GLUTAMATE-MEDIATED NEUROPLASTICITY DEFICITS IN MOOD DISORDERS

Leah R. Reznikov, Jim R. Fadel and Lawrence P. Reagan

I Introduction

The resiliency of an organism depends upon its ability to adapt to stressful events or circumstances. The cognitive and behavioral components of resiliency require neuronal adaptations involving a number of brain regions and neurotransmitter systems. Neuroplasticity is a broad term referring to a collection of events critical for neuronal adaptation, including those that occur at the molecular, cellular and systemic levels. While a number of different signaling molecules contribute to neuroplasticity-related changes in neural function, most forms of neuroplasticity require the involvement of glutamate, the primary fast-acting excitatory neurotransmitter in the mammalian brain. Substantial evidence suggests an important role for glutamate in long-term potentiation (LTP), regulation of spine density, and synaptic reorganization, events thought to impact an organism's overall behavior and adaptive potential. Indeed, it has been suggested that altered or impaired neuroplasticity may contribute to a variety of pathological states associated with dysregulation of mood [1]. Thus, the goal of this chapter is to focus on glutamate's role in neuroplasticity in brain structures associated with regulation of mood and emotional behaviors, with particular emphasis on psychiatric illnesses such as major depressive disorder.

II The glutamatergic system

Glutamate is the primary excitatory neurotransmitter in the mammalian brain [2]. De novo synthesis of glutamate arises predominantly from either glutamine or glucose metabolites, although recycling of glutamate from the synaptic cleft via high-affinity neuronal and astrocytic glutamate transporters also occurs. Studies also indicate that glutamate–cystine exchangers may play an important role in glutamate availability [3]. Thus, glutamate synthesis and availability are tightly regulated by both neuronal and non-neuronal mechanisms.

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It is well established that multiple metabotropic and ionotropic receptors are involved in mediating the effects of glutamate [2]. Three main types of ionotropic receptors exist, including amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate, and *N*-methyl-D-aspartate (NMDA) receptors. The ionotropic receptors are critical mediators of fast excitatory transmission, and therefore are involved in a wide variety of functions. The metabotropic glutamate receptor (mGluR) family consists of eight members, mGlu1R–mGluR8. Structurally, members of the mGluR family display a seven transmembrane domain structure similar to that observed in other G-protein-coupled receptors [4]. The mGluR family is widely distributed throughout the CNS and can be located either pre- and postsynaptically, as well as extrasynaptically, making these receptors an attractive therapeutic target for a variety of pathologies [5].

III Glutamatergic projections and anatomical substrates of mood-related disorders

Psychiatric disorders such as major depressive illness are tremendously heterogeneous in terms of etiology and manifestation. Thus, they certainly reflect dysfunction of numerous brain regions and circuits. Nonetheless, several structures that serve as key "nodes" in cortico–limbic circuitry have received greater attention due to their consistent apparent involvement in several aspects of these disorders. One example is the prefrontal cortex (PFC), a frontal lobe structure critical for executive functions and motivational behavior [6]. The PFC is highly interconnected to both cortical and subcortical structures, allowing it to modulate cognition, as well as limbic activity [7]. Recent evidence suggests that in certain depressive illness patients, the degree to which executive functions are impaired predicts the outcome of antidepressant efficacy (greater impairment equals poorer efficacy) [8]. Additionally, one of the most consistent findings associated with depressed individuals is alterations in PFC volume [9].

Similarly, recent evidence suggests that posttraumatic stress disorder (PTSD) patients display altered PFC activity during associative learning and memory [10], as well as during processing of fearful stimuli [11]. Individuals diagnosed with other anxiety disorders such as blood-injection-injury phobia also display decreased activation of the medial PFC during presentation of

phobia-relevant stimuli [12]. This finding is congruent with data suggesting that cerebral blood flow is reduced in the PFC during presentation of anxiety-provoking cues in individuals suffering from simple animal phobias [13]. Therefore, evidence continues to suggest that the PFC plays an integral role in the etiology of several psychiatric illnesses.

Another structure that has gained considerable attention over the past decade is the amygdala, a key limbic loop structure located in the temporal lobe of the brain [14]. The amygdala receives excitatory glutamatergic inputs from multiple sources, including thalamic and cortical regions, and also sends glutamatergic projections to various target sites [15]. These glutamatergic afferents are critical for relaying "affective significance of sensory events", and in general are essential for the acquisition and expression of conditioned fear behaviors [16]. Evidence suggests that depressive illness patients have impaired functioning in emotional tasks involving the amygdala [17], while others have reported a positive correlation between amygdalar metabolism and negative affect in depressed individuals [18]. There is inconsistency in the evidence regarding whether or not depressed individuals show structural changes in the amygdala, and in cases where structural changes are observed, directionality is not always consistent [7]. These disparities may be related to differences in methodology, illness duration, patient history, sex, age, and sample size, and therefore suggest that the amygdala may exhibit time- and treatment-dependent changes. If true, then it is possible that the amygdala may be an important initiation site for (or contributor to) structural changes observed in other brain regions of depressive illness patients. Another complicating factor is the anatomical heterogeneity of the amygdalar complex, since human imaging studies generally lack the spatial resolution required to document subregion-specific alterations in amygdalar volume.

