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ARTICLE

Pathophysiology of mood disorders in temporal lobe epilepsy

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Abstract
Objective: There is accumulating evidence that the limbic system is pathologically involved in cases of psychiatric comorbidities in temporal lobe epilepsy (TLE) patients. Our objective was to develop a conceptual framework describing how neuropathological, neurochemical and electrophysiological aspects might contribute to the development of psychiatric symptoms in TLE and the putative neurobiological mechanisms that cause mood disorders in this patient subgroup. *Methods:* In this review, clinical, experimental and neuropathological findings, as well as neurochemical features of the limbic system were examined together to enhance our understanding of the association between TLE and psychiatric comorbidities. Finally, the value of animal models in epilepsy and mood disorders was discussed. *Conclusions:* TLE and psychiatric symptoms coexist more frequently than chance would predict. Alterations and neurotransmission disturbance among critical anatomical networks, and impaired or aberrant plastic changes might predispose patients with TLE to mood disorders. Clinical and experimental studies of the effects of seizures on behavior and electrophysiological patterns may offer a model of how limbic seizures increase the vulnerability of TLE patients to precipitants of psychiatric symptoms.

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Early observations and clinical aspects

Association between epilepsy and depression has been observed for over 2,400 years. As reviewed by Kanner,[1] Hippocrates stated that "*Melancholics ordinarily become epileptics, and epileptics, melancholics: what determines the preference is the direction the malady takes; if it bears upon the body, epilepsy, if upon the intelligence, melancholy*". Studies published during the second half of the XIX century also recognized that patients with epilepsy often presented with depressed mood, languidness, misanthropy and suicidal tendency.[2] Depression is generally defined by the presence of certain behaviors and thought patterns. Some of the major symptoms include low mood, reduced interest or pleasure in all activities, appetite changes, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, worthlessness or excessive guilt, reduced ability to think or concentrate and frequent morbid thought of death or suicidal ideation.[3] Depressive symptoms are often poorly recognized, and inadequate treatment might lead to a significantly impaired quality of life.[4]

In present numbers, the prevalence of depression in patients with recurrent seizures ranges from 20% to 80%.[5,6] The phenomenology of depression in epilepsy is a matter of debate. The most frequent symptoms include feelings of anhedonia, guilt and suicidal ideation. Other authors also report high anxiety, neuroticism, hostility, feelings of depersonalization, and rare manic and depressive-psychotic manifestations.[2] Presentation of depressive symptoms in epilepsy is often milder than in major depression,[7,8] but they are source of significant disruption in patients' daily activities, social relations, quality of life and require pharmacologic therapy to remit.[5] Depressive symptoms in epilepsy can be classified in 3 categories: (I) major depressive disorder, meeting Diagnostic and Statistical Manual, 4th edition (DSM-IV) diagnostic criteria; (II) atypical depression or dysthymia; or (III) a dysthymic-like disorder with intermittent symptoms that can be milder than those of major depression.[6] According to their temporal relationship with seizures, depressive symptoms can be ictal, peri-ictal or interictal, the latest being the most frequent.[5]

Until mid-XX century, depression in epilepsy was thought to be mostly of the "reactive" type,[9-11] in which depressive symptoms may be a reaction to stresses in life, including the effect of any underlying conditions. Indeed, as emphasized by Robertson and Trimble,[2] influential events such as "(...) repeated distressing episodes of loss of consciousness leading to morbidity, loss of self-esteem, and, often, personal embarrassment. The difficulty of getting a job, the social stigmatization, and the recurrent loss of dignity that the epileptic patient faces must be important provoking factors for the ensuing depression". However, studies from the last two decades have demonstrated biochemical, neuropathological and neurophysiologic changes mediating the development of mood disorders,[10] meaning that it is more usual for depression in epilepsy to be of the "endogenous" type.[12,13] As noted by Kanner *et al.*,[14] depression in epilepsy is often a combination of intrinsic and extrinsic processes that act synergistically.

In the late 1970's, Rodin *et al*. reported that patients with temporal lobe epilepsy (TLE) showed higher depression scores than patients with other types of epilepsy.[15] A few years later, a similar study suggested that patients with complex partial seizures that secondarily generalized had worse scores when compared with those with primarily generalized convulsive seizures.[16] Regarding seizure type, other studies have shown that depression is more frequent in patients with non-epileptic seizures than in those with epileptic seizures.[17] In pediatric patients, depression is also more frequent in cases with focal complex partial seizures than in patients with primarily generalized seizures.[18] Although seizure frequency or intractability[19] might not be related to the severity of depression, it is known that seizure type,[8,18] duration of epilepsy and antiepileptic drugs[8] are related to different levels of depressive symptomatology. By the same token, it has been recently found that the presence of secondarily generalized seizures is more frequent in adult mesial TLE patients with psychiatric comorbidities than in mesial TLE patients without psychiatric symptoms.[20] In fact, patients with mesial TLE seem particularly prone to comorbid depression.[21]

Atypical features may affect 20%[22] to 70%[23] of patients with depressive symptoms. In 1923, Kraepelin described a pleomorphic affective disorder in epilepsy, coined by Blumer et al.[24] "interictal dysphoric disorder", characterized by labile depressive symptoms (depressive mood, lack of energy, pain, insomnia), labile affective symptoms (fear, anxiety), and the presence of irritability and outbursts of aggressive/euphoric behavior as key symptoms. The prevalence of interictal dysphoria in TLE is about 17%.[25] Dysphoria is considered a psychopathological entity closer related to bipolar rather than unipolar mood disorders. In fact, one of the most famous historic figures presenting six of the seven cardinal symptoms of interictal dysphoric disorder was Vincent van Gogh,[26] who also exhibited signs of interictal personality.[27] Dysphoric symptoms may also occur in patients with chronic diseases other than TLE - such as migraine and different focal epilepsies[25,28] - as well as in premenstrual dysphoria.[29] Despite the high frequency of interictal dysphoria in epilepsy cases, classic bipolar disorder (type I) is rare,[8] ranging up to 1.4%.[30] Bipolar symptoms tend to be milder in patients with epilepsy than in pure bipolar patients, which often present fluctuating mood disturbances, rapid cycling of mood episodes and more frequent hallucinations.[31]

In addition to mood disorders, personality disorders other than the commonest interictal type[27] are also frequent in patients with epilepsy. In a series of TLE patients with hippocampal sclerosis from our epilepsy surgery center, 41.4% presented at least one Axis I diagnosis, according to DSM-IV criteria.[32] The majority (19.4%) had depression, 10.7% psychosis, 5.9% interictal dysphoric disorder, and 5.4% anxiety disorders. Personality disorders (Axis II) occurred in 12.4% of the patients, and, in some cases, overlapped with Axis I diagnosis. Most frequent traits were borderline, histrionic, epileptic personality disorder, antisocial, narcissistic, schizoid, and passive-aggressive personality.[32] Predominance of DSM-IV cluster A (paranoid, schizotypal, schizoid) and B (borderline, histrionic, antisocial, narcissistic), over cluster C personality disorders (avoidant, dependent, obsessive-compulsive) may indicate presence of non-epileptic seizures.[33] Other authors also reported high incidence of dependent-childish behavior[31] and deficits in social cognition.[34] Considering the type of epilepsy, patients with juvenile myoclonic epilepsy are more impulsive than

non-epileptic controls,[35] and adult patients with epileptic seizures present higher scores of schizoid, antisocial, histrionic, avoidant, dependent, passive aggressive and depressive traits compared to controls.[36] Also, a higher proportion of patients with epileptic seizures and personality disorders fits within DSM-IV cluster C when compared to patients with non-epileptic seizures.[33] Interestingly, schizoid, obsessive-compulsive and avoidance traits are correlated with epilepsy duration, but not with anxiety or depression presence.[36] Depersonalization and derealization traits are more frequent in patients with non-epileptic seizures than on those with epileptic seizures.[37] Several data suggest that epilepsy is not a primary pathophysiologic mechanism for developing dissociative symptoms[38,39] and that the presence of anxiety and depression is an important factor.[40] On the other hand, several data since Hughlings Jackson's in the late XIX century have found similarities between the so-called dreamy states or experiential phenomena[41] and behaviors redolent of depersonalization.[42]

Suicide is more common in people with epilepsy than in the general population, and the mortality ratio is further raised in those with TLE and those treated surgically.[43] Risk factors for suicide include: presence of mood disorders (depression and bipolar disorder) and other psychiatric disorders (for example schizophrenia-like psychosis), personality disorders (specially borderline personality disorder), substance abuse, self-destructive behavior, previous suicide attempts, chronic illness, stigmatization of epilepsy, periictal suicidal impulses and pharmacological treatment.[44] In a large study of more than ten thousand patients with epilepsy, five suicides were registered during a 12-year period and all occurred in patients with long-standing complex partial seizures and dysphoric disorder a short time after achieving full control of seizures.[45] In electroconvulsive treatment (ECT), controlled seizures can be elicited by a bifronto-temporal stimulus above the threshold for a generalized tonic-clonic seizure. Furthermore, most patients with endogenous depression who receive ECT recover completely or improve considerably.[46] Could chronic seizures also have a protective effect in comorbid endogenous depression cases, similar to what is seen in forced normalization? Landolt's early observations included dysphoric disorders on normalization of the electroencephalogram,[47] and the emergence or worsening of psychopathology on suppression of seizure activity has been widely reported.[45] As summarized by Blumer *et al.*,[45] when seizures are decreased or controlled, dysphoric symptoms, depressive mood and psychosis tend to be exacerbated, but the precise nature of the seizure-suppressing mechanisms is insufficiently understood.

Comorbidity does not necessarily imply causality; quoting Gabb et al.,[48] "(...) epilepsy begets depression, but does depression beget epilepsy?" Supporting the idea, a history of depression preceding the onset of epilepsy is up to six times more frequent in patients than in controls.[49,50] Such cases would fit within the endogenous depression type, and suggest the possibility of common pathogenic mechanisms operant in both disorders.[14] Possible neuropathological, neurochemical and electrophysiological mechanisms will be explored in the next sections.

Neuropathological aspects

In a series of one hundred patients with temporal lobe lesions (tumors, atrophy or cryptogenic), ninety-five had paroxysmal psychiatric manifestations such as hallucinations, perceptual illusions, disturbances of emotion or mood, personality disorders (mostly schizoid traits) and automatisms.[11] The predominant mood disorders were depression and anxiety, the latter resembling dysphoric features. Indeed, presence of mesial temporal sclerosis has been considered a predisposing factor for the development of mood disorders in focal epilepsy.[21] Although temporal lobe involvement seems unequivocal in depression manifestation,[51] paralimbic structures such as temporal and prefrontal cortex are also compromised.[52,53] Focal hypometabolism in ipsilateral orbitofrontal cortex is usually found in TLE patients with depression when compared with TLE patients without depression; after epilepsy surgery, patients in whom depression developed only postoperatively also show hypometabolism in the ipsilateral orbitofrontal region.[52] Interestingly, Rajkowska et al.[54] have previously demonstrated significant decrease in cortical thickness, neuronal sizes and neuronal and glial densities within the orbitofrontal cortex of pure depressed patients.

Monoaminergic neurotransmission is classically related with major depression, mostly because the mechanism of action of antidepressant drugs that augments these neurotransmitters in the synapses.[55] Positron-emission tomography (PET) imaging studies have shown reduced binding of serotonin (5-HT) receptor 1A in frontal, temporal and limbic cortex[56] and in the raphe[57] in depressive patients when compared with controls. A deficit in the density of postsynaptic serotonergic receptors also has been identified in the hippocampus and amygdala of patients who committed suicide.[58] Furthermore, impaired serotonin transmission, consisting of an excessive density of serotonergic somatodendritic 5-HT_{1A} autoreceptors in the dorsal raphe has been found in suicide victims with major depression.[59] Similar 5-HT alterations are found in TLE patients. A PET study using a 5-HT_{1A} receptor antagonist showed reduced affinity in mesial temporal structures ipsilateral to the seizure focus in TLE patients with and without hippocampal atrophy.[60] Reduction in 5-HT_{1A} binding was also found in the raphe nucleus and in ipsilateral thalamic regions.[60] Another study investigating TLE patients found decreased affinity of 5-HT_{1A} in the epileptogenic hippocampus, amygdala, anterior cingulate, and lateral temporal neocortex ipsilateral to the seizure focus, as well as in the contralateral hippocampus.[61] Studies conducted in TLE patients with comorbid depression also indicate abnormalities in serotonergic neurotransmission. 5-HT_{1A} receptor binding in TLE patients with major depression show decreased signal when compared with TLE patients without depression, independent of the side of the lesion and the degree of hippocampal sclerosis.[62] Another PET study found an inverse correlation between the severity of depressive symptoms and the affinity of 5-HT_{1A} binding in the ipsilateral hippocampus, and a positive correlation between the severity of depressive symptoms and the magnitude of hippocampal abnormalities.[63]

Brain regions involved in both TLE and depression include the temporal lobes with hippocampus, amygdala, entorhinal and temporal cortex, the frontal lobes, subcortical structures such as basal ganglia and thalamus, and the connecting pathways.[64] Neuropathological data on TLE and comorbid

depression are scant. Recent data suggest that there is a structural basis for psychiatric symptoms in patients with TLE. There is evidence of N-Methyl-D-aspartate (NMDA) receptor subunit NR1 up-regulation in the dentate gyrus molecular layer in unmedicated TLE patients with depressed mood when compared to TLE patients without psychiatric comorbidities.[65] In addition to that, in our series of hippocampi from mesial TLE patients with depression we found CA4 neuronal density as high as in non-epileptic controls, and increased mossy fiber sprouting when compared with mesial TLE patients without psychiatric history.[20] Although antidepressant treatment does not cause mossy fiber sprouting, chronic administration of fluoxetine causes robust changes in the serotonergic modulation of the mossy fiber synaptic transmission in mice.[66] Serotonin is able to potentiate the mossy fiber synaptic transmission, and chronic fluoxetine reduces the synaptic potentiation induced by higher concentrations of serotonin; meanwhile, low concentrations of serotonin might enhance synaptic potentiation, which represent the stabilization of the serotonergic modulation.[67] In mesial TLE with depression, enhanced mossy fiber sprouting might act as a protection against depressive symptoms, or conversely, the increased sprouting could represent an insufficient compensatory response to the chronic or subsequent stress provoked by depressive episodes.[20] Further cellular physiological studies in animal models would be important in order to clarify the involvement of the dentate gyrus and mossy fibers in psychiatric disorders, since the clinical significance of sprouting remains to be elucidated.[67]

In the last two decades, several neuropathological studies have been done with *post-mortem* brain samples from patients with major depression, especially in fronto-limbic regions. Gross morphological changes such as focal lesions are not present in depression (as usually found in TLE – for review see [68]), but cytomorphological differences between depressed and control subjects can be demonstrated at the microscopic level.[69] Reduced glial density in depressive disorder is found in prefrontal cortex,[54] entorhinal cortex and amygdale.[70] In fact, amygdalar glial reduction seems pathognomonic, and mostly related to astrocytes[71] or oligodendrocytes.[72] The cortical regions where neuronal pathology has been detected include the hippocampus, orbitofrontal, prefrontal and cingulate cortex, without clear definition whether a true loss of cells underlies reductions in cell density and size.[69] Other evidences of neuronal pathology comprise reductions in the precursor form of brain-derived neurotrophic factor (BDNF) in the hippocampus of specimens with major depression,[73] although treatment with antidepressants may increase hippocampal BDNF protein expression.[74] In the prefrontal cortex, reduced glutamic acid decarboxylase (GAD) expression is seen in unmedicated patients with major depression, but not in antidepressant medicated patients.[75] There is similar gamma-aminobutyric acid (GABA) depletion assessed through calcium-binding proteins staining in prefrontal interneurons,[76] and possible diminished local serotonin release in subjects with major depression.[59] In agreement with those findings, the use of GABA agonists and antagonists is able to modulate depressive symptoms, and chronic administration of antidepressant drugs induce marked changes in GABAergic function.[77] Furthermore, several anticonvulsant and GABA-mimetic agents possess mood stabilizing and antidepressant properties.[77,78] Patients with TLE show decreased expression of glutamate transporters in the dentate gyrus,[79] as well as patients with major depressive disorder in the frontal brain regions, striatum and hippocampus, leading to increased glutamatergic neurotransmission.[80,81] Hasler et al. showed that levels of glutamate/glutamine and GABA were decreased in prefrontal dorsomedial and ventromedial regions of patients with major depression.[82] Imaging studies have also shown a decrease in glutamate in the anterior cingulate cortex of adults[83] and children[84] with depression. In unmedicated adults with depressive disorder, decreased GABA levels and synthesis in dorsomedial, dorsalanterolateral prefrontal, and ventromedial prefrontal regions and occipital regions were found.[78,85] In addition, treatment with the NMDA antagonist ketamine has shown improvement of depressive symptoms in patients with major depression, and in patients with treatment-resistant major depression.[86,87]

Imaging studies in bipolar disorder have shown increased amygdala, hippocampus and temporal lