.
- [110] Ge S, Goh EL, Sailor KA, Kitabatake Y, Ming GL, Song H. GABA regulates synaptic integration of newly generated neurons in the adult brain. *Nature*. 2006;439(7076):589-93. Epub 2005/12/13.
- [111] Halim ND, Weickert CS, McClintock BW, Weinberger DR, Lipska BK. Effects of chronic haloperidol and clozapine treatment on neurogenesis in the adult rat hippocampus. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 2004;29(6):1063-9. Epub 2004/03/11.
- [112] Hanson ND, Nemeroff CB, Owens MJ. Lithium, but not fluoxetine or the corticotropin-releasing factor receptor 1 receptor antagonist R121919, increases cell proliferation in the adult dentate gyrus. *The Journal of pharmacology and experimental therapeutics*. 2011;337(1):180-6. Epub 2011/01/12.
- [113] Luo C, Xu H, Li XM. Quetiapine reverses the suppression of hippocampal neurogenesis caused by repeated restraint stress. *Brain research*. 2005;1063(1):32-9. Epub 2005/11/08.
- [114] Jaholkowski P, Kiryk A, Jedynak P, Ben Abdallah NM, Knapska E, Kowalczyk A, et al. New hippocampal neurons are not obligatory for memory formation; cyclin D2

knockout mice with no adult brain neurogenesis show learning. *Learning & memory*. 2009;16(7):439-51. Epub 2009/06/26.

- [115] Sahay A, Scobie KN, Hill AS, O'Carroll CM, Kheirbek MA, Burghardt NS, et al. Increasing adult hippocampal neurogenesis is sufficient to improve pattern separation. *Nature*. 2011;472(7344):466-70. Epub 2011/04/05.
- [116] Gorman JM, Docherty JP. A hypothesized role for dendritic remodeling in the etiology of mood and anxiety disorders. *The Journal of neuropsychiatry and clinical neurosciences*. 2010;22(3):256-64. Epub 2010/08/06.
- [117] Duman RS, Li N. A neurotrophic hypothesis of depression: role of synaptogenesis in the actions of NMDA receptor antagonists. *Philosophical transactions of the Royal Society of London Series B, Biological sciences*. 2012;367(1601):2475-84. Epub 2012/07/25.
- [118] Holtmaat A, Svoboda K. Experience-dependent structural synaptic plasticity in the mammalian brain. *Nature reviews Neuroscience*. 2009;10(9):647-58. Epub 2009/08/21.
- [119] Yoshihara Y, De Roo M, Muller D. Dendritic spine formation and stabilization. *Current opinion in neurobiology*. 2009;19(2):146-53. Epub 2009/06/16.
- [120] Bhatt DH, Zhang S, Gan WB. Dendritic spine dynamics. *Annual review of physiology*. 2009;71:261-82. Epub 2009/07/07.
- [121] Bourne JN, Harris KM. Balancing structure and function at hippocampal dendritic spines. *Annual review of neuroscience*. 2008;31:47-67. Epub 2008/02/21.
- [122] Matsuzaki M, Honkura N, Ellis-Davies GC, Kasai H. Structural basis of long-term potentiation in single dendritic spines. *Nature*. 2004;429(6993):761-6. Epub 2004/06/11.
- [123] Zhou Q, Homma KJ, Poo MM. Shrinkage of dendritic spines associated with long-term depression of hippocampal synapses. *Neuron*. 2004;44(5):749-57. Epub 2004/12/02.
- [124] Conrad CD. What is the functional significance of chronic stress-induced CA3 dendritic retraction within the hippocampus? *Behavioral and cognitive neuroscience reviews*. 2006;5(1):41-60. Epub 2006/07/04.
- [125] Michelsen KA, van den Hove DL, Schmitz C, Segers O, Prickaerts J, Steinbusch HW. Prenatal stress and subsequent exposure to chronic mild stress influence dendritic spine density and morphology in the rat medial prefrontal cortex. *BMC neuroscience*. 2007;8:107. Epub 2007/12/21.
- [126] Sousa N, Lukoyanov NV, Madeira MD, Almeida OF, Paula-Barbosa MM. Reorganization of the morphology of hippocampal neurites and synapses after stress-induced damage correlates with behavioral improvement. *Neuroscience*. 2000;97(2):253-66. Epub 2000/05/09.
- [127] Cook SC, Wellman CL. Chronic stress alters dendritic morphology in rat medial prefrontal cortex. *Journal of neurobiology*. 2004;60(2):236-48. Epub 2004/07/22.



- [128] Radley JJ, Sisti HM, Hao J, Rocher AB, McCall T, Hof PR, et al. Chronic behavioral stress induces apical dendritic reorganization in pyramidal neurons of the medial prefrontal cortex. *Neuroscience*. 2004;125(1):1-6. Epub 2004/03/31.
- [129] Arnone D, McIntosh AM, Ebmeier KP, Munafo MR, Anderson IM. Magnetic resonance imaging studies in unipolar depression: systematic review and meta-regression analyses. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology*. 2012;22(1):1-16. Epub 2011/07/05.
- [130] Kang HJ, Voleti B, Hajszan T, Rajkowska G, Stockmeier CA, Licznarski P, et al. Decreased expression of synapse-related genes and loss of synapses in major depressive disorder. *Nature medicine*. 2012;18(9):1413-7. Epub 2012/08/14.
- [131] Holderbach R, Clark K, Moreau JL, Bischofberger J, Normann C. Enhanced long-term synaptic depression in an animal model of depression. *Biological psychiatry*. 2007;62(1):92-100. Epub 2006/12/05.
- [132] Li W, Liu L, Liu YY, Luo J, Lin JY, Li X, et al. Effects of electroconvulsive stimulation on long-term potentiation and synaptophysin in the hippocampus of rats with depressive behavior. *The journal of ECT*. 2012;28(2):111-7. Epub 2012/04/26.
- [133] Xu L, Anwyl R, Rowan MJ. Behavioural stress facilitates the induction of long-term depression in the hippocampus. *Nature*. 1997;387(6632):497-500. Epub 1997/05/29.
- [134] Bhagya V, Srikumar BN, Raju TR, Rao BS. Chronic escitalopram treatment restores spatial learning, monoamine levels, and hippocampal long-term potentiation in an animal model of depression. *Psychopharmacology*. 2011;214(2):477-94. Epub 2010/11/06.
- [135] Matsumoto M, Tachibana K, Togashi H, Tahara K, Kojima T, Yamaguchi T, et al. Chronic treatment with milnacipran reverses the impairment of synaptic plasticity induced by conditioned fear stress. *Psychopharmacology*. 2005;179(3):606-12. Epub 2004/12/25.
- [136] Cooke JD, Grover LM, Spangler PR. Venlafaxine treatment stimulates expression of brain-derived neurotrophic factor protein in frontal cortex and inhibits long-term potentiation in hippocampus. *Neuroscience*. 2009;162(4):1411-9. Epub 2009/05/26.
- [137] O'Connor JJ, Rowan MJ, Anwyl R. Use-dependent effects of acute and chronic treatment with imipramine and buspirone on excitatory synaptic transmission in the rat hippocampus in vivo. *Naunyn-Schmiedeberg's archives of pharmacology*. 1993;348(2):158-63. Epub 1993/08/01.
- [138] Stewart CA, Reid IC. Repeated ECS and fluoxetine administration have equivalent effects on hippocampal synaptic plasticity. *Psychopharmacology*. 2000;148(3):217-23. Epub 2001/02/07.
- [139] Huang GJ, Ben-David E, Tort Piella A, Edwards A, Flint J, Shifman S. Neurogenomic evidence for a shared mechanism of the antidepressant effects of exercise and chronic fluoxetine in mice. *PloS one*. 2012;7(4):e35901. Epub 2012/05/05.

- [140] Wang JW, David DJ, Monckton JE, Battaglia F, Hen R. Chronic fluoxetine stimulates maturation and synaptic plasticity of adult-born hippocampal granule cells. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2008;28(6):1374-84. Epub 2008/02/08.
- [141] Hajszan T, MacLusky NJ, Leranth C. Short-term treatment with the antidepressant fluoxetine triggers pyramidal dendritic spine synapse formation in rat hippocampus. *The European journal of neuroscience*. 2005;21(5):1299-303. Epub 2005/04/09.
- [142] Bedrosian TA, Weil ZM, Nelson RJ. Chronic citalopram treatment ameliorates depressive behavior associated with light at night. *Behavioral neuroscience*. 2012;126(5):654-8. Epub 2012/08/15.
- [143] Norrholm SD, Ouimet CC. Altered dendritic spine density in animal models of depression and in response to antidepressant treatment. *Synapse*. 2001;42(3):151-63. Epub 2001/12/18.
- [144] Restivo L, Roman F, Dumuis A, Bockaert J, Marchetti E, Ammassari-Teule M. The promnesic effect of G-protein-coupled 5-HT<sub>4</sub> receptors activation is mediated by a potentiation of learning-induced spine growth in the mouse hippocampus. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 2008;33(10):2427-34. Epub 2007/12/14.
- [145] Tajiri M, Hayata-Takano A, Seiriki K, Ogata K, Hazama K, Shintani N, et al. Serotonin 5-HT<sub>7</sub> receptor blockade reverses behavioral abnormalities in PACAP-deficient mice and receptor activation promotes neurite extension in primary embryonic hippocampal neurons: therapeutic implications for psychiatric disorders. *Journal of molecular neuroscience : MN*. 2012;48(3):473-81. Epub 2012/07/31.
- [146] Luthi A, Laurent JP, Figurov A, Muller D, Schachner M. Hippocampal long-term potentiation and neural cell adhesion molecules L1 and NCAM. *Nature*. 1994;372(6508):777-9. Epub 1994/12/22.
- [147] Gascon E, Vutskits L, Kiss JZ. Polysialic acid-neural cell adhesion molecule in brain plasticity: from synapses to integration of new neurons. *Brain research reviews*. 2007;56(1):101-18. Epub 2007/07/31.
- [148] Guirado R, Sanchez-Matarredona D, Varea E, Crespo C, Blasco-Ibanez JM, Nacher J. Chronic fluoxetine treatment in middle-aged rats induces changes in the expression of plasticity-related molecules and in neurogenesis. *BMC neuroscience*. 2012;13:5. Epub 2012/01/10.
- [149] Murphy KJ, Foley AG, O'Connell A W, Regan CM. Chronic exposure of rats to cognition enhancing drugs produces a neuroplastic response identical to that obtained by complex environment rearing. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 2006;31(1):90-100. Epub 2005/07/01.

- [150] Sairanen M, O'Leary OF, Knuuttila JE, Castren E. Chronic antidepressant treatment selectively increases expression of plasticity-related proteins in the hippocampus and medial prefrontal cortex of the rat. *Neuroscience*. 2007;144(1):368-74. Epub 2006/10/20.
- [151] Varea E, Blasco-Ibanez JM, Gomez-Climent MA, Castillo-Gomez E, Crespo C, Martinez-Guijarro FJ, et al. Chronic fluoxetine treatment increases the expression of PSA-NCAM in the medial prefrontal cortex. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 2007;32(4):803-12. Epub 2006/08/11.
- [152] Frasca A, Fumagalli F, Ter Horst J, Racagni G, Murphy KJ, Riva MA. Olanzapine, but not haloperidol, enhances PSA-NCAM immunoreactivity in rat prefrontal cortex. *The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum*. 2008;11(5):591-5. Epub 2008/07/03.
- [153] Mackowiak M, Dudys D, Chocyk A, Wedzony K. Repeated risperidone treatment increases the expression of NCAM and PSA-NCAM protein in the rat medial prefrontal cortex. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology*. 2009;19(2):125-37. Epub 2008/12/02.
