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Review

Dysfunctional hippocampal activity affects emotion and cognition in mood disorders

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ABSTRACT

Mood disorders, such as major depressive disorder (MDD), bipolar disorder and generalized anxiety disorder usually comprise mood related as well as cognitive symptoms and the interaction between these symptoms is still not clear. Most antidepressant drugs have a positive effect on mood but do not treat the cognitive dysfunctions or even aggravate the symptoms. In this review we will evaluate the association between mood and cognition in the context of mood disorders. In the first section we will summarize the brain circuits at the intersection between cognition and emotion, highlighting the role of the hippocampus. In the second section, we will survey the contribution of the glutamate and GABA systems in the pathophysiology of mood disorders, making an effort to understand the link between emotions and cognition and how novel therapeutic approaches deal with them. In the third section we will explore the monoamine involvement in the emotion/cognition duality in the context of mood disorders. Finally we will underline the role of synaptic plasticity and neurogenesis in depression. We consider that a broader knowledge about the integrative mechanisms involved in specific aspects of mood disorders is crucial in the development of more powerful and effective antidepressant drugs.

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1. Introduction

Mood disorders, such as major depressive disorder (MDD), bipolar disorder and generalized anxiety disorder, implicate brain systems involved in the regulation of several psychological functions, from affective states (mood, anxiety, fear, reward processing and motivation) to cognition (attention, problem solving and memory), as well as stress responses and neurovegetative functions. So far, the presence of cognitive impairment in these affective disorders suggests that brain structures responsible for emotional expressions and cognitive functions are linked to each other, but how cognitive and depressive symptoms are related is still not clear. Originally, the assumption was that cognitive deficits were a consequence of the depressed state (Beck, 1967), thus by treating depressive symptoms with traditional antidepressants (monoamine based-drugs) cognitive deficits would disappear. Most of the antidepressants however, while having a positive effect on mood, do not treat the accompanied cognitive dysfunctions or even aggravate the symptoms. Tricyclic antidepressants (TCAs) impair cognition because of their anticholinergic, antiadrenergic and antihistaminergic properties (Riedel et al., 1995) and most selective serotonin reuptake inhibitors (SSRIs) tend to impair vigilance (Schmitt et al., 2002). These findings suggest that in depressive syndrome, cognitive deficits exist independent of depressive mood (Austin et al., 2001). However, some antidepressants have been shown to improve both emotional and cognitive deficits in MDD patients. For example, moclobemide, a MAO-A inhibitor, is considered a cognition-enhancing antidepressant in elderly depressed patients (Anand et al., 2005; Ramaekers et al., 1994) while reboxetine, a norepinephrine reuptake inhibitor (NRI) has also been shown to have positive effects on cognition (Ferguson et al., 2003).

2. The hippocampus and connected brain areas in mood disorders

In recent years, an increasing number of neuroimaging, neuropathological and lesion studies have sought to identify the brain anomalies associated with mood disorders. A challenge currently facing the field is to assimilate the large and growing body of data to understand the neural circuitry underlying these disorders. Neuroimaging studies have demonstrated volume reduction of several brain structures in mood disorders, such as cingulate cortex, prefrontal cortex, striatum, hippocampus and amygdala. On the other hand, consistently with an elevated stimulation of the hypothalamic–pituitary–adrenal axis observed in depression, the pituitary and adrenal glands appear increased in patients with MDD. Although these different areas have been associated with specific aspects of mood disorders, it is likely that the interaction and connectivity per se are key factors for keeping mood stability and cognitive integrity (Fig. 1). Thus, a complete dissection of the circuits is probably not relevant. Instead we need to consider the integrated function of these circuits.

2.1. *The hippocampus*

The hippocampus is one of the most highly connected areas of the brain, and although it has traditionally been considered the "memory area", the hippocampus has started to emerge as a brain integrator of emotion and cognition (Small et al., 2011). This idea is reinforced by findings of reduced hippocampal volume in several mood disorders, especially in MDD (Campbell et al., 2004; Stockmeier et al., 2004; Videbech and Ravnkilde, 2004). Structural MRI studies in elderly and young adult depressed patients has reported that volume reduction of the hippocampus correlates with the duration of illness (Bell-McGinty et al., 2002; MacQueen et al., 2003) and decrease in hippocampal gray matter over a three-year period with MDD (Frodl et al., 2008). Together with these structural changes, abnormal hippocampal functioning has been associated with cognitive impairment in depressed patients (Bremner et al., 2004; Deckersbach et al., 2006). In addition, in patients with MDD, Gould et al. (2007) found impaired spatial memory during a navigation task based on virtual reality, a task previously showed to reflect hippocampal activation (Maguire et al., 1998; Tsigos and Chrousos, 2002) and to be impaired after hippocampal damage (Spiers et al., 2001a, 2001b). More recently, using a similar virtual reality spatial navigation task, a functional study found abnormal theta activity of right anterior hippocampus and parahippocampal cortices in depressed patients compared to healthy subjects (Cornwell et al., 2010). However, not only cognitive aspects of depression have been associated with the hippocampus. Using a rodent model of depression, Airan et al. (2007) documented increased neural transmission in the CA1 hippocampal area that was decreased with administration of the antidepressant imipramine (TCAs). Accordingly, recent

published data from our lab using electrophysiological tools on a genetic rat model of depression (the Flinders Sensitive Line, FSL) (Overstreet et al., 2005) have reported increased basal glutamatergic transmission in the CA1 area of the hippocampus compared to control rats (Gómez-Galán et al., in press). One aspect that may contribute to the hippocampal dysfunction in mood disorders is the particular sensitivity of the hippocampus to glucocorticoids (Hoschl and Hajek, 2001; McEwen, 2007). Although stress is a protective mechanism of adaptation to threatening situations, chronic stress progressively leads to pathological states like anxiety disorders or depression and negatively influences cognitive performance (Conrad et al., 1996; Luine et al., 1994). In fact, one of the most commonly used animal models of depression is the chronic mild stress model (CMS) (Willner et al., 1992).

2.2. *The HPA axis*

The hypothalamic–pituitary–adrenal (HPA) axis is the major neuroendocrine system that controls reactions to stress and regulates many body processes, including mood and emotions. The HPA axis, in response to stressful stimuli, releases corticotrophin-releasing hormone (CRH) from the paraventricular nucleus of the hypothalamus, which in turn acts on pituitary gland stimulating the release of adrenocorticotropin (ACTH) into the circulation. Glucocorticoids are secreted from the adrenal gland under ACTH control. A negative feedback mediated by glucocorticoids on the hypothalamus, pituitary and higher brain centers ensures the equilibrium of the system (Kellendonk et al., 2002; Tsigos and Chrousos, 2002).

The hippocampus is one of the neuronal targets of the HPA axis through glucocorticoid action (Herman et al., 1989) and increased hippocampal levels of glucocorticoids have a negative effect on learning (Bodnoff et al., 1995; Diamond et al., 1994). Given the fact that glucocorticoids compromise hippocampal neuronal survival and that depressive disorders are associated with sustained hyperactivity of the HPA axis and increased glucocorticoids levels (Pariante and Miller, 2001; Vreeburg et al., 2009), it has been suggested that dysfunction of the HPA axis might be responsible for the smaller hippocampal volume observed in patients with MDD (Vreeburg et al., 2009). Furthermore, antidepressant-like effects have been shown after administration of CRH-R1 antagonists in animal models of depression (Chaki et al., 2004; Overstreet and Griebel, 2004; Overstreet et al., 2004). It is clear that both hippocampal morphology changes and impaired HPA activity are key features associated to mood disorders, however the exact mechanism of interaction between these two aspects remains to be elucidated.

2.3. *The amygdala*

The amygdala, a limbic structure related to emotional behavior, is popularly referred to as the fear center of the brain. In humans, bilateral amygdala lesions entail deficits in the recognition of fearful expressions and, conversely, fearful faces evoke robust responses in the amygdala, as shown in neuroimaging studies (Davis et al., 1997; LeDoux, 1998). The amygdala is however involved in more than evoking fear. Activation of the amygdala by different stimuli, such as stress or emotional arousal, strengthens the storage of different kinds of information through the amygdala widespread network of efferent projections to other brain regions such as the prefrontal cortex (PFC) and the hippocampus (Kim et al., 2011; Pikkarainen et al., 1999; Salzman and Fusi, 2010). Intense emotional events or chronic exposure to stressful experiences can create traumatic memories and even result in the development of mood and anxiety disorders, including post-traumatic stress disorder (PTSD) and MDD (McEwen, 1998, 2007; Roozendaal et al., 2009). In fact, neuroimaging studies in depressed patients have revealed increased activity of the amygdala during emotion face recognition task compared to healthy subjects (Peluso et al., 2009; Sheline et al., 2001). Studies in animal models indicate that acute and chronic stress induced long-term functional and morphological alterations in specific amygdala nuclei accompanied by hippocampal morphology alterations. It has been proposed that these changes might underlie the cognitive impairments, anxiety-like behavior and mood alterations observed after stress (Roozendaal et al., 2009).

2.4. *The prefrontal cortex*

Dysfunction of the prefrontal cortex (PFC) is a central feature of many psychiatric disorders. Decreased neuronal and glia density (Rajkowska et al., 2001) and altered functioning have been described in PFC in MDD as well as in PTSD (Liberzon and Phan, 2003; Pizzagalli et al., 2004) and fMRI-studies show reduced activity in PFC in MDD that is reversed when depressive state has remitted (Drevets, 2000; Samuelson, 2011). In healthy humans, PFC is consistently reported to be involved in memory storage and in several emotional aspects, including reward (Gamo and Arnsten, 2011). In fact, functional interactions between the amygdala and PFC mediate emotional influences over cognitive processes, such as decision-making, and cognitive regulation of emotion (Salzman and Fusi, 2010). Several associations between clinical features of MDD and PFC dysfunction have been found. For example, characteristic activity patterns recorded in PFC of depressed patients correlate with the observed sadness, psychomotor retardation, anxiety and impaired episodic memory (Brody et al., 2001a, 2001b). Supporting the implication of PFC in mood and emotional disorders, repetitive transcranial magnetic stimulation on this area has antidepressant-like effects on depressed patients (Schutter and van Honk, 2005). Moreover, the study of time-directed associations of brain areas activity in depressed patients has shown that hippocampus activation predicts a decrease of activity in dorsolateral PFC (DLPFC) (Hamilton et al., 2011). It has been suggested that this strengthened inhibition of DLPFC from the hippocampus might impair PFC-accumbens connectivity (O'Donnell and Grace, 1995), resulting in an impairment of the striatal dopamine system that might be related to the emergence of anhedonia in depression (Hamilton et al., 2011).

3. Glutamate and GABA in cognitive and emotional symptoms

3.1. *Regulation of glutamate transmission*

Glutamate is the major excitatory synaptic neurotransmitter in the central nervous system (CNS) (McEntee and Crook, 1993).

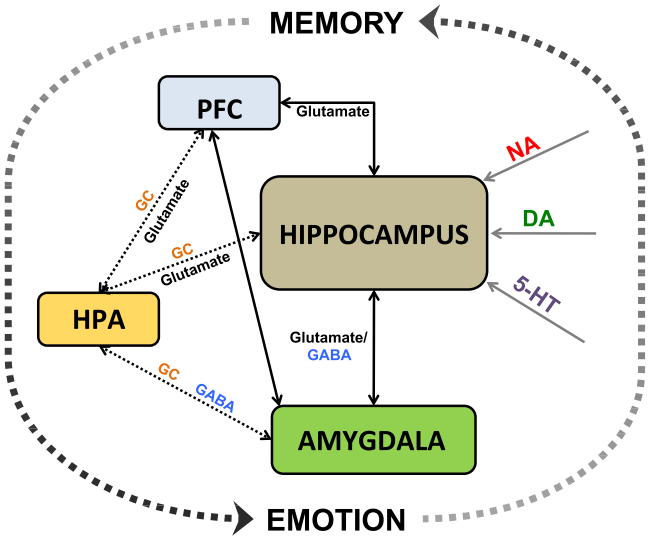

Fig. 1 – Graphical abstract illustrating the hippocampal connections with other regions of the brain that are implicated in processing memory and emotions in mood disorders. Pointed arrows represent GABAergic and glutamatergic afferents to the paraventricular nucleus of the hypothalamic–pituitary–adrenal axis as well as the main targets of the glucocorticoid innervation. Black arrows represent reciprocal glutamatergic/GABAergic innervations between PFC, AMY and hippocampus. Gray arrows show monoaminergic innervation of the hippocampus. NA, noradrenaline; DA, dopamine; 5-HT, serotonin; GC glucocorticoids. PFC, prefrontal cortex; HPA, hypothalamic–pituitary–adrenal axis.

Recently, attention has focused on problems in CNS glutamatergic system in depression (Hashimoto, 2009; Kondo et al., 2011; Tokita et al., 1996) with clinical studies reporting glutamatergic abnormalities in plasma, serum, cerebrospinal fluid and brain tissue of depressed patients (for review, see Sanacora et al., 2008).

At the presynaptic terminal, glutamate is packed into synaptic vesicles by vesicular glutamate transporters (vGlut 1–3) to be released into the synapse. Upon release, glutamate exerts its action through binding to and activating two classes of specific receptors: ionotropic (AMPA, NMDA and kainate receptors) and metabotropic (mGluRs: Groups I, II and III). Glutamate is cleared from the extracellular space via high-affinity excitatory amino acid transporters (EAATs) located in the membrane of neighboring glial cells (EAAT1–2) or on neurons (EAAT3–4). In the glia (primarily in astrocytes) glutamate is converted into glutamine via the action of glutamine synthetase (GS). Glutamine is then transported back into the glutamatergic neuron, where it is hydrolyzed by glutaminase back into glutamate. Abnormalities at any step in the regulation of glutamate transmission will affect the efficiency of the system (Fig. 2).

Clinical studies have shown alterations of glutamate regulation at different brain regions in patients with MDD. For example, decreased EAAT1 and EAAT2 have been found in the cerebral cortex (Choudary et al., 2005) and locus coeruleus (LC) of depressed patients (Bernard et al., 2010). This might be relevant since glutamate transporters are crucial for the maintenance of synaptic glutamate concentration and thereby protect neurons and glia from glutamate excitotoxicity. More recently, a genome-wide association study revealed SLC6A15, a neuron-specific neutral amino acid transporter, as a susceptibility gene for MDD (Kohli et al., 2011). Besides its role in neuronal amino acid transport, SLC6A15 is presumably involved in glutamate synthesis (Broer et al., 2006) and has an important role in the regulation of glutamate transmission (Tapiero et al., 2002).

Supporting the role of EAAT1 and EAAT2 in depression, blockade of these transporters induces anhedonia in rats (Bechtholt-Gompf et al., 2010) while reduced expression of the vesicular glutamate transporter 1 (VGlut1) increases vulnerability to depressive-like behavior in mice (Garcia-Garcia et al., 2009; Tordera et al., 2007). Recently, using a rat model of depression (the FSL) our lab has found reduced expression levels of hippocampal EAAT1 and, possibly related to that, increased glutamate neurotransmission in CA1 pyramidal cells (Gómez-Galán et al., in press). Interestingly, all these animal studies, including ours, have reported hippocampal-memory deficits accompanying the depressive-like behavior. Using the CMS paradigm many laboratories have suggested discrete yet potentially interacting mechanisms in the genesis of glutamatergic abnormalities (Pittenger and Duman, 2008). These mechanisms include neuroplasticity (Santarelli et al., 2003), neurogenesis (Berton and Nestler, 2006; Tsankova et al., 2006) and dysfunctional astrocytic regulation of glutamate transmission (McNally et al., 2008; Sanacora et al., 2003) and they have all been associated with memory deficits (Bruel-Jungerman et al., 2007; Fonken et al., 2011).

3.2. *Antidepressant drugs targeting glutamate transmission*

Several classes of glutamatergic drugs possess antidepressant properties. Ketamine for example, has anxiolytic and antidepressant-like effects in animal models (Engin et al., 2009) and more importantly, it has a fast-acting antidepressant effect in patients suffering from MDD (Berman et al., 2000; Price and Drevets, 2010; Zarate et al., 2006). Ketamine is an uncompetitive

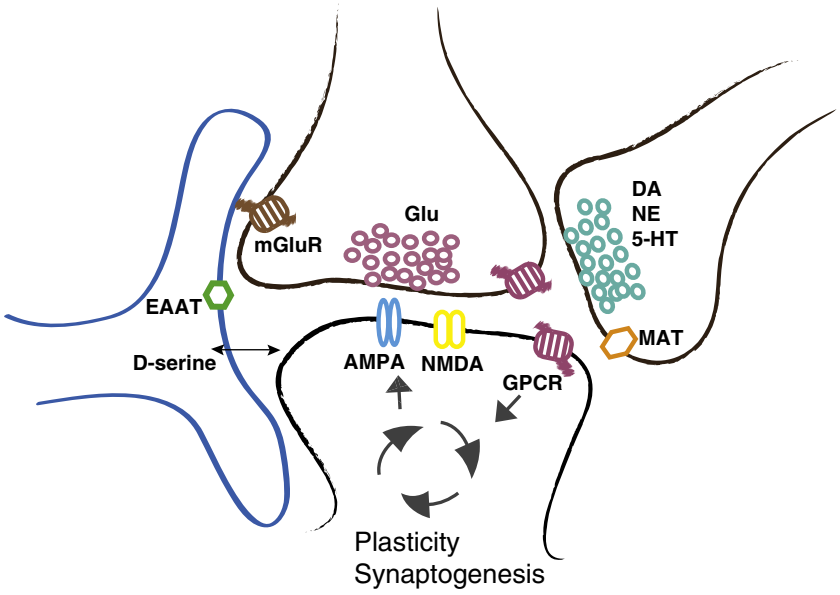

Fig. 2 – Schematic representation of glutamate transmission regulation (above, pre-synaptic terminal; below, post-synaptic bouton), with an astrocytic process (in blue, on the left) and monoaminergic modulation (on the right). Astrocytes regulate transmission through glutamate reuptake and D-serine release whereas monoamines can modulate synaptic strength by activating intracellular signaling cascades through G-protein coupled receptors either pre- or postsynaptically. EAAT: excitatory amino acid transporter; mGluR: metabotropic glutamate receptor; Glu: glutamate; AMPA and NMDA: glutamate receptors; GPCR: G-protein coupled receptors; DA: dopamine; NE: noradrenaline; 5-HT: serotonin; MAT: monoamine transporter.

NMDA receptor antagonist widely used for the induction and maintenance of general anesthesia. One proposed mechanism of action for ketamine is through activation of the brain-derived neurotrophic factor (BDNF) in an activity-dependent way (Autry et al., 2011). In healthy humans, acute and chronic administration of ketamine impairs episodic memory, semantic processing and manipulation, but not maintenance of working memory (for review, see Morgan and Curran, 2006). However, the effect of ketamine on the neurocognitive dysfunctions associated with depression, especially on hippocampal-dependent memory, has not been explored yet in the context of depression, but it will help to discern the relationship between mood and cognition in mood disorders.

As an alternative to ketamine, riluzole, a drug used for the treatment of amyotrophic lateral sclerosis, has been proven to have antidepressant properties (Sanacora et al., 2007; Zarate et al., 2004, 2005). Riluzole reduces glutamate release (Doble, 1996) as well as increases glutamate reuptake by enhancing the activity of EAAT1/EAAT2 (Fumagalli et al., 2008). At the cognitive level, riluzole has been reported to reduce memory loss and hippocampus damage in gerbils subjected to a forebrain ischemia (Malgouris et al., 1989). However, the effect of riluzole on the cognitive dysfunctions associated with mood disorders has not been analyzed yet.

3.3. *GABA system in mood disorders*

As a variant of the glutamate hypothesis of depression, it has been proposed that the balance between the inhibition and excitation is important for both emotional and cognitive health. Clinical studies have reported reduced GABA levels in the plasma and cerebrospinal fluid of depressed patients (Gerner and Hare, 1981; Petty and Schlesser, 1981; Petty and Sherman, 1984). In addition, genetic studies in MDD patients have reported changes in gene expression levels and subunit composition of GABA-A receptors, perhaps reflecting a compensatory mechanism due to the low GABA levels associated with depression. For example, in post-mortem studies from depressed versus non-depressed suicide victims, reductions in the expression of GABA alpha1, 3, 4 and delta subunit mRNAs, or increased expressions of alpha5, gamma2, and delta subunit mRNAs were found in the frontopolar cortex and in the DLPFC, respectively; a selective up-regulation of alpha5 mRNA was also found in the anterior cingulate cortex (for review see Luscher et al., 2011). All of these regions of the cortico-limbic system are critically involved in MDD (Seminowicz et al., 2004). Interestingly, GABA-A receptor containing alpha5 subunit is highly expressed in the hippocampus and cingulate cortex (Pirker et al., 2000). In the last years several studies have pointed to selective alpha5-inverse agonists as therapeutic agents for cognitive impairment (Atack, 2011; Gabriella and Giovanna, 2010). Indeed, mice with targeted deletion of the alpha5 subunit showed higher memory performance in several behavioral tasks, such as fear conditioning and water maze (Collinson et al., 2002; Crestani et al., 2002). Another GABA subunit important for mood disorders is the gamma subunit. The heterozygous GABA-A receptor gamma-subunit knockout mice display anxiety and depressive-like behavior accompanied with cognitive

deficits (for review see Luscher et al., 2011). These knockout mice also present elevated baseline corticosterone concentrations, a key feature in MDD (Shen et al., 2010). Benzodiazepines (BZDs) are classical drugs mainly prescribed for anxiolysis, sedation, seizure suppression and muscle relaxation that act on the GABA-A receptor potentiating the inhibitory effects of GABA. Studies in MDD patients have revealed that the BZDs alprazolam and adinazolam elicit antidepressant effects similar to widely prescribed antidepressants (Jonas and Hearron, 1996; Remick et al., 1988). A major problem with BZDs in their use as antidepressants is the central sedative effect due to their affinity for the alpha1 subunit of GABA-A receptor (for review see Rudolph and Knoflach, 2011) and the development of BZDs dependence (Tan et al., 2011). In the last years several drugs have been developed to act selectively on alpha2/alpha3 subunits, showing non-sedating anxiolytic properties (for review see Atack, 2010; Rudolph and Knoflach, 2011). The use of selective α_2/α_3 GABA-A receptor modulators, such as TPA023, as novel antidepressants is currently a matter of study (for review see Mohler, 2012).

3.4. *Stress and glucocorticoids regulating glutamate and GABA transmission*

The glutamate/GABA balance can be affected by increased glucocorticoid levels caused by stress. Long-term treatment with corticosterone induces depressive-like behavior and memory deficits (Patten et al., 1996). Moreover, long-term exposure to corticosterone modulates the levels of several proteins regulating glutamate and GABA transmission in the hippocampus. In rats, chronic corticosterone administration decreased the protein levels of hippocampal metabotropic glutamate receptor 5 (mGluR5) (Iyo et al., 2010) in line with neuroimaging studies showing reduced mGluR5 in MDD (Deschwanden et al., 2011). Moreover, in rodents, early-life stress (such as maternal separation) induces depressive-like behavior that persists until senescence. This behavior is accompanied by long lasting effects on the expression levels of several hippocampal proteins involved in the glutamate/GABA cycling, such as glutamate and GABA transporters (EAAT1–2, VGluT1–2 and vesicular GABA transporter (vGAT)) and NMDA receptors (Martisova et al., 2012). In addition, corticosterone acutely affects glutamate transmission acting both pre- and postsynaptically (Karst et al., 2005). The postsynaptic effect is proposed to occur through increased trafficking of GluR2 to the surface (Groc et al., 2008).

4. Monoaminergic modulation of mood and memory

4.1. *The monoamine hypothesis of depression*

The monoamine hypothesis of depression came from the observation that drugs affecting the monoaminergic system have an effect on mood. Originally it was assumed that a deficiency in the noradrenergic and serotonergic systems might account for depressive states (Duman et al., 1997; Hirschfeld, 2000; Owens, 2004). Monoamines provide for the so-called slow neurotransmission, as they activate G-protein coupled receptors (GPCRs) and lead to intracellular events that affect the fast synaptic transmission of glutamate and GABA. The monoaminergic system is widely spread throughout the brain and underlies several psychological functions such as cognition and learning processes, arousal, mood and reward (Arnsten and Pliszka, 2011; Canli and Lesch, 2007; Nieoullon and Coquerel, 2003). Therefore, it is not surprising that alterations found in the monoamine system in several psychiatric or neurological diseases may underlie symptoms related to different areas, from mood and reward to attention, cognition and memory. Surely the monoaminergic systems are involved in the therapeutic effect of most antidepressants, but the specific role in the pathophysiology of depression is still unclear. For example, the prevalence of residual symptoms after monoamine-based antidepressant treatment and the high percentage of MDD patients resistant to antidepressant therapy point to the involvement of other neuromodulators. This is particular evident when looking at cognitive symptoms. Tetracyclic antidepressants (TECAs), such as mianserine, and the classic TCAs, such as desipramine, typically exert detrimental effects on declarative memory function (Gorenstein et al., 2006; van Laar et al., 2002; Wingen et al., 2006) while SSRIs, such as sertraline, paroxetine or citalopram, can assert different effects on declarative memory depending on their specific pharmacological profile. Interestingly, compared to SSRI treated-group, two clinical studies showed better efficacy on memory function for duloxetine and reboxetine, a combined serotonin and noradrenaline reuptake inhibitor (SNRI) and a NRI, respectively (Ferguson et al., 2003; Herrera-Guzman et al., 2009).

4.2. *Dopamine behind emotional and cognitive symptoms*

Besides the importance of the serotonergic and noradrenergic systems in mood disorders, increased attention has been given to the role of dopamine (Dunlop and Nemeroff, 2007; Nutt, 2006). Human pathologies and animal model of diseases such as Parkinson's disease (PD), mainly characterized by dopamine system degeneration, offer indirect evidences about the dopaminergic involvement at the intersection between mood and cognition (Dunlop and Nemeroff, 2007; Nieoullon and Coquerel, 2003). In PD, motor symptoms are usually paired with cognitive impairments (Kulisevsky and Pagonabarraga, 2009), with the cognitive symptoms being related to the stage of the disease (Aarsland et al., 2003; Liu et al., 2011). Furthermore, in these patients memory deficits are often associated with both apathy and depression (Butterfield et al., 2010; Ishihara and Brayne, 2006; Martinez-Martin and Damian, 2010; Varanese et al., 2011), suggesting a common pathogenetic mechanism for mood, motor and cognitive disturbances. Indeed, dopamine is well-known to be involved in both anhedonia (among the major symptoms of depression) (Dailly et al., 2004; Gorwood, 2008) and cognitive functions linked to behavioral reinforcement and learning processes. For example, dopamine has been proposed to provide a novelty-evoked reinforcement signal to the hippocampus, facilitating the storage of new memories (Lisman and Grace, 2005). It is possible that the dual characteristic played by dopamine represents a critical stage in the genesis of mood and cognitive symptoms in depression. In fact, ongoing work in our lab points to an involvement of dopamine in the beneficial effect of SNRI on cognition. Finally, it has been shown

that exposure to single unavoidable and uncontrollable aversive experience inhibits dopamine release in the nucleus accumbens and impairs the response to reward and aversive stimuli (Cabib and Puglisi-Allegra, 1996). Thus, the involvement of the dopamine system in response to stress may mediate the effect of stressful life events in exacerbating some depressive symptoms. Reinforcing the role of dopamine in cognition, a study proposed the "correlative triad among age, dopamine and cognition" (Backman et al., 2006), in which age is accompanied by reduction of dopamine biomarkers throughout the brain (dopamine D1 and D2 receptors and dopamine transporters) and with a physiological decline of several cognitive functions in multiple areas (episodic memory, executive functions and working memory, speed and efficiency of processing). Thus dopamine provides an interesting target for the emotional and cognitive symptoms of depression.

5. Synaptic plasticity in mood disorders

5.1. *Morphological and functional plasticity alterations in depression*

Plasticity, both morphological and functional, is crucial for memory storage (Neves et al., 2008). In addition, decreased plasticity has also been proposed to increase the threshold for adaptation (Krishnan and Nestler, 2008) making the individual more vulnerable to negative input (Gotlib and Joormann, 2010). Short- and long-term morphological changes are explored as mechanisms affected in mood disorders. Reduced spine and synapse density has been shown in post-mortem studies of depressed patients (Rosoklija et al., 2000) as well as in animal models (Chen et al., 2010), and these features are restored with antidepressants (Li et al., 2010). BDNF, a trophic factor important for the rearrangement of synapses, is consistently decreased in the serum of depressed patients, and importantly, its levels increase in response to antidepressant medication (Castrén et al., 2007; Matrisciano et al., 2009; Sen et al., 2008; Shimizu et al., 2003). Recently, activity-dependent BDNF synthesis has also been proposed as a possible mechanism for the antidepressant effect of ketamine (Autry et al., 2011). In addition to the morphological connectivity, the functional connectivity of synapses (i.e. synaptic plasticity) is also affected in depression (Bessa et al., 2009). For example, attenuation of LTP (long term potentiation) is observed in the hippocampal CA1 area of FSL rats (Ryan et al., 2009) and enhancement of CA1-LTD (long term depression) in rats after CMS (Holderbach et al., 2007).