Heightened amygdalar activity has also been described in PTSD patients during processing of fearful stimuli [11], although some studies indicate that amygdalar activation in individuals with social phobia is decreased during presentation of anxiety-provoking mental imagery [19]. Still others report that individuals with social anxiety disorders display enhanced amygdala activation during processing of emotionally relevant stimuli [20]. Collectively, the amygdala appears to be a critical player in both depressive illness and anxiety-related disorders.

A final structure that has received much attention is the hippocampus, a limbic structure also critical for regulating emotional behaviors as well as cognitive processes [1]. The hippocampus has reciprocal glutamatergic connections with a number of cortical and subcortical structures, including the amygdala [21] and PFC [22]. Deficits in hippocampus-dependent cognitive tasks have been described in subsets of depressive illness patients [1], and, interestingly, marked reductions in hippocampus volume are consistently found in a variety of depressive illness patients. There has also been speculation that hippocampus deficits may underlie some of the feelings of worthlessness, hopelessness, guilt, doom, and suicidality that accompany depression [23].

Recent evidence demonstrates that PTSD patients display altered hippocampus activity during associative learning and memory [10], whereas individuals diagnosed with social anxiety disorder display decreased activation of the hippocampus during mental imagery of an "anxiogenic social situation" [19]. Decreased cerebral blood flow to the hippocampus has also been noted in individuals diagnosed with small animal phobias during presentation of phobia-relevant stimuli [13]. Thus, abnormalities in the hippocampus appear to be associated with a variety of disease states, and therefore further investigation of whether alterations in this structure serve as cause or consequence in psychiatric illness will provide greater insight regarding the anatomical substrates of mood-related disorders.

IV Glutamatergic alterations in psychiatric illness: clinical evidence

Depressive illness

Alterations in central glutamatergic transmission have been described in a variety of types of depression. For example, some studies indicate that increased glutamate levels are present in brain structures of depressed individuals [2], whereas examination of other structures such as the anterior cingulate gyrus indicate that glutamine-to-glutamate ratio (Glx) is decreased [24]. This finding is echoed by reports indicating that glutamate levels in the anterior cingulate of subpopulations of pediatric depressive illness patients are also decreased [25]. Of importance is the observation that electroconvulsive therapy can reverse glutamate deficiencies in the anterior cingulate of depressed adults [26], suggesting that glutamate abnormalities in this

region may be critical in the etiology of depression. More recent evidence also suggests that suicidal ideation in depressed individuals is associated with genes that encode ionotropic glutamate receptors [27], whereas others report a positive correlation between plasma glutamate levels and severity of depression [28].

Anxiety disorders

A substantial amount of evidence suggests that glutamate may be involved in the pathophysiology of anxiety disorders. For example, recent clinical data indicate that anterior cingulate Glx predicts symptom severity in female obsessive-compulsive disorder patients [29], whereas individuals diagnosed with social anxiety disorder have increased brain glutamate concentrations [30]. In addition to these direct measurements, circumstantial evidence also exists. For instance, subsets of individuals diagnosed with PTSD display cortical hyperexcitability, a finding supportive of potential alterations in glutamatergic transmission [31]. It has also been reported that use of ketamine, an NMDA glutamate receptor antagonist, increases PTSD symptoms in subsets of patient populations [32]. Lastly, the evidence continues to suggest that glutamatergic drugs are efficacious in treating obsessive-compulsive disorder, PTSD, generalized anxiety disorder, and social phobia [33].

Neuroplasticity deficits in depressive illness
Structure
• Deceased volumes in hippocampus and prefrontal cortex
• Increased/decreased volume in amygdala
• Alteration in neuronal size and density
Functions
• Alterations in cerebral blood flow and metabolism
• Neuropsychological deficits in memory, attention, anxiety
Glutamate neuropharmacology
• Reduced glutamate receptor expression and binding activity
• Reduced glial glutamate transporter activity
• Altered glutamate neurochemical profiles

Table 1. Neuroplasticity deficits in depressive illness.

V Understanding glutamate's involvement in neuroplasticity: functional implications in relation to psychiatric illness

Clinical studies are limited in their ability to identify the underlying electrophysiological, neuroanatomical and neuropharmacological deficits that ultimately contribute to psychiatric illness. However, it is plausible that glutamatergic alterations may promote dysregulated neuroplasticity and subsequent manifestation of psychiatric illness (see Table 1). For these reasons, preclinical investigations have relied upon experimental models, including chronic stress paradigms, for the study of psychiatric diseases such as depressive illness. Such studies provide important information regarding

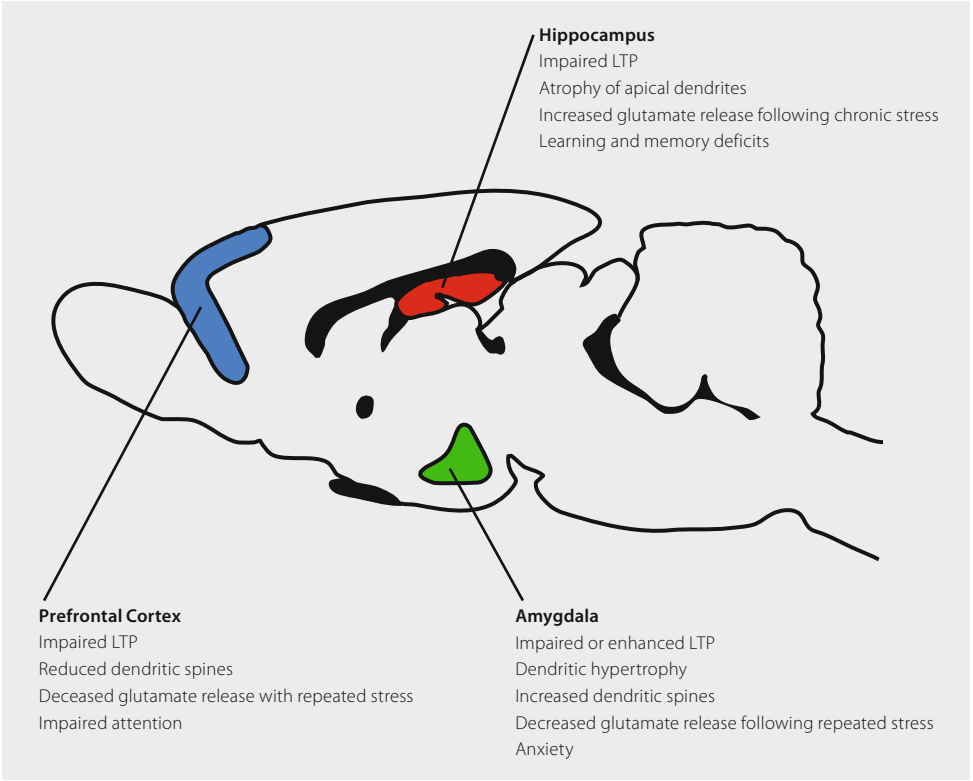

Figure 1. Stress-induced changes in neuroplasticity in animal models: associated glutamatergic and behavioral alterations. In preclinical models of depressive illness, animals subjected to chronic or repeated stress paradigms exhibit deficits in neuroplasticity in the prefrontal cortex (blue), hippocampus (red), or the amygdala (green). This may include electrophysiological deficits such as impairments in long-term potentiation (LTP), neuroanatomical alterations such as changes in dendritic morphology or neuronal spine density and alterations in glutamatergic neurochemical profiles. Ultimately, these structural, neurophysiological and pharmacological changes may contribute to the development of cognitive-behavioral deficits initiated by stress. See text for details.

stress-related effects upon brain plasticity. Indeed, animals subjected to stress exhibit features that are strikingly similar to those observed in depressive patients, including structural and functional alterations in the HC, PFC and amygdala (See Figure 1). Importantly, these preclinical models confirm and extend clinical observations that deficits in the glutamatergic system may be part of the core etiological mechanisms of depressive illness.

Long-term potentiation

LTP is a form of synaptic plasticity thought to represent a cellular correlate of learning and memory [34]. In simple terms, LTP involves the strengthening of synaptic connections as a result of increased activity, a phenomenon utilizing NMDA and AMPA glutamate receptors. Several structures in the CNS exhibit LTP, including the hippocampus, amygdala, thalamus, striatum, cortex and PFC. While LTP in these structures shares many features associated with learning tasks in animals, less is known regarding whether LTP induction results in memory consolidation and concomitant behavioral changes [35]. Yet promising work from the amygdala, a critical structure involved in emotional learning, may provide some of the most compelling evidence linking LTP to learning and memory. For example, LeDoux and colleagues report that fear-conditioning, an amygdala-dependent form of learning, involves LTP-like processes [36], whereas high-frequency stimulation of the thalamo–amygdalar pathway enhances acoustic-mediated evoked field potentials in the amygdala [37]. Furthermore, administration of agents that interfere with LTP impairs acquisition of fear-conditioning in animal models [35]. Collectively, these data strengthen the argument that LTP represents a physiologically relevant model of learning and memory.