- [154] Evans GJ, Cousin MA. Tyrosine phosphorylation of synaptophysin in synaptic vesicle recycling. *Biochemical Society transactions*. 2005;33(Pt 6):1350-3. Epub 2005/10/26.
- [155] Drigues N, Poltyrev T, Bejar C, Weinstock M, Youdim MB. cDNA gene expression profile of rat hippocampus after chronic treatment with antidepressant drugs. *Journal of neural transmission*. 2003;110(12):1413-36. Epub 2003/12/11.
- [156] Rapp S, Baader M, Hu M, Jennen-Steinmetz C, Henn FA, Thome J. Differential regulation of synaptic vesicle proteins by antidepressant drugs. *The pharmacogenomics journal*. 2004;4(2):110-3. Epub 2004/01/07.
- [157] Rodriguez JJ, Davies HA, Silva AT, De Souza IE, Peddie CJ, Colyer FM, et al. Long-term potentiation in the rat dentate gyrus is associated with enhanced Arc/Arg3.1 protein expression in spines, dendrites and glia. *The European journal of neuroscience*. 2005;21(9):2384-96. Epub 2005/06/04.
- [158] Chowdhury S, Shepherd JD, Okuno H, Lyford G, Petralia RS, Plath N, et al. Arc/Arg3.1 interacts with the endocytic machinery to regulate AMPA receptor trafficking. *Neuron*. 2006;52(3):445-59. Epub 2006/11/08.
- [159] Peebles CL, Yoo J, Thwin MT, Palop JJ, Noebels JL, Finkbeiner S. Arc regulates spine morphology and maintains network stability in vivo. *Proceedings of the National Academy of Sciences of the United States of America*. 2010;107(42):18173-8. Epub 2010/10/06.
- [160] Rial Verde EM, Lee-Osbourne J, Worley PF, Malinow R, Cline HT. Increased expression of the immediate-early gene arc/arg3.1 reduces AMPA receptor-mediated synaptic transmission. *Neuron*. 2006;52(3):461-74. Epub 2006/11/08.

- [161] Pei Q, Zetterstrom TS, Sprakes M, Tordera R, Sharp T. Antidepressant drug treatment induces Arc gene expression in the rat brain. *Neuroscience*. 2003;121(4):975-82. Epub 2003/10/29.
- [162] Huang EJ, Reichardt LF. Trk receptors: roles in neuronal signal transduction. *Annual review of biochemistry*. 2003;72:609-42. Epub 2003/04/05.
- [163] Berry A, Bellisario V, Capoccia S, Tirassa P, Calza A, Alleva E, et al. Social deprivation stress is a triggering factor for the emergence of anxiety- and depression-like behaviours and leads to reduced brain BDNF levels in C57BL/6J mice. *Psychoneuroendocrinology*. 2012;37(6):762-72. Epub 2011/10/07.
- [164] De Vry J, Prickaerts J, Jetten M, Hulst M, Steinbusch HW, van den Hove DL, et al. Recurrent long-lasting tethering reduces BDNF protein levels in the dorsal hippocampus and frontal cortex in pigs. *Hormones and behavior*. 2012;62(1):10-7. Epub 2012/05/16.
- [165] Hamani C, Machado DC, Hipolide DC, Dubiela FP, Suchecki D, Macedo CE, et al. Deep brain stimulation reverses anhedonic-like behavior in a chronic model of depression: role of serotonin and brain derived neurotrophic factor. *Biological psychiatry*. 2012;71(1):30-5. Epub 2011/10/18.
- [166] Nibuya M, Takahashi M, Russell DS, Duman RS. Repeated stress increases catalytic TrkB mRNA in rat hippocampus. *Neuroscience letters*. 1999;267(2):81-4. Epub 1999/07/10.
- [167] Yazir Y, Utkan T, Aricioglu F. Inhibition of neuronal nitric oxide synthase and soluble guanylate cyclase prevents depression-like behaviour in rats exposed to chronic unpredictable mild stress. *Basic & clinical pharmacology & toxicology*. 2012;111(3):154-60. Epub 2012/03/06.
- [168] Zhang Y, Gu F, Chen J, Dong W. Chronic antidepressant administration alleviates frontal and hippocampal BDNF deficits in CUMS rat. *Brain research*. 2010;1366:141-8. Epub 2010/10/06.
- [169] Burke TF, Advani T, Adachi M, Monteggia LM, Hensler JG. Sensitivity of hippocampal 5-HT1A receptors to mild stress in BDNF-deficient mice. *The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum*. 2012:1-15. Epub 2012/05/12.
- [170] Taliaz D, Stall N, Dar DE, Zangen A. Knockdown of brain-derived neurotrophic factor in specific brain sites precipitates behaviors associated with depression and reduces neurogenesis. *Molecular psychiatry*. 2010;15(1):80-92. Epub 2009/07/22.
- [171] Gonul AS, Akdeniz F, Taneli F, Donat O, Eker C, Vahip S. Effect of treatment on serum brain-derived neurotrophic factor levels in depressed patients. *European archives of psychiatry and clinical neuroscience*. 2005;255(6):381-6. Epub 2005/04/06.

- [172] Karege F, Perret G, Bondolfi G, Schwald M, Bertschy G, Aubry JM. Decreased serum brain-derived neurotrophic factor levels in major depressed patients. *Psychiatry research*. 2002;109(2):143-8. Epub 2002/04/03.
- [173] Lee BH, Kim H, Park SH, Kim YK. Decreased plasma BDNF level in depressive patients. *Journal of affective disorders*. 2007;101(1-3):239-44. Epub 2006/12/19.
- [174] Shimizu E, Hashimoto K, Okamura N, Koike K, Komatsu N, Kumakiri C, et al. Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants. *Biological psychiatry*. 2003;54(1):70-5. Epub 2003/07/05.
- [175] Choi MJ, Kang RH, Lim SW, Oh KS, Lee MS. Brain-derived neurotrophic factor gene polymorphism (Val66Met) and citalopram response in major depressive disorder. *Brain research*. 2006;1118(1):176-82. Epub 2006/09/19.
- [176] Kang RH, Chang HS, Wong ML, Choi MJ, Park JY, Lee HY, et al. Brain-derived neurotrophic factor gene polymorphisms and mirtazapine responses in Koreans with major depression. *Journal of psychopharmacology*. 2010;24(12):1755-63. Epub 2009/06/06.
- [177] Laje G, Lally N, Mathews D, Brutsche N, Chemerinski A, Akula N, et al. Brain-Derived Neurotrophic Factor Val66Met Polymorphism and Antidepressant Efficacy of Ketamine in Depressed Patients. *Biological psychiatry*. 2012;72(11):e27-8. Epub 2012/07/10.
- [178] Mamounas LA, Altar CA, Blue ME, Kaplan DR, Tessarollo L, Lyons WE. BDNF promotes the regenerative sprouting, but not survival, of injured serotonergic axons in the adult rat brain. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2000;20(2):771-82. Epub 2000/01/13.
- [179] Mamounas LA, Blue ME, Siuciak JA, Altar CA. Brain-derived neurotrophic factor promotes the survival and sprouting of serotonergic axons in rat brain. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 1995;15(12):7929-39. Epub 1995/12/01.
- [180] Assareh N, ElBatsh MM, Marsden CA, Kendall DA. The effects of chronic administration of tranylcypromine and rimonabant on behaviour and protein expression in brain regions of the rat. *Pharmacology, biochemistry, and behavior*. 2012;100(3):506-12. Epub 2011/11/01.
- [181] Balu DT, Hoshaw BA, Malberg JE, Rosenzweig-Lipson S, Schechter LE, Lucki I. Differential regulation of central BDNF protein levels by antidepressant and non-antidepressant drug treatments. *Brain research*. 2008;1211:37-43. Epub 2008/04/25.