5.2. *Plasticity related to cognitive and mood impairments*

The well-known role of plasticity in memory and its proposed role in depression raise several questions regarding this mechanism. For example, are the cognitive disturbances observed in depressed patients an epiphenomenon caused by the alterations of the brain circuits controlling the emotions? Or do they occur through independent mechanisms? In our study using the FSL depression model we could dissociate the synaptic origins of cognitive deficits from depression-related deficits (Gómez-Galán et al., in press). We confirmed the prominent reduction in LTP in CA1 pyramidal cells (Ryan et al., 2009) and we showed that these rats display cognitive deficit. Interestingly, FSL rats presented decreased hippocampal D-serine levels. D-serine is an amino acid mainly released by astrocytes with high affinity for the glycine-binding site on the NR1 NMDA receptor subunit (Mothet et al., 2000) and has been proven to be necessary for hippocampal LTP (Henneberger et al., 2010). When we treated FSL rats with acute and chronic D-serine we rescued the LTP phenotype as well as the cognitive deficit, but not the depressive-like symptoms in the forced swim test (Gómez-Galán et al., in press). Thus, in our study we suggested that decreased hippocampal D-serine levels in FSL rats might serve as a safety mechanism to prevent NMDA receptor over-activation caused by the increased hippocampal glutamate transmission (observed as an increase in the spontaneous excitatory transmission). Although this mechanism might protect the brain against toxicity it is apparently not the cause for the characteristic depressive-symptoms of FSL rats. Nevertheless, another paper has recently reported an antidepressant effect after acute D-serine treatment in a stress-sensitive strain of rats (Wistar Kyoto (WKY)) (Malkesman et al., 2011). Malkesman et al. suggested that the antidepressant-like effect of D-serine is mediated by the activation of the NR1 subunit of NMDA receptors. Thus, the role of D-serine in depression and the role for plasticity in emotional symptoms are still not clarified.

5.3. *Antidepressant modulation of plasticity*

The theory that synaptic plasticity is involved in depression is reinforced by the fact that antidepressant drugs as well as electroconvulsive therapy effectively modulate synaptic plasticity in the dentate gyrus (DG) and CA1 subfields of the hippocampus and in other areas of the brain (De Murtas et al., 2004; Stewart and Reid, 2000; Vetencourt et al., 2008; Von Frijtag et al., 2001). However, the effect of antidepressants on LTP is not clear and depends on drug class as well as the protocol of stimulation. In the last decade, testing different antidepressants on normal rats (TCA, SSRI and SNRI), some studies have shown reduced hippocampal LTP after antidepressant treatment (Cooke et al., 2009; Petrie et al., 2000). However, other studies have evaluated the antidepressant effect on hippocampal LTP using different animal models of depression. For instance, escitalopram restored CA1-LTP and monoamine levels in neonatal clomipramine-exposed rats (Bhagya et al., 2011). Additionally, the negative effects of acute stress on synaptic plasticity (Calabrese et al., 2009; Pittenger and Duman, 2008) were counteracted with tianeptine, a selective serotonin reuptake enhancer (SSRE) without altering the stress-induced increase of corticosterone levels (Campbell et al., 2008). Finally, given the interest of dopaminergic drugs as potential antidepressants, it is worth noting the role of dopamine in regulating hippocampal synaptic plasticity during the storage of new information in the CA1 area. In the hippocampus, persistent LTP and LTD need the simultaneous release of glutamate and dopamine receptor activation (Frey et al., 1990) while in rodents the exposure to a novel environment facilitates the induction of in vivo LTP in CA1 hippocampal synapses and, significantly, this feature can be prevented by dopamine D1/D5 receptor blocker (Li et al., 2003).

6. Neurogenesis

In addition to synaptic plasticity, neuronal networks can be modified through neurogenesis. This is particularly true in the hippocampus, one of the few areas where neurogenesis occurs in the adult brain. In the last decade, studies in animal models have shown that neurogenesis is necessary for the antidepressant action of different drugs (Airan et al., 2007; Jiang et al., 2005; Santarelli et al., 2003), but not all the antidepressants require neurogenesis to be effective (Bessa et al., 2009; David et al., 2007; Holick et al., 2008; Meshi et al., 2006). Impaired adult neurogenesis is not an etiological factor for depression since ablation of neurogenesis does not elicit a depression-like or anxiety-like phenotype in rodents (Airan et al., 2007; Santarelli et al., 2003). However, reduction or blockade of neurogenesis in rodents affects fear conditioning, synaptic plasticity in the DG (Saxe et al., 2006), spatial long-term memory and working memory (Winocur et al., 2006). Increasing adult hippocampal neurogenesis by enhancing the survival of adult-born cells in the DG of genetically manipulated mice improves pattern separation without having any anxiolytic or antidepressant-like effect (Sahay et al., 2011). These results leave open the question whether adult hippocampal neurogenesis contributes to the regulation of emotions, although the same authors propose that other antidepressant-dependent modifications of neural circuitry together with the increase in adult hippocampal neurogenesis must be needed to produce the beneficial effects of antidepressants on mood. For example, a study using the CMS model proved that antidepressant action does not depend only on neurogenesis but is also associated with neuronal remodeling in the hippocampus (DG, CA3 and CA1) and PFC, suggesting re-establishment of neuronal plasticity as the basis for mood restoration by antidepressants (Bessa et al., 2009).

7. Implications

Biological processes underlying mood and cognition integrate at multiple anatomical and functional levels—making it impossible to consider them completely unrelated but still providing for some independence. Along the review we have highlighted the role of glutamate in memory as well as emotional symptoms of depression, with an overlapping role of neuromodulators such as monoamines. We have focused mainly on the role of the hippocampus since it is morphologically and functionally affected in mood disorders and it is also clearly linked to memory functions. Despite of that, we argue that targeting the hippocampus is not sufficient to treat all the symptoms associated with a depressive state, supporting the hypothesis of complex circuitry integration at the crosslink between mood and cognition. As an illustration of the importance of keeping the system balanced it is commonly reported that antidepressant drugs lead to memory deficits, and cognitive enhancers can induce anxiety.

Thus, to design treatments for mood disorders we need a deep understanding in how and where this integration occurs. Recent advances in targeted genetic manipulations and optogenetics, making it possible to drive specific pathways, will be important for further experiments. In combination with in vivo studies of network activity in animal models that reproduce specific characteristics of human symptomatology we can gain a better understanding of the interface between cognition and emotion in affective disorders.

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REFERENCES

Aarsland, D., Andersen, K., Larsen, J.P., Lolk, A., 2003. Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. Arch. Neurol. 60, 387–392.

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

Anand, A., Li, Y., Wang, Y., Wu, J., Gao, S., Bukhari, L., Mathews, V.P., Kalnin, A., Lowe, M.J., 2005. Activity and connectivity of brain mood regulating circuit in depression: a functional magnetic resonance study. Biol. Psychiatry 57, 1079–1088.

Arnsten, A.F.T., Pliszka, S.R., 2011. Catecholamine influences on prefrontal cortical function: relevance to treatment of attention deficit/hyperactivity disorder and related disorders. Pharmacol. Biochem. Behav. 99, 211–216.

Atack, J.R., 2010. GABAA receptor alpha2/alpha3 subtype-selective modulators as potential nonsedating anxiolytics. Curr. Top. Behav. Neurosci. 2, 331–360.

Atack, J.R., 2011. GABAA receptor subtype-selective modulators. I. Alpha2/alpha3-selective agonists as non-sedating anxiolytics. Curr. Top. Med. Chem. 11, 1176–1202.

Austin, M.-P., Mitchell, P., Goodwin, G.M., 2001. Cognitive deficits in depression: possible implications for functional neuropathology. Br. J. Psychiatry 178, 200–206.

Autry, A.E., Adachi, M., Nosyreva, E., Na, E.S., Los, M.F., Cheng, P.F., Kavalali, E.T., Monteggia, L.M., 2011. NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. Nature 475, 91–95.

Backman, L., Nyberg, L., Lindenberger, U., Li, S.-C., Farde, L., 2006. The correlative triad among aging, dopamine, and cognition: current status and future prospects. Neurosci. Biobehav. Rev. 30, 791–807.

Bechtholt-Gompf, A.J., Walther, H.V., Adams, M.A., Carlezon Jr., W.A., Ongur, D., Cohen, B.M., 2010. Blockade of astrocytic glutamate uptake in rats induces signs of anhedonia and impaired spatial memory. Neuropsychopharmacology 35, 2049–2059.

Beck, D., 1967. Indication for psychoanalytic short time therapy. Z. Psychosom. Med. Psychoanal. 13, 257–265.

Bell-McGinty, S., Butters, M.A., Meltzer, C.C., Greer, P.J., Reynolds 3rd, C.F., Becker, J.T., 2002. Brain morphometric abnormalities in geriatric depression: long-term neurobiological effects of illness duration. Am. J. Psychiatry 159, 1424–1427.

Berman, R.M., Cappiello, A., Anand, A., Oren, D.A., Heninger, G.R., Charney, D.S., Krystal, J.H., 2000. Antidepressant effects of ketamine in depressed patients. Biol. Psychiatry 47, 351–354.

Bernard, R., Kerman, I.A., Thompson, R.C., Jones, E.G., Bunney, W.E., Barchas, J.D., Schatzberg, A.F., Myers, R.M., Akil, H., Watson, S.J., 2010. Altered expression of glutamate signaling, growth factor, and glia genes in the locus coeruleus of patients with major depression. Mol. Psychiatry 16, 634–646.

Berton, O., Nestler, E.J., 2006. New approaches to antidepressant drug discovery: beyond monoamines. Nat. Rev. Neurosci. 7, 137–151.

Bessa, J.M., Ferreira, D., Melo, I., Marques, F., Cerqueira, J.J., Palha, J.A., Almeida, O.F., Sousa, N., 2009. The mood-improving actions of antidepressants do not depend on neurogenesis but are associated with neuronal remodeling. Mol. Psychiatry 14 (764–73), 739.

Bhagya, V., Srikumar, B., Raju, T., Shankaranarayana Rao, B., 2011. Chronic escitalopram treatment restores spatial learning, monoamine levels, and hippocampal long-term potentiation in an animal model of depression. Psychopharmacology 214, 477–494.

Bodnoff, S.R., Humphreys, A.G., Lehman, J.C., Diamond, D.M., Rose, G.M., Meaney, M.J., 1995. Enduring effects of chronic corticosterone treatment on spatial learning, synaptic plasticity, and hippocampal neuropathology in young and mid-aged rats. J. Neurosci. 15, 61–69.

Bremner, J.D., Vythilingam, M., Vermetten, E., Vaccarino, V., Charney, D.S., 2004. Deficits in hippocampal and anterior cingulate functioning during verbal declarative memory encoding in midlife major depression. Am. J. Psychiatry 161, 637–645.

Brody, A.L., Barsom, M.W., Bota, R.G., Saxena, S., 2001a. Prefrontal–subcortical and limbic circuit mediation of major depressive disorder. Semin. Clin. Neuropsychiatry 6, 102–112.

Brody, A.L., Saxena, S., Mandelkern, M.A., Fairbanks, L.A., Ho, M.L., Baxter, L.R., 2001b. Brain metabolic changes associated with symptom factor improvement in major depressive disorder. Biol. Psychiatry 50, 171–178.

Broer, A., Tietze, N., Kowalczuk, S., Chubb, S., Munzinger, M., Bak, L.K., Broer, S., 2006. The orphan transporter v7-3 (slc6a15) is a Na+-dependent neutral amino acid transporter (B0AT2). Biochem. J. 393, 421–430.

Bruel-Jungerman, E., Rampon, C., Laroche, S., 2007. Adult hippocampal neurogenesis, synaptic plasticity and memory: facts and hypotheses. Rev. Neurosci. 18, 93–114.

Butterfield, L.C., Cimino, C.R., Oelke, L.E., Hauser, R.A., Sanchez-Ramos, J., 2010. The independent influence of apathy and depression on cognitive functioning in Parkinson's disease. Neuropsychology 24, 721–730.

Cabib, S., Puglisi-Allegra, S., 1996. Stress, depression and the mesolimbic dopamine system. Psychopharmacology 128, 331–342.

Calabrese, F., Molteni, R., Racagni, G., Riva, M.A., 2009. Neuronal plasticity: a link between stress and mood disorders. Psychoneuroendocrinology 34 (Supplement 1), S208–S216.

Campbell, S., Marriott, M., Nahmias, C., MacQueen, G.M., 2004. Lower hippocampal volume in patients suffering from depression: a meta-analysis. Am. J. Psychiatry 161, 598–607.

Campbell, A.M., Park, C.R., Zoladz, P.R., Munoz, C., Fleshner, M., Diamond, D.M., 2008. Pre-training administration of tianeptine, but not propranolol, protects hippocampus-dependent memory from being impaired by predator stress. Eur. Neuropsychopharmacol. 18, 87–98.

Canli, T., Lesch, K.-P., 2007. Long story short: the serotonin transporter in emotion regulation and social cognition. Nat. Neurosci. 10, 1103–1109.

Castrén, E., Vıikar, V., Rantamäki, T., 2007. Role of neurotrophic factors in depression. Curr. Opin. Pharmacol. 7, 18–21.

Chaki, S., Nakazato, A., Kennis, L., Nakamura, M., Mackie, C., Sugiura, M., Vinken, P., Ashton, D., Langlois, X., Steckler, T., 2004. Anxiolytic- and antidepressant-like profile of a new CRF1 receptor antagonist, R278995/CRA0450. Eur. J. Pharmacol. 485, 145–158.

Chen, F., Madsen, T.M., Wegener, G., Nyengaard, J.R., 2010. Imipramine treatment increases the number of hippocampal synapses and neurons in a genetic animal model of depression. Hippocampus 20, 1376–1384.

Choudary, P.V., Molnar, M., Evans, S.J., Tomita, H., Li, J.Z., Vawter, M.P., Myers, R.M., Bunney Jr., W.E., Akil, H., Watson, S.J., Jones, E.G., 2005. Altered cortical glutamatergic and GABAergic signal transmission with glial involvement in depression. Proc. Natl. Acad. Sci. U. S. A. 102, 15653–15658.

Collinson, N., Kuenzi, F.M., Jarolimek, W., Maubach, K.A., Cothliff, R., Sur, C., Smith, A., Otu, F.M., Howell, O., Atack, J.R., McKernan, R.M., Seabrook, G.R., Dawson, G.R., Whiting, P.J., Rosahl, T.W., 2002. Enhanced learning and memory and altered GABAergic synaptic transmission in mice lacking the alpha 5 subunit of the GABAA receptor. J. Neurosci. 22, 5572–5580.

Conrad, C.D., Galea, L.A., Kuroda, Y., McEwen, B.S., 1996. Chronic stress impairs rat spatial memory on the Y maze, and this effect is blocked by tianeptine pretreatment. Behav. Neurosci. 110, 1321–1334.

Cooke, J.D., Grover, L.M., Spangler, P.R., 2009. Venlafaxine treatment stimulates expression of brain-derived neurotrophic factor protein in frontal cortex and inhibits long-term potentiation in hippocampus. Neuroscience 162, 1411–1419.

Cornwell, B.R., Salvadore, G., Colon-Rosario, V., Latov, D.R., Holroyd, T., Carver, F.W., Coppola, R., Manji, H.K., Zarate Jr., C.A., Grillon, C., 2010. Abnormal hippocampal functioning and impaired spatial navigation in depressed individuals: evidence from whole-head magnetoencephalography. Am. J. Psychiatry 167, 836–844.

Crestani, F., Keist, R., Fritschy, J.M., Benke, D., Vogt, K., Prut, L., Bluthmann, H., Mohler, H., Rudolph, U., 2002. Trace fear conditioning involves hippocampal alpha5 GABA(A) receptors. Proc. Natl. Acad. Sci. U. S. A. 99, 8980–8985.

Dailly, E., Chenu, F., Renard, C.E., Bourin, M., 2004. Dopamine, depression and antidepressants. Fundam. Clin. Pharmacol. 18, 601–607.

David, D.J., Klemenhagen, K.C., Holick, K.A., Saxe, M.D., Mendez, I., Santarelli, L., Craig, D.A., Zhong, H., Swanson, C.J., Hegde, L.G., Ping, X.I., Dong, D., Marzabadi, M.R., Gerald, C.P., Hen, R., 2007. Efficacy of the MCHR1 antagonist N-[3-(1-{[4-(3, 4-difluorophenoxy)phenyl]methyl}(4-piperidyl))-4-methylphen yl]-2-methylpropanamide (SNAP 94847) in mouse models of anxiety and depression following acute and chronic administration is independent of hippocampal neurogenesis. J. Pharmacol. Exp. Ther. 321, 237–248.

Davis, M., Walker, D.L., Lee, Y., 1997. Roles of the amygdala and bed nucleus of the stria terminalis in fear and anxiety measured with the acoustic startle reflex. Possible relevance to PTSD. Ann. N. Y. Acad. Sci. 821, 305–331.

De Murtas, M., Tatarelli, R., Girardi, P., Vicini, S., 2004. Repeated electroconvulsive stimulation impairs long-term depression in the neostriatum. Biol. Psychiatry 55, 472–476.

Deckersbach, T., Dougherty, D.D., Savage, C., McMurrich, S., Fischman, A.J., Nierenberg, A., Sachs, G., Rauch, S.L., 2006. Impaired recruitment of the dorsolateral prefrontal cortex and hippocampus during encoding in bipolar disorder. Biol. Psychiatry 59, 138–146.

Deschwanden, A., Karolewicz, B., Feyissa, A.M., Treyer, V., Ametamey, S.M., Johayem, A., Burger, C., Auberson, Y.P., Sovago, J., Stockmeier, C.A., Buck, A., Hasler, G., 2011. Reduced metabotropic glutamate receptor 5 density in major depression determined by [(11)C]ABP688 PET and postmortem study. Am. J. Psychiatry 168, 727–734.

Diamond, D.M., Fleshner, M., Rose, G.M., 1994. Psychological stress repeatedly blocks hippocampal primed burst potentiation in behaving rats. Behav Brain Res. 62, 1–9.

Doble, A., 1996. The pharmacology and mechanism of action of riluzole. Neurology 47, S233–S241.

Drevets, W.C., 2000. Functional anatomical abnormalities in limbic and prefrontal cortical structures in major depression. Prog. Brain Res. 126, 413–431.

Duman, R.S., Heninger, G.R., Nestler, E.J., 1997. A molecular and cellular theory of depression. Arch. Gen. Psychiatry 54, 597–606.
Dunlop, B.W., Nemeroff, C.B., 2007. The role of dopamine in the pathophysiology of depression. Arch. Gen. Psychiatry 64, 327–337.
Engin, E., Treit, D., Dickson, C.T., 2009. Anxiolytic- and antidepressant-like properties of ketamine in behavioral and neurophysiological animal models. Neuroscience 161, 359–369.
Ferguson, J.M., Wesnes, K.A., Schwartz, G.E., 2003. Reboxetine versus paroxetine versus placebo: effects on cognitive functioning in depressed patients. Int. Clin. Psychopharmacol. 18, 9–14.
Fonken, L.K., Xu, X., Weil, Z.M., Chen, G., Sun, Q., Rajagopalan, S., Nelson, R.J., 2011. Air pollution impairs cognition, provokes depressive-like behaviors and alters hippocampal cytokine expression and morphology. Mol. Psychiatry 16, 987–995.
Frey, U., Schroeder, H., Matthies, H., 1990. Dopaminergic antagonists prevent long-term maintenance of posttetanic LTP in the CA1 region of rat hippocampal slices. Brain Res. 522, 69–75.
Frodl, T.S., Koutsouleris, N., Bottlender, R., Born, C., Jager, M., Scupin, I., Reiser, M., Moller, H.J., Meisenzahl, E.M., 2008. Depression-related variation in brain morphology over 3 years: effects of stress? Arch. Gen. Psychiatry 65, 1156–1165.
Fumagalli, E., Funicello, M., Rauen, T., Gobbi, M., Mennini, T., 2008. Riluzole enhances the activity of glutamate transporters GLAST, GLT1 and EAAC1. Eur. J. Pharmacol. 578, 171–176.
Gabriella, G., Giovanna, C., 2010. Gamma-aminobutyric acid type A (GABA(A)) receptor subtype inverse agonists as therapeutic agents in cognition. Methods Enzymol. 485, 197–211.
Gamo, N.J., Arnsten, A.F., 2011. Molecular modulation of prefrontal cortex: rational development of treatments for psychiatric disorders. Behav. Neurosci. 125, 282–296.
Garcia-Garcia, A.L., Elizalde, N., Matrov, D., Harro, J., Wojcik, S.M., Venzala, E., Ramirez, M.J., Del Rio, J., Tordera, R.M., 2009. Increased vulnerability to depressive-like behavior of mice with decreased expression of VGLUT1. Biol. Psychiatry 66, 275–282.
Gerner, R.H., Hare, T.A., 1981. CSF GABA in normal subjects and patients with depression, schizophrenia, mania, and anorexia nervosa. Am. J. Psychiatry 138, 1098–1101.
Gómez-Galán, M., De Bundel, D., Van Eeckhaut, A., Smolders, I., Lindskog, M., in press. Dysfunctional astrocytic regulation of glutamate transmission in a rat model of depression. Mol. Psychiatry AOP.
Gorenstein, C., de Carvalho, S., Artes, R., Moreno, R., Marcourakis, T., 2006. Cognitive performance in depressed patients after chronic use of antidepressants. Psychopharmacology 185, 84–92.
Gorwood, P., 2008. Neurobiological mechanisms of anhedonia. Dialogues Clin. Neurosci. 10, 291–299.
Gotlib, I.H., Joormann, J., 2010. Cognition and depression: current status and future directions. Annu. Rev. Clin. Psychol. 6, 285–312.
Gould, N.F., Holmes, M.K., Fantie, B.D., Luckenbaugh, D.A., Pine, D.S., Gould, T.D., Burgess, N., Manji, H.K., Zarate Jr., C.A., 2007. Performance on a virtual reality spatial memory navigation task in depressed patients. Am. J. Psychiatry 164, 516–519.
Groc, L., Choquet, D., Chaouloff, F., 2008. The stress hormone corticosterone conditions AMPAR surface trafficking and synaptic potentiation. Nat. Neurosci. 11, 868–870.
Hamilton, J.P., Chen, G., Thomason, M.E., Schwartz, M.E., Gotlib, I.H., 2011. Investigating neural primacy in Major Depressive Disorder: multivariate Granger causality analysis of resting-state fMRI time-series data. Mol. Psychiatry 16, 763–772.
Hashimoto, K., 2009. Emerging role of glutamate in the pathophysiology of major depressive disorder. Brain Res. Rev. 61, 105–123.
Henneberger, C., Papouin, T., Oliet, S.H.R., Rusakov, D.A., 2010. Long-term potentiation depends on release of d-serine from astrocytes. Nature 463, 232–236.
Herman, J.P., Patel, P.D., Akil, H., Watson, S.J., 1989. Localization and regulation of glucocorticoid and mineralocorticoid receptor messenger RNAs in the hippocampal formation of the rat. Mol. Endocrinol. 3, 1886–1894.
Herrera-Guzman, I., Gudayol-Ferre, E., Herrera-Abarca, J.E., Herrera-Guzman, D., Montelongo-Pedraza, P., Padrus Blozquez, F., Peru Cebollero, M., Guardia-Olmos, J., 2009. Major Depressive Disorder in recovery and neuropsychological functioning: effects of selective serotonin reuptake inhibitor and dual inhibitor depression treatments on residual cognitive deficits in patients with Major Depressive Disorder in recovery. J. Affect. Disord. 123, 341–350.
Hirschfeld, R., 2000. History and evolution of the monoamine hypothesis of depression. J. Clin. Psychiatry 61, 4–6.
Holderbach, R., Clark, K., Moreau, J.L., Bischofberger, J., Normann, C., 2007. Enhanced long-term synaptic depression in an animal model of depression. Biol. Psychiatry 62, 92–100.
Holick, K.A., Lee, D.C., Hen, R., Dulawa, S.C., 2008. Behavioral effects of chronic fluoxetine in BALB/cJ mice do not require adult hippocampal neurogenesis or the serotonin 1A receptor. Neuropsychopharmacology 33, 406–417.
Hoschl, C., Hajek, T., 2001. Hippocampal damage mediated by corticosteroids—a neuropsychiatric research challenge. Eur. Arch. Psychiatry Clin. Neurosci. 251 (Suppl. 2), II81–II88.
Ishihara, L., Brayne, C., 2006. A systematic review of depression and mental illness preceding Parkinson's disease. Acta Neurol. Scand. 113, 211–220.
Iyo, A.H., Feyissa, A.M., Chandran, A., Austin, M.C., Regunathan, S., Karolewicz, B., 2010. Chronic corticosterone administration down-regulates metabotropic glutamate receptor 5 protein expression in the rat hippocampus. Neuroscience 169, 1567–1574.
Jiang, W., Zhang, Y., Xiao, L., Van Cleemput, J., Ji, S.P., Bai, G., Zhang, X., 2005. Cannabinoids promote embryonic and adult hippocampus neurogenesis and produce anxiolytic- and antidepressant-like effects. J. Clin. Invest. 115, 3104–3116.
Jonas, J.M., Hearron Jr., A.E., 1996. Alprazolam and suicidal ideation: a meta-analysis of controlled trials in the treatment of depression. J. Clin. Psychopharmacol. 16, 208–211.
Karst, H., Berger, S., Turiault, M., Tronche, F., Schütz, G.n., Joëls, M., 2005. Mineralocorticoid receptors are indispensable for nongenomic modulation of hippocampal glutamate transmission by corticosterone. Proc. Natl. Acad. Sci. U. S. A. 102, 19204–19207.
Kellendonk, C., Gass, P., Kretz, O., Schutz, G., Tronche, F., 2002. Corticosteroid receptors in the brain: gene targeting studies. Brain Res. Bull. 57, 73–83.
Kim, M.J., Loucks, R.A., Palmer, A.L., Brown, A.C., Solomon, K.M., Marchante, A.N., Whalen, P.J., 2011. The structural and functional connectivity of the amygdala: from normal emotion to pathological anxiety. Behav. Brain Res. 223, 403–410.
Kohli, M.A., Lucae, S., Saemann, P.G., Schmidt, M.V., Demirkan, A., Hek, K., Czamara, D., Alexander, M., Salyakina, D., Ripke, S., Hoehn, D., Specht, M., Menke, A., Hennings, J., Heck, A., Wolf, C., Ising, M., Schreiber, S., Czisch, M., Muller, M.B., Uhr, M., Bettecken, T., Becker, A., Schramm, J., Rietschel, M., Maier, W., Bradley, B., Ressler, K.J., Nothen, M.M., Cichon, S., Craig, I.W., Breen, G., Lewis, C.M., Hofman, A., Tiemeier, H., van Duijn, C.M., Holsboer, F., Muller-Myhsok, B., Binder, E.B., 2011. The neuronal transporter gene SLC6A15 confers risk to major depression. Neuron 70, 252–265.
Kondo, D.G., Hellem, T.L., Sung, Y.-H., Kim, N., Jeong, E.-K., DelMastro, K.K., Shi, X., Renshaw, P.F., 2011. Magnetic resonance spectroscopy studies of pediatric major depressive disorder. Depress. Res. Treat. 13. doi:10.1155/2011/650450.
Krishnan, V., Nestler, E.J., 2008. Linking molecules to mood: new insight into the biology of depression. Am. J. Psychiatry 167, 1305–1320.