The clinical importance of these observations is underscored by data indicating that stress, a well-documented environmental factor associated with a variety of psychiatric diseases such as depression [38], modulates LTP in animal models. For example, acute stress has been shown to impair hippocampus [39] and PFC LTP [40;41], whereas in the amygdala acute stress can either impair [42] or enhance LTP [43]. Repeated or chronic stress, conditions capable of producing depressive-like states in animal models [44], impair hippocampus [43] and PFC LTP [45], but not amygdalar LTP [43]. Moreover, it has been proposed that stress-induced modulation of LTP may

contribute to the maintenance of traumatic memories associated with PTSD [31]. Therefore, altered LTP in these structures may account for cognitive and behavioral deficits observed in disease states such as anxiety, depressive illness and/or PTSD [43,46]. Further support for this statement is provided by evidence indicating that agents associated with mood stabilization modulate LTP. Thus, although measuring LTP is not feasible in human populations, the preclinical evidence suggests that altered LTP may serve as a key player in certain psychiatric diseases and that some mood-stabilizing agents may mediate their effects via modulation of LTP-like processes.

Morphological plasticity

Alterations in neuronal morphology, including dendritic length and branching, spine density, and volume, have been widely described in a variety of CNS structures. While the exact mechanisms underlying morphological plasticity are not entirely known, evidence continues to support a role for glutamate. For example, it was originally proposed that increased spine volume in HC dentate gyrus neurons was elicited by glutamate-mediated events [47]. Subsequent studies illustrate that brief exposure of mature HC neurons to glutamate increases the spine cross-sectional area [48], whereas others report an intimate involvement of glutamate transmission in regulation of spine density [49]. More recent evidence suggests that glutamate receptor activation stimulates growth of new postsynaptic processes in HC neurons [50].

Mechanistically, it is believed that activation of both NMDA and AMPA glutamate receptors contributes to these types of morphological plasticity [48]. However, it is important to note that excessive glutamate receptor modulation has been associated with destabilization of synaptic structure [51], as well as loss of axonal neurofilament proteins [52]. Therefore, further studies are necessary to more thoroughly explore the conditions which dictate the dualistic role of glutamate in morphological plasticity.

The functional significance of morphological plasticity can be viewed on a very simplistic level as having importance for defining intrinsic membrane properties of, as well as communication between, neurons [53]. Yet, morphological changes in adult rat brain structures occur readily under pathologically relevant conditions. For example, increased dendritic branching in the

basolateral complex of the amygdala is observed following 10 days of immobilization stress, an event associated with enhanced amygdala-dependent behaviors [54]. Conversely, atrophy of hippocampus apical dendrites occurs following 21 days of chronic restraint stress, a phenomenon associated with spatial learning and memory deficits. Morphological changes also reportedly occur in the PFC following 21 days of chronic stress and are associated with impaired attention-selection processes [55]. Other animal models of PTSD [56] and depression [57] also display morphological abnormalities in various brain structures.

Importantly, stress-associated alterations in morphological plasticity in animal models can be mitigated or blocked by agents associated with mood stabilization [54]. Perhaps restoration or normalization of glutamatergic tone underlies this phenomenon. For example, pharmacological manipulation of the glutamatergic system mitigates stress-induced morphological changes in the hippocampus of animal models [1,54,58], whereas the antidepressant tianeptine, a modulator of glutamatergic transmission, inhibits stress-induced morphological changes in both the hippocampus and amygdala [54]. Indeed, our most recent evidence suggests that tianeptine "normalizes" glutamate efflux in the central amygdala (CeA) of rats subjected to repeated stress, whereas a similar phenomenon also takes place in the hippocampus of animals subjected to chronic stress (Figure 2). Lastly, clinical data suggest that structural abnormalities in a number of brain regions are present in numerous disease states. For example, abnormalities in amygdalar volume have been described in subpopulations of depressive illness patients [7], as well as individuals with PTSD [59]. Similarly, the hippocampus displays structural abnormalities in subsets of individuals diagnosed with major depressive disorder [60] and PTSD [61], whereas structural alterations in the PFC have been described in populations of patients diagnosed with bipolar disorder [62] and PTSD [63].