- [182] De Foubert G, Carney SL, Robinson CS, Destexhe EJ, Tomlinson R, Hicks CA, et al. Fluoxetine-induced change in rat brain expression of brain-derived neurotrophic factor varies depending on length of treatment. *Neuroscience*. 2004;128(3):597-604. Epub 2004/09/24.



- [183] Khundakar AA, Zetterstrom TS. Biphasic change in BDNF gene expression following antidepressant drug treatment explained by differential transcript regulation. *Brain research*. 2006;1106(1):12-20. Epub 2006/07/18.
- [184] Zhang F, Zhou H, Wilson BC, Shi JS, Hong JS, Gao HM. Fluoxetine protects neurons against microglial activation-mediated neurotoxicity. *Parkinsonism & related disorders*. 2012;18 Suppl 1:S213-7. Epub 2011/12/23.
- [185] Serra-Millas M, Lopez-Vilchez I, Navarro V, Galan AM, Escolar G, Penades R, et al. Changes in plasma and platelet BDNF levels induced by S-citalopram in major depression. *Psychopharmacology*. 2011;216(1):1-8. Epub 2011/02/11.
- [186] Yoshimura R, Mitoma M, Sugita A, Hori H, Okamoto T, Umene W, et al. Effects of paroxetine or milnacipran on serum brain-derived neurotrophic factor in depressed patients. *Progress in neuro-psychopharmacology & biological psychiatry*. 2007;31(5):1034-7. Epub 2007/04/27.
- [187] Tamburella A, Micale V, Navarria A, Drago F. Antidepressant properties of the 5-HT4 receptor partial agonist, SL65.0155: behavioral and neurochemical studies in rats. *Progress in neuro-psychopharmacology & biological psychiatry*. 2009;33(7):1205-10. Epub 2009/07/15.
- [188] Agostinho FR, Reus GZ, Stringari RB, Ribeiro KF, Pfaffenseller B, Stertz L, et al. Olanzapine plus fluoxetine treatment increases Nt-3 protein levels in the rat prefrontal cortex. *Neuroscience letters*. 2011;497(2):99-103. Epub 2011/05/07.
- [189] Pae CU, Marks DM, Han C, Patkar AA, Steffens D. Does neurotrophin-3 have a therapeutic implication in major depression? *The International journal of neuroscience*. 2008;118(11):1515-22. Epub 2008/10/15.
- [190] Araque A, Navarrete M. Glial cells in neuronal network function. *Philosophical transactions of the Royal Society of London Series B, Biological sciences*. 2010;365(1551):2375-81. Epub 2010/07/07.
- [191] Butt AM. ATP: a ubiquitous gliotransmitter integrating neuron-glia networks. *Seminars in cell & developmental biology*. 2011;22(2):205-13. Epub 2011/03/08.
- [192] Paradise MB, Naismith SL, Norrie LM, Graeber MB, Hickie IB. The role of glia in late-life depression. *International psychogeriatrics / IPA*. 2012;24(12):1878-90. Epub 2012/08/10.
- [193] Oh DH, Son H, Hwang S, Kim SH. Neuropathological abnormalities of astrocytes, GABAergic neurons, and pyramidal neurons in the dorsolateral prefrontal cortices of patients with major depressive disorder. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology*. 2012;22(5):330-8. Epub 2011/10/04.
- [194] Rajkowska G, Miguel-Hidalgo JJ. Gliogenesis and glial pathology in depression. *CNS & neurological disorders drug targets*. 2007;6(3):219-33. Epub 2007/05/22.

- [195] Connor TJ, Leonard BE. Depression, stress and immunological activation: the role of cytokines in depressive disorders. *Life sciences*. 1998;62(7):583-606. Epub 1998/02/24.
- [196] Khairova RA, Machado-Vieira R, Du J, Manji HK. A potential role for pro-inflammatory cytokines in regulating synaptic plasticity in major depressive disorder. *The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum*. 2009;12(4):561-78. Epub 2009/02/20.