Kulisevsky, J., Pagonabarraga, J., 2009. Cognitive impairment in Parkinson's disease: tools for diagnosis and assessment. Mov. Disord. 24, 1103–1110.
LeDoux, J., 1998. Fear and the brain: where have we been, and where are we going? Biol. Psychiatry 44, 1229–1238.
Li, S., Cullen, W.K., Anwyl, R., Rowan, M.J., 2003. Dopamine-dependent facilitation of LTP induction in hippocampal CA1 by exposure to spatial novelty. Nat. Neurosci. 6, 526–531.
Li, N., Lee, B., Liu, R.-J., Banasr, M., Dwyer, J.M., Iwata, M., Li, X.-Y., Aghajanian, G., Duman, R.S., 2010. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. Science 329, 959–964.
Liberzon, I., Phan, K.L., 2003. Brain-imaging studies of posttraumatic stress disorder. CNS Spectr. 8, 641–650.
Lisman, J.E., Grace, A.A., 2005. The hippocampal-VTA loop: controlling the entry of information into long-term memory. Neuron 46, 703–713.
Liu, J.H., Li, X.S., Ye, J., Gao, L.H., Zhang, Z.P., Wu, W., Yao, L., Zhang, J., 2011. Cognitive impairments in Parkinson's disease. Aging Ment. Health 1–8.
Luine, V., Villegas, M., Martinez, C., McEwen, B.S., 1994. Repeated stress causes reversible impairments of spatial memory performance. Brain Res. 639, 167–170.
Luscher, B., Shen, Q., Sahir, N., 2011. The GABAergic deficit hypothesis of major depressive disorder. Mol. Psychiatry 16, 383–406.
MacQueen, G.M., Campbell, S., McEwen, B.S., Macdonald, K., Amano, S., Joffe, R.T., Nahmias, C., Young, L.T., 2003. Course of illness, hippocampal function, and hippocampal volume in major depression. Proc. Natl. Acad. Sci. U. S. A. 100, 1387–1392.
Maguire, E.A., Burgess, N., Donnett, J.G., Frackowiak, R.S., Frith, C.D., O'Keefe, J., 1998. Knowing where and getting there: a human navigation network. Science 280, 921–924.
Malgouris, C., Bardot, F., Daniel, M., Pellis, F., Rataud, J., Uzan, A., Blanchard, J.C., Laduron, P.M., 1989. Riluzole, a novel antiglutamate, prevents memory loss and hippocampal neuronal damage in ischemic gerbils. J. Neurosci. 9, 3720–3727.
Malkesman, O., Austin, D.R., Tragon, T., Wang, G., Rompala, G., Hamidi, A.B., Cui, Z., Young, W.S., Nakazawa, K., Zarate, C.A., Manji, H.K., Chen, G., 2011. Acute d-serine treatment produces antidepressant-like effects in rodents. Int. J. Neuropsychopharmacol. 1–14.
Martinez-Martin, P., Damian, J., 2010. Parkinson disease: depression and anxiety in Parkinson disease. Nat. Rev. Neurol. 6, 243–245.
Martisova, E., Solas, M., Horrillo, I., Ortega, J.E., Meana, J.J., Tordera, R.M.a., Ramirez, M.J., 2012. Long lasting effects of early-life stress on glutamatergic/GABAergic circuitry in the rat hippocampus. Neuropharmacology 62 (5–6), 1944–1953.
Matrisciano, F., Bonaccorso, S., Ricciardi, A., Scaccianoce, S., Panaccione, I., Wang, L., Ruberto, A., Tatarelli, R., Nicoletti, F., Girardi, P., Shelton, R.C., 2009. Changes in BDNF serum levels in patients with major depression disorder (MDD) after 6 months treatment with sertraline, escitalopram, or venlafaxine. J. Psychiatr. Res. 43, 247–254.
McEntee, W.J., Crook, T.H., 1993. Glutamate: its role in learning, memory, and the aging brain. Psychopharmacology (Berl) 111, 391–401.
McEwen, B.S., 1998. Protective and damaging effects of stress mediators. N. Engl. J. Med. 338, 171–179.
McEwen, B.S., 2007. Physiology and neurobiology of stress and adaptation: central role of the brain. Physiol. Rev. 87, 873–904.
McNally, L., Bhagwagar, Z., Hannestad, J., 2008. Inflammation, glutamate, and glia in depression: a literature review. CNS Spectr. 13, 501–510.
Meshi, D., Drew, M.R., Saxe, M., Ansorge, M.S., David, D., Santarelli, L., Malapani, C., Moore, H., Hen, R., 2006. Hippocampal neurogenesis is not required for behavioral effects of environmental enrichment. Nat. Neurosci. 9, 729–731.
Mohler, H., 2012. The GABA system in anxiety and depression and its therapeutic potential. Neuropharmacology 62, 42–53.
Morgan, C.J., Curran, H.V., 2006. Acute and chronic effects of ketamine upon human memory: a review. Psychopharmacology (Berl) 188, 408–424.
Mothet, J.P., Parent, A.T., Wolosker, H., Brady Jr., R.O., Linden, D.J., Ferris, C.D., Rogawski, M.A., Snyder, S.H., 2000. D-serine is an endogenous ligand for the glycine site of the N-methyl-D-aspartate receptor. Proc. Natl. Acad. Sci. U. S. A. 97, 4926–4931.
Neves, G., Cooke, S.F., Bliss, T.V.P., 2008. Synaptic plasticity, memory and the hippocampus: a neural network approach to causality. Nat. Rev. Neurosci. 9, 65–75.
Nieoullon, A., Coquerel, A., 2003. Dopamine: a key regulator to adapt action, emotion, motivation and cognition. Curr. Opin. Neurol. 16, S3–S9.
Nutt, D.J., 2006. The role of dopamine and norepinephrine in depression and antidepressant treatment. J. Clin. Psychiatry 67 (Suppl. 6), 3–8.
O'Donnell, P., Grace, A., 1995. Synaptic interactions among excitatory afferents to nucleus accumbens neurons: hippocampal gating of prefrontal cortical input. J. Neurosci. 15, 3622–3639.
Overstreet, D.H., Griebel, G., 2004. Antidepressant-like effects of CRF1 receptor antagonist SSR125543 in an animal model of depression. Eur. J. Pharmacol. 497, 49–53.
Overstreet, D.H., Keeney, A., Hogg, S., 2004. Antidepressant effects of citalopram and CRF receptor antagonist CP-154,526 in a rat model of depression. Eur. J. Pharmacol. 492, 195–201.
Overstreet, D.H., Friedman, E., Mathe, A.A., Yadid, G., 2005. The Flinders Sensitive Line rat: a selectively bred putative animal model of depression. Neurosci. Biobehav. Rev. 29, 739–759.
Owens, M.J., 2004. Selectivity of antidepressants: from the monoamine hypothesis of depression to the SSRI revolution and beyond. J. Clin. Psychiatry 65 (Suppl. 4), 5–10.
Pariante, C.M., Miller, A.H., 2001. Glucocorticoid receptors in major depression: relevance to pathophysiology and treatment. Biol. Psychiatry 49, 391–404.
Patten, S.B., Williams, J.V., Love, E.J., 1996. Self-reported depressive symptoms following treatment with corticosteroids and sedative-hypnotics. Int. J. Psychiatry Med. 26, 15–24.
Peluso, M.A., Glahn, D.C., Matsuo, K., Monkul, E.S., Najt, P., Zamarripa, F., Li, J., Lancaster, J.L., Fox, P.T., Gao, J.H., Soares, J.C., 2009. Amygdala hyperactivation in untreated depressed individuals. Psychiatry Res. 173, 158–161.
Petrie, R.X.A., Reid, I.C., Stewart, C.A., 2000. The N-methyl-d-aspartate receptor, synaptic plasticity, and depressive disorder: A critical review. Pharmacol. Ther. 87, 11–25.
Petty, F., Schlesser, M.A., 1981. Plasma GABA in affective illness. A preliminary investigation. J. Affect. Disord. 3, 339–343.
Petty, F., Sherman, A.D., 1984. Plasma GABA levels in psychiatric illness. J. Affect. Disord. 6, 131–138.
Pikkarainen, M., Ronkko, S., Savander, V., Insausti, R., Pitkanen, A., 1999. Projections from the lateral, basal, and accessory basal nuclei of the amygdala to the hippocampal formation in rat. J. Comp. Neurol. 403, 229–260.
Pirker, S., Schwarzer, C., Wieselthaler, A., Sieghart, W., Sperk, G., 2000. GABA(A) receptors: immunocytochemical distribution of 13 subunits in the adult rat brain. Neuroscience 101, 815–850.
Pittenger, C., Duman, R.S., 2008. Stress, depression, and neuroplasticity: a convergence of mechanisms. Neuropsychopharmacology 33, 88–109.
Pizzagalli, D.A., Oakes, T.R., Fox, A.S., Chung, M.K., Larson, C.L., Abercrombie, H.C., Schaefer, S.M., Benca, R.M., Davidson, R.J., 2004. Functional but not structural subgenual prefrontal cortex abnormalities in melancholia. Mol. Psychiatry 9 (325), 393–405.
Price, J.L., Drevets, W.C., 2010. Neurocircuitry of mood disorders. Neuropsychopharmacology 35, 192–216.
Rajkowska, G., Halaris, A., Selemon, L.D., 2001. Reductions in neuronal and glial density characterize the dorsolateral prefrontal cortex in bipolar disorder. Biol. Psychiatry 49, 741–752.

Ramaekers, J.G., van Veggel, L.M., O'Hanlon, J.F., 1994. A cross-study comparison of the effects of moclobemide and brofaromine on actual driving performance and estimated sleep. Clin. Neuropharmacol. 17 (Suppl. 1), S9–S18.
Remick, R.A., Keller, F.D., Buchanan, R.A., Gibson, R.E., Fleming, J.A., 1988. A comparison of the efficacy and safety of alprazolam and desipramine in depressed outpatients. Can. J. Psychiatry 33, 590–594.
Riedel, W., Hogervorst, E., Leboux, R., Verhey, F., van Praag, H., Jolles, J., 1995. Caffeine attenuates scopolamine-induced memory impairment in humans. Psychopharmacology (Berl) 122, 158–168.
Roozendaal, B., McEwen, B.S., Chattarji, S., 2009. Stress, memory and the amygdala. Nat. Rev. Neurosci. 10, 423–433.
Rosoklija, G., Toomayan, G., Ellis, S.P., Keilp, J., Mann, J.J., Latov, N., Hays, A.P., Dwork, A.J., 2000. Structural abnormalities of subicular dendrites in subjects with schizophrenia and mood disorders: preliminary findings. Arch. Gen. Psychiatry 57, 349–356.
Rudolph, U., Knoflach, F., 2011. Beyond classical benzodiazepines: novel therapeutic potential of GABAA receptor subtypes. Nat. Rev. Drug Discov. 10, 685–697.
Ryan, B., Musazzi, L., Mallei, A., Tardito, D., Gruber, S.H.M., El Khoury, A., Anwyl, R., Racagni, G., MathÈ, A.A., Rowan, M.J., Popoli, M., 2009. Remodelling by early-life stress of NMDA receptor-dependent synaptic plasticity in a gene–environment rat model of depression. Int. J. Neuropsychopharmacol. 12, 553–559.
Sahay, A., Scobie, K.N., Hill, A.S., O'Carroll, C.M., Kheirbek, M.A., Burghardt, N.S., Fenton, A.A., Dranovsky, A., Hen, R., 2011. Increasing adult hippocampal neurogenesis is sufficient to improve pattern separation. Nature 472, 466–470.
Salzman, C.D., Fusi, S., 2010. Emotion, cognition, and mental state representation in amygdala and prefrontal cortex. Annu. Rev. Neurosci. 33, 173–202.
Samuelson, K.W., 2011. Post-traumatic stress disorder and declarative memory functioning: a review. Dialogues Clin. Neurosci. 13, 346–351.
Sanacora, G., Rothman, D.L., Mason, G., Krystal, J.H., 2003. Clinical studies implementing glutamate neurotransmission in mood disorders. Ann. N. Y. Acad. Sci. 1003, 292–308.
Sanacora, G., Kendell, S.F., Levin, Y., Simen, A.A., Fenton, L.R., Coric, V., Krystal, J.H., 2007. Preliminary evidence of riluzole efficacy in antidepressant-treated patients with residual depressive symptoms. Biol. Psychiatry 61, 822–825.
Sanacora, G., Zarate, C.A., Krystal, J.H., Manji, H.K., 2008. Targeting the glutamatergic system to develop novel, improved therapeutics for mood disorders. Nat. Rev. Drug Discov. 7, 426–437.
Santarelli, L., Saxe, M., Gross, C., Surget, A., Battaglia, F., Dulawa, S., Weisstaub, N., Lee, J., Duman, R., Arancio, O., Belzung, C., Hen, R., 2003. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. Science 301, 805–809.
Saxe, M.D., Battaglia, F., Wang, J.W., Malleret, G., David, D.J., Monckton, J.E., Garcia, A.D., Sofroniew, M.V., Kandel, E.R., Santarelli, L., Hen, R., Drew, M.R., 2006. Ablation of hippocampal neurogenesis impairs contextual fear conditioning and synaptic plasticity in the dentate gyrus. Proc. Natl. Acad. Sci. U. S. A. 103, 17501–17506.
Schmitt, F.A., Cragar, D., Ashford, J.W., Reisberg, B., Ferris, S., Mobius, H.J., Stoffler, A., 2002. Measuring cognition in advanced Alzheimer's disease for clinical trials. J. Neural Transm. Suppl. 135–148.
Schutter, D.J., van Honk, J., 2005. A framework for targeting alternative brain regions with repetitive transcranial magnetic stimulation in the treatment of depression. J. Psychiatry Neurosci. 30, 91–97.
Seminowicz, D.A., Mayberg, H.S., McIntosh, A.R., Goldapple, K., Kennedy, S., Segal, Z., Rafi-Tari, S., 2004. Limbic-frontal circuitry in major depression: a path modeling metanalysis. NeuroImage 22, 409–418.
Sen, S., Duman, R., Sanacora, G., 2008. Serum brain-derived neurotrophic factor, depression, and antidepressant medications: meta-analyses and implications. Biol. Psychiatry 64, 527–532.
Sheline, Y.I., Barch, D.M., Donnelly, J.M., Ollinger, J.M., Snyder, A.Z., Mintun, M.A., 2001. Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. Biol. Psychiatry 50, 651–658.
Shen, Q., Lal, R., Luellen, B.A., Earnheart, J.C., Andrews, A.M., Luscher, B., 2010. gamma-Aminobutyric acid-type A receptor deficits cause hypothalamic–pituitary–adrenal axis hyperactivity and antidepressant drug sensitivity reminiscent of melancholic forms of depression. Biol. Psychiatry 68, 512–520.
Shimizu, E., Hashimoto, K., Okamura, N., Koike, K., Komatsu, N., Kumakiri, C., Nakazato, M., Watanabe, H., Shinoda, N., Okada, S., Iyo, M., 2003. Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants. Biol. Psychiatry 54, 70–75.
Small, S.A., Schobel, S.A., Buxton, R.B., Witter, M.P., Barnes, C.A., 2011. A pathophysiological framework of hippocampal dysfunction in ageing and disease. Nat. Rev. Neurosci. 12, 585–601.
Spiers, H.J., Burgess, N., Hartley, T., Vargha-Khadem, F., O'Keefe, J., 2001a. Bilateral hippocampal pathology impairs topographical and episodic memory but not visual pattern matching. Hippocampus 11, 715–725.
Spiers, H.J., Burgess, N., Maguire, E.A., Baxendale, S.A., Hartley, T., Thompson, P.J., O'Keefe, J., 2001b. Unilateral temporal lobectomy patients show lateralized topographical and episodic memory deficits in a virtual town. Brain 124, 2476–2489.
Stewart, C.A., Reid, I.C., 2000. Repeated ECS and fluoxetine administration have equivalent effects on hippocampal synaptic plasticity. Psychopharmacology (Berl) 148, 217–223.
Stockmeier, C.A., Mahajan, G.J., Konick, L.C., Overholser, J.C., Jurjus, G.J., Meltzer, H.Y., Uylings, H.B., Friedman, L., Rajkowska, G., 2004. Cellular changes in the postmortem hippocampus in major depression. Biol. Psychiatry 56, 640–650.
Tan, K.R., Rudolph, U., Luscher, C., 2011. Hooked on benzodiazepines: GABAA receptor subtypes and addiction. Trends Neurosci. 34, 188–197.
Tapiero, H., Mathe, G., Couvreur, P., Tew, K.D., 2002. II. Glutamine and glutamate. Biomed. Pharmacother. 56, 446–457.
Tokita, Y., Bessho, Y., Masu, M., Nakamura, K., Nakao, K., Katsuki, M., Nakanishi, S., 1996. Characterization of excitatory amino acid neurotoxicity in N-methyl-D-aspartate receptor-deficient mouse cortical neuronal cells. Eur. J. Neurosci. 8, 69–78.
Tordera, R.M., Totterdell, S., Wojcik, S.M., Brose, N., Elizalde, N., Lasheras, B., Del Rio, J., 2007. Enhanced anxiety, depressive-like behaviour and impaired recognition memory in mice with reduced expression of the vesicular glutamate transporter 1 (VGLUT1). Eur. J. Neurosci. 25, 281–290.
Tsankova, N.M., Berton, O., Renthal, W., Kumar, A., Neve, R.L., Nestler, E.J., 2006. Sustained hippocampal chromatin regulation in a mouse model of depression and antidepressant action. Nat. Neurosci. 9, 519–525
Tsigos, C., Chrousos, G.P., 2002. Hypothalamic–pituitary–adrenal axis, neuroendocrine factors and stress. J. Psychosom. Res. 53, 865–871.
van Laar, M.v.L., Volkerts, E.V., Verbaten, M.V., Trooster, S.T., van Megen, H.v.M., Kenemans, J.K., 2002. Differential effects of amitriptyline, nefazodone and paroxetine on performance and brain indices of visual selective attention and working memory. Psychopharmacology 162, 351–363.

Varanese, S., Perfetti, B., Ghilardi, M.F., Di Rocco, A., 2011. Apathy, but not depression, reflects inefficient cognitive strategies in Parkinson's disease. PLoS One 6, e17846.

Vetencourt, J.F.M., Sale, A., Viegi, A., Baroncelli, L., De Pasquale, R., O'Leary, O.F., Castren, E., Maffei, L., 2008. The antidepressant fluoxetine restores plasticity in the adult visual cortex. Science 320, 385–388.

Videbech, P., Ravnkilde, B., 2004. Hippocampal volume and depression: a meta-analysis of MRI studies. Am. J. Psychiatry 161, 1957–1966.

Von Frijtag, J.C., Kamal, A., Reijmers, L.G., Schrama, L.H., van den Bos, R., Spruijt, B.M., 2001. Chronic imipramine treatment partially reverses the long-term changes of hippocampal synaptic plasticity in socially stressed rats. Neurosci. Lett. 309, 153–156.

Vreeburg, S.A., Hoogendijk, W.J., van Pelt, J., Derijk, R.H., Verhagen, J.C., van Dyck, R., Smit, J.H., Zitman, F.G., Penninx, B.W., 2009. Major depressive disorder and hypothalamic–pituitary–adrenal axis activity: results from a large cohort study. Arch. Gen. Psychiatry 66, 617–626.

Willner, P., Muscat, R., Papp, M., 1992. Chronic mild stress-induced anhedonia: a realistic animal model of depression. Neurosci. Biobehav. Rev. 16, 525–534.

Wingen, M., Langer, S., Ramaekers, J.G., 2006. Verbal memory performance during subchronic challenge with a selective serotonergic and a mixed action antidepressant. Hum. Psychopharmacol. Clin. Exp. 21, 473–479.

Winocur, G., Wojtowicz, J.M., Sekeres, M., Snyder, J.S., Wang, S., 2006. Inhibition of neurogenesis interferes with hippocampus-dependent memory function. Hippocampus 16, 296–304.

Zarate Jr., C.A., Payne, J.L., Quiroz, J., Sporn, J., Denicoff, K.K., Luckenbaugh, D., Charney, D.S., Manji, H.K., 2004. An open-label trial of riluzole in patients with treatment-resistant major depression. Am. J. Psychiatry 161, 171–174.

Zarate Jr., C.A., Quiroz, J.A., Singh, J.B., Denicoff, K.D., De Jesus, G., Luckenbaugh, D.A., Charney, D.S., Manji, H.K., 2005. An open-label trial of the glutamate-modulating agent riluzole in combination with lithium for the treatment of bipolar depression. Biol. Psychiatry 57, 430–432.

Zarate Jr., C.A., Singh, J.B., Carlson, P.J., Brutsche, N.E., Ameli, R., Luckenbaugh, D.A., Charney, D.S., Manji, H.K., 2006. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch. Gen. Psychiatry 63, 856–864.