Treatment implications

A substantial amount of literature suggests that glutamate homeostasis may be an important therapeutic target for several disease states. Indeed, pharmacological alteration of glutamatergic transmission produces anxiolytic effects in a variety of amygdala-dependent behaviors, including in

the fear-potentiated startle and elevated plus maze tests [33]. It has also been reported that clonidine administration in male rats alleviates memory impairments by correcting hippocampus glutamate hypofunction [64]. As stated above, we recently demonstrated that administration of the antidepressant tianeptine normalizes stress-mediated glutamate release in the rat amygdala, a finding that can be interpreted to indicate that a potential mechanism of some mood-stabilizing drugs may include modulation of glutamate release. Indeed, the accumulated data from preclinical studies demonstrate that tianeptine reverses and/or inhibits stress-induced deficits in glutamatergic neuroplasticity in the hippocampus, amygdala, and PFC. These preclinical studies would therefore suggest that tianeptine mediates its clinically relevant effects through normalization of glutamatergic tone, which would restore neuroplasticity in depressive illness patients. These

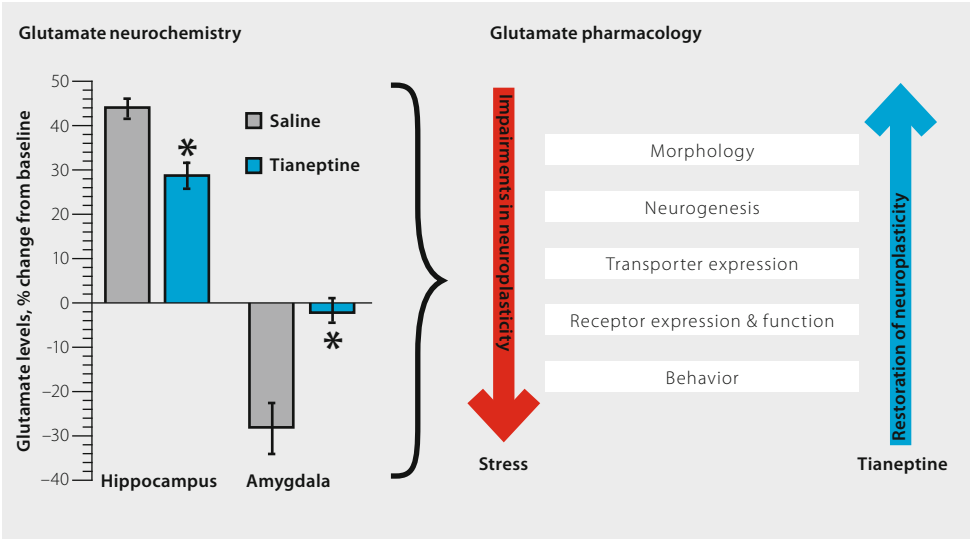

Figure 2. Effects of antidepressant administration on stress-mediated alterations in glutamate efflux in control and repeatedly stressed animals. Stress elicits significant increases in glutamate levels in the hippocampus, but decreases glutamate levels in the amygdala (gray bars). These stress-induced alterations in glutamatergic tone may be an initiating factor for deficits in glutamate pharmacology and physiology in the hippocampus, amygdala and prefrontal cortex that impair neuroplasticity (red arrow). Importantly, stress effects upon glutamatergic neurochemical profiles can be inhibited by the antidepressant tianeptine (blue bars), which provides a potential mechanism through which tianeptine restores stress-mediated deficits in glutamate neuroplasticity in the CNS (blue arrow). Moreover, these results indicate that antidepressants that target the glutamatergic system may provide important and innovative therapeutic interventions in the treatment of mood disorders like major depressive disorder. (Bar graph illustrates changes in glutamate levels in the hippocampus and amygdala in animals given saline [gray] or tianeptine [blue] treatment during an experimental model of depression. Asterisk denotes a significant difference from saline-treated animal.)

novel and innovative mechanisms of action establish tianeptine as a pioneer in new treatment strategies for patients with mood disorders. Interestingly, growing clinical evidence also suggests that agents associated with modulation of glutamate transmission may be efficacious in the treatment of several types of psychiatric illnesses. For example, lamotrigine [65] and riluzole [66], compounds that reduce glutamate transmission, are effective in subsets of patients diagnosed with depressive illness. Subchronic administration of lithium in healthy volunteers has also been reported to reduce glutamate transmission in some CNS structures [67], whereas use of mGluR agonist LY354740 reduces fear-potentiated startle in humans [68].