- [197] Sheline YI, Price JL, Yan Z, Mintun MA. Resting-state functional MRI in depression unmasks increased connectivity between networks via the dorsal nexus. *Proceedings of the National Academy of Sciences of the United States of America*. 2010;107(24):11020-5. Epub 2010/06/11.
- [198] Kavalali ET, Monteggia LM. Synaptic Mechanisms Underlying Rapid Antidepressant Action of Ketamine. *The American journal of psychiatry*. 2012. Epub 2012/10/05.
- [199] Salvatore G, van der Veen JW, Zhang Y, Marenco S, Machado-Vieira R, Baumann J, et al. An investigation of amino-acid neurotransmitters as potential predictors of clinical improvement to ketamine in depression. *The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum*. 2012;15(8):1063-72. Epub 2011/11/02.
- [200] Scheidegger M, Walter M, Lehmann M, Metzger C, Grimm S, Boeker H, et al. Ketamine decreases resting state functional network connectivity in healthy subjects: implications for antidepressant drug action. *PloS one*. 2012;7(9):e44799. Epub 2012/10/11.
- [201] Blier P, de Montigny C. Serotonin and drug-induced therapeutic responses in major depression, obsessive-compulsive and panic disorders. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 1999;21(2 Suppl):91S-8S. Epub 1999/08/05.
- [202] Watanabe Y, Gould E, McEwen BS. Stress induces atrophy of apical dendrites of hippocampal CA3 pyramidal neurons. *Brain research*. 1992;588(2):341-5. Epub 1992/08/21.
- [203] Pavlides C, Nivon LG, McEwen BS. Effects of chronic stress on hippocampal long-term potentiation. *Hippocampus*. 2002;12(2):245-57. Epub 2002/05/10.
- [204] Cieslik K, Sowa-Kucma M, Ossowska G, Legutko B, Wolak M, Opoka W, et al. Chronic unpredictable stress-induced reduction in the hippocampal brain-derived neurotrophic factor (BDNF) gene expression is antagonized by zinc treatment. *Pharmacological reports : PR*. 2011;63(2):537-43. Epub 2011/05/24.
- [205] Liu W, Zhou C. Corticosterone reduces brain mitochondrial function and expression of mitofusin, BDNF in depression-like rodents regardless of exercise preconditioning. *Psychoneuroendocrinology*. 2012;37(7):1057-70. Epub 2012/01/17.
- [206] Wellman CL. Dendritic reorganization in pyramidal neurons in medial prefrontal cortex after chronic corticosterone administration. *Journal of neurobiology*. 2001;49(3):245-53. Epub 2001/12/18.

- [207] Pavlides C, Watanabe Y, McEwen BS. Effects of glucocorticoids on hippocampal long-term potentiation. *Hippocampus*. 1993;3(2):183-92. Epub 1993/04/01.
- [208] Novati A, Hulshof HJ, Koolhaas JM, Lucassen PJ, Meerlo P. Chronic sleep restriction causes a decrease in hippocampal volume in adolescent rats, which is not explained by changes in glucocorticoid levels or neurogenesis. *Neuroscience*. 2011;190:145-55. Epub 2011/07/02.
- [209] Mirescu C, Peters JD, Noiman L, Gould E. Sleep deprivation inhibits adult neurogenesis in the hippocampus by elevating glucocorticoids. *Proceedings of the National Academy of Sciences of the United States of America*. 2006;103(50):19170-5. Epub 2006/12/01.
- [210] Tartar JL, Ward CP, McKenna JT, Thakkar M, Arrigoni E, McCarley RW, et al. Hippocampal synaptic plasticity and spatial learning are impaired in a rat model of sleep fragmentation. *The European journal of neuroscience*. 2006;23(10):2739-48. Epub 2006/07/05.
- [211] Zobel A, Jessen F, von Widdern O, Schuhmacher A, Hofels S, Metten M, et al. Unipolar depression and hippocampal volume: impact of DNA sequence variants of the glucocorticoid receptor gene. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*. 2008;147B(6):836-43. Epub 2008/02/21.
- [212] Janssen J, Hulshoff Pol HE, de Leeuw FE, Schnack HG, Lampe IK, Kok RM, et al. Hippocampal volume and subcortical white matter lesions in late life depression: comparison of early and late onset depression. *Journal of neurology, neurosurgery, and psychiatry*. 2007;78(6):638-40. Epub 2007/01/11.
- [213] McKinnon MC, Yucel K, Nazarov A, MacQueen GM. A meta-analysis examining clinical predictors of hippocampal volume in patients with major depressive disorder. *Journal of psychiatry & neuroscience : JPN*. 2009;34(1):41-54. Epub 2009/01/07.
- [214] Li CT, Lin CP, Chou KH, Chen IY, Hsieh JC, Wu CL, et al. Structural and cognitive deficits in remitting and non-remitting recurrent depression: a voxel-based morphometric study. *NeuroImage*. 2010;50(1):347-56. Epub 2009/11/26.
- [215] Cheng YQ, Xu J, Chai P, Li HJ, Luo CR, Yang T, et al. Brain volume alteration and the correlations with the clinical characteristics in drug-naïve first-episode MDD patients: a voxel-based morphometry study. *Neuroscience letters*. 2010;480(1):30-4. Epub 2010/07/03.
- [216] Cole J, Costafreda SG, McGuffin P, Fu CH. Hippocampal atrophy in first episode depression: a meta-analysis of magnetic resonance imaging studies. *Journal of affective disorders*. 2011;134(1-3):483-7. Epub 2011/07/13.
- [217] Kronmüller KT, Schröder J, Kohler S, Gotz B, Victor D, Unger J, et al. Hippocampal volume in first episode and recurrent depression. *Psychiatry research*. 2009;174(1):62-6. Epub 2009/10/06.

- [218] Sexton CE, Mackay CE, Ebmeier KP. A Systematic Review and Meta-Analysis of Magnetic Resonance Imaging Studies in Late-Life Depression. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry*. 2012. Epub 2012/03/03.
- [219] Geerlings MI, Brickman AM, Schupf N, Devanand DP, Luchsinger JA, Mayeux R, et al. Depressive symptoms, antidepressant use, and brain volumes on MRI in a population-based cohort of old persons without dementia. *Journal of Alzheimer's disease : JAD*. 2012;30(1):75-82. Epub 2012/03/02.
- [220] Steffens DC, McQuoid DR, Payne ME, Potter GG. Change in hippocampal volume on magnetic resonance imaging and cognitive decline among older depressed and nondepressed subjects in the neurocognitive outcomes of depression in the elderly study. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry*. 2011;19(1):4-12. Epub 2010/09/03.
- [221] Chu CL, Liang CK, Chou MY, Lin YT, Pan CC, Lu T, et al. Decreased plasma brain-derived neurotrophic factor levels in institutionalized elderly with depressive disorder. *Journal of the American Medical Directors Association*. 2012;13(5):434-7. Epub 2011/09/29.
- [222] Nifosi F, Toffanin T, Follador H, Zonta F, Padovan G, Pigato G, et al. Reduced right posterior hippocampal volume in women with recurrent familial pure depressive disorder. *Psychiatry research*. 2010;184(1):23-8. Epub 2010/09/08.
- [223] Boccardi M, Almici M, Bresciani L, Caroli A, Bonetti M, Monchieri S, et al. Clinical and medial temporal features in a family with mood disorders. *Neuroscience letters*. 2010;468(2):93-7. Epub 2009/10/31.
- [224] Ansell EB, Rando K, Tuit K, Guarnaccia J, Sinha R. Cumulative adversity and smaller gray matter volume in medial prefrontal, anterior cingulate, and insula regions. *Biological psychiatry*. 2012;72(1):57-64. Epub 2012/01/06.

IntechOpen