VI Conclusions

Significant progress has been made in discerning the neurochemical and neuroanatomical correlates of many psychiatric diseases. Out of these efforts a growing appreciation of the role of glutamate and neuroplasticity has evolved. Considering the temporal disparity between the neurochemical response to psychiatric drug treatment (which occurs on a timescale of minutes to hours) and the therapeutic response (which typically occurs within weeks), it is interesting to postulate that glutamate may serve as a key neurochemical mediator linking these distinct phenomena. Thus, although additional studies are necessary to define this relationship more thoroughly, the evidence to date suggests that glutamate transmission in the CNS, with its widespread distribution and rich variety of receptor subtypes and regulatory elements, possesses key clinical significance as a promising novel therapeutic target.

References

1 Kasper S, McEwen BS: Neurobiological and clinical effects of the antidepressant tianeptine. CNS Drugs 2008; 22:15-26.

2 Sanacora G, Zarate CA, Krystal JH, Manji HK: Targeting the glutamatergic system to develop novel, improved therapeutics for mood disorders. Nat Rev Drug Discov 2008; 7:426-437.

3 Baker DA, Xi ZX, Shen H, et al.: The origin and neuronal function of in vivo nonsynaptic glutamate. J. Neurosci 2002; 22,9134-9141.

4 Bhave G, Nadin BM, Brasier DJ, et al.: Membrane topology of a metabotropic glutamate receptor. J Biol Chem 2003, 278:30294-30301.

5 Muly EC, Mania I, Guo JD, Rainnie DG: Group II metabotropic glutamate receptors in anxiety circuitry: correspondence of physiological response and subcellular distribution. J Comp Neurol 2007; 505:682-700.

6 Bae JN, MacFall JR, Krishnan KR, et al.: Dorsolateral prefrontal cortex and anterior cingulate cortex white matter alterations in late-life depression. Biol Psychiatry 2006; 60:1356-1363.

7 Soares JC, Mann JJ: 1997. The anatomy of mood disorders--review of structural neuroimaging studies. Biol Psychiatry 1997; 41:86-106.

8 Alexopoulos GS, Kiosses DN, Heo M, et al.: Executive dysfunction and the course of geriatric depression. Biol Psychiatry 2005; 58:204-210.

9 Drevets WC, Ongur D, Price JL: 1998. Neuroimaging abnormalities in the subgenual prefrontal cortex: implications for the pathophysiology of familial mood disorders. Mol. Psychiatry 1998; 3:220-221.

10 Werner NS, Meindl T, Engel RR, et al.: Hippocampal function during associative learning in patients with posttraumatic stress disorder. J Psychiatr Res 2009; 43:304-318.

11 Bryant RA, Kemp AH, Felmingham KL, et al.: Enhanced amygdala and medial prefrontal activation during nonconscious processing of fear in posttraumatic stress disorder: an fMRI study. Hum Brain Mapp 2008; 29:517-523.

12 Hermann A, Schafer A, Walter B, et al.: Diminished medial prefrontal cortex activity in blood-injection-injury phobia. Biol Psychol 2007; 75:124-130.

13 Fredrikson M, Fischer H, Wik G: Cerebral blood flow during anxiety provocation. J Clin Psychiatry 1997; 58 Suppl 16:16-21.

14 LeDoux JE: Emotion circuits in the brain. Annu Rev Neurosci 2003; 23:155-184.

15 McDonald AJ: Glutamate and aspartate immunoreactive neurons of the rat basolateral amygdala: colocalization of excitatory amino acids and projections to the limbic circuit. J Comp Neurol 1996; 365:367-379.

16 Miserendino MJ, Sananes CB, Melia KR, Davis M: Blocking of acquisition but not expression of conditioned fear-potentiated startle by NMDA antagonists in the amygdala. Nature 1990; 345:716-718.

17 Sheline YI, Gado MH, Price JL: Amygdala core nuclei volumes are decreased in recurrent major depression. Neuroreport 1998; 9:2023-2028.

18 Abercrombie HC, Schaefer SM, Larson CL, et al.: Metabolic rate in the right amygdala predicts negative affect in depressed patients. NeuroReport 1998; 9:3301-3307.

19 Kilts CD, Kelsey JE, Knight B, et al.: The neural correlates of social anxiety disorder and response to pharmacotherapy. Neuropsychopharmacology 2006; 31:2243-2253.

20 Stein MB, Simmons AN, Feinstein JS, Paulus MP: Increased amygdala and insula activation during emotion processing in anxiety-prone subjects. Am J Psychiatry 2007; 164:318-327.

21 Saunders RC, Rosene DL, Van Hoesen GW: Comparison of the efferents of the amygdala and the hippocampal formation in the rhesus monkey: II. Reciprocal and non-reciprocal connections. J Comp Neurol 1988; 271:185-207.

22 Hoover WB, Vertes RP: Anatomical analysis of afferent projections to the medial prefrontal cortex in the rat. Brain Struct Funct 2007; 212:149-179.

23 Nestler EJ, Barrot M, DiLeone RJ, et al.: Neurobiology of depression. Neuron 2002; 34:13-25.

24 Hasler G, van der Veen JW, Tumonis T, , et al.: Reduced prefrontal glutamate/glutamine and gamma-aminobutyric acid levels in major depression determined using proton magnetic resonance spectroscopy. Arch Gen Psychiatry 2007; 64:193-200.

25 Mirza Y, Tang J, Russell A, et al.: Reduced anterior cingulate cortex glutamatergic concentrations in childhood major depression. J Am Acad Child Adolesc Psychiatry 2004; 43:341-348.

26 Pfleiderer B, Michael N, Erfurth A, et al.: Effective electroconvulsive therapy reverses glutamate/glutamine deficit in the left anterior cingulum of unipolar depressed patients. Psychiatry Res 2003; 122:185-192.

27 Laje G, Paddock S, Manji H, et al.: Genetic markers of suicidal ideation emerging during citalopram treatment of major depression. Am J Psychiatry 2007; 164:1530-1538.

28 Mitani H, Shirayama Y, Yamada T, et al.: Correlation between plasma levels of glutamate, alanine and serine with severity of depression. Prog Neuropsychopharmacol Biol Psychiatry 2006; 30:1155-1158.

29 Yucel M, Wood SJ, Wellard RM, et al.: Anterior cingulate glutamate-glutamine levels predict symptom severity in women with obsessive-compulsive disorder. Aust N Z J Psychiatry 2008; 42:467-477.

30 Pollack MH, Jensen JE, Simon NM, et al.: High-field MRS study of GABA, glutamate and glutamine in social anxiety

disorder: response to treatment with levetiracetam. Prog Neuropsychopharmacol Biol Psychiatry 2008; 32:739-743.
31 Centonze D, Palmieri MG, Boffa L, et al.: Cortical hyperexcitability in post-traumatic stress disorder secondary to minor accidental head trauma: a neurophysiologic study. J Psychiatry Neurosci 2005; 30:127-132.
32 Schonenberg M, Reichwald U, Domes G, et al.: Effects of peritraumatic ketamine medication on early and sustained posttraumatic stress symptoms in moderately injured accident victims. Psychopharmacology (Berl) 2005; 182:420-425.
33 Cortese BM, Phan KL: The role of glutamate in anxiety and related disorders. CNS Spectr 2005; 10:820-830.
34 Lynch MA: Long-term potentiation and memory. Physiol Rev 2004; 84:87-136.
35 Sah P, Westbrook RF, Luthi A: Fear conditioning and long-term potentiation in the amygdala: what really is the connection? Ann N Y Acad Sci 2008; 1129:88-95.
36 Rogan MT, Staubli UV, LeDoux JE: Fear conditioning induces associative long-term potentiation in the amygdala. Nature 1997; 390:604-607.
37 Rogan MT, LeDoux JE: LTP is accompanied by commensurate enhancement of auditory-evoked responses in a fear conditioning circuit. Neuron 1995; 15, 127-136.
38 Hammen C: Stress and depression. Ann Rev Clin Psychol 2004; 1:293-319.
39 Garcia R, Musleh W, Tocco G, et al.: Time-dependent blockade of STP and LTP in hippocampal slices following acute stress in mice. Neurosci Lett 1997; 233:41-44.
40 Maroun M, Richter-Levin G: Exposure to acute stress blocks the induction of long-term potentiation of the amygdala-prefrontal cortex pathway in vivo. J Neurosci 2003; 23:4406-4409.
41 Rocher C, Spedding M, Munoz C, Jay TM: Acute stress-induced changes in hippocampal/prefrontal circuits in rats: effects of antidepressants. Cereb Cortex2004; 14:224-229.
42 Kavushansky A, Richter-Levin G: Effects of stress and corticosterone on activity and plasticity in the amygdala. J Neurosci Res 2006; 84:1580-1587.
43 Vouimba RM, Yaniv D, Diamond D, Richter-Levin G: Effects of inescapable stress on LTP in the amygdala versus the dentate gyrus of freely behaving rats. Eur J Neurosci 2004; 19:1887-1894.
44 Nestler EJ, Gould E, Manji H, et al.: Preclinical models: status of basic research in depression. Biol Psychiatry 2002; 52:503-528.
45 Cerqueira JJ, Mailliet F, Almeida OF, et al.: The prefrontal cortex as a key target of the maladaptive response to stress. J Neurosci 2007; 27:2781-2787.
46 Petrie RX, Reid IC, Stewart CA: The *N*-methyl-D-aspartate receptor, synaptic plasticity, and depressive disorder. Pharmacol Ther 2000; 87:11-25.
47 Fifkova E, Van Harreveld A: Long-lasting morphological changes in dendritic spines of dentate granular cells following stimulation of the entorhinal area. J Neurocytol 1977; 6:211-230.
48 Sapoznik S, Ivenshitz M, Segal M: Age-dependent glutamate induction of synaptic plasticity in cultured hippocampal neurons. Learn Mem 2006; 13:719-727.
49 McKinney RA, Luthi A, Bandtlow CE, et al.: Selective glutamate receptor antagonists can induce or prevent axonal sprouting in rat hippocampal slice cultures. Proc Natl Acad Sci USA 1999; 96:11631-11636.
50 Richards DA, Mateos JM, Hugel S, et al.: Glutamate induces the rapid formation of spine head protrusions in hippocampal slice cultures. Proc Natl Acad Sci USA 2005; 102:6166-6171.
51 Halpain S, Hipolito A, Saffer L: Regulation of F-actin stability in dendritic spines by glutamate receptors and calcineurin. J Neurosci 1998; 18:9835-9844.
52 Chung RS, McCormack GH, King AE, et al.: Glutamate induces rapid loss of axonal neurofilament proteins from cortical neurons in vitro. Exp Neurol 2005; 193:481-488.
53 Zhang ZW: Maturation of layer V pyramidal neurons in the rat prefrontal cortex: intrinsic properties and synaptic function. J Neurophysiol 2004; 91:1171-1182.
54 McEwen BS, Chattarji S: Molecular mechanisms of neuroplasticity and pharmacological implications: the example of tianeptine. Eur Neuropsychopharmacol 2004; 14 Suppl 5:S497-S502.
55 Liston C, Miller MM, Goldwater DS, et al.: Stress-induced alterations in prefrontal cortical dendritic morphology predict selective impairments in perceptual attentional set-shifting. J Neurosci 2006; 26:7870-7874.
56 Cui H, Sakamoto H, Higashi S, Kawata M: Effects of single-prolonged stress on neurons and their afferent inputs in the amygdala. Neuroscience 2008; 152:703-712.
57 Reines A, Cereseto M, Ferrero A, et al.: Neuronal cytoskeletal alterations in an experimental model of depression. Neuroscience 2004; 129:529-538.
58 Reagan LP, Rosell DR, Wood GE, Spedding M, et al.: Chronic restraint stress up-regulates GLT-1 mRNA and protein expression in the rat hippocampus: reversal by tianeptine. Proc Natl Acad Sci USA 2004; 101:2179-2184.
59 Pavlisa G, Papa J, Pavic L, Pavlisa G: Bilateral MR volumetry of the amygdala in chronic PTSD patients. Coll Antropol 2006; 30:565-568.
60 MacMaster FP, Mirza Y, Szeszko PR, et al.: Amygdala and hippocampal volumes in familial early onset major depressive disorder. Biol Psychiatry 2008; 63:385-390.
61 Pavic L, Gregurek R, Rados M, et al.: Smaller right hippocampus in war veterans with posttraumatic stress disorder. Psychiatry Res 2007; 154:191-198.

62 Haldane M, Cunningham G, Androutsos C, Frangou S: Structural brain correlates of response inhibition in Bipolar Disorder. I J Psychopharmacol 2008; 22:138-143.

63 Geuze E, Westenberg HG, Heinecke A, de Kloet CS, et al.: Thinner prefrontal cortex in veterans with posttraumatic stress disorder. Neuroimage 2008; 41:675-681.

64 Bardgett ME, Points M, Ramsey-Faulkner C, Topmiller J, et al.: The effects of clonidine on discrete-trial delayed spatial alternation in two rat models of memory loss. Neuropsychopharmacology 2008; 33:1980-1991.

65 Hahn CG, Gyulai L, Baldassano CF, Lenox RH: The current understanding of lamotrigine as a mood stabilizer. J Clin Psychiatry 2004; 65:791-804.

66 Zarate CA, Jr, Payne JL, Quiroz J, Sporn J, et al.: An open-label trial of riluzole in patients with treatment-resistant major depression. Am J Psychiatry 2004; 161:171-174.

67 Shibuya-Tayoshi S, Tayoshi S, Sumitani S, Ueno S, et al.: Lithium effects on brain glutamatergic and GABAergic systems of healthy volunteers as measured by proton magnetic resonance spectroscopy. Prog Neuropsychopharmacol Biol Psychiatry 2008; 32:249-256.

68 Grillon C, Cordova J, Levine LR, Morgan CA, III: Anxiolytic effects of a novel group II metabotropic glutamate receptor agonist (LY354740) in the fear-potentiated startle paradigm in humans. Psychopharmacology (Berl) 2003; 168:446-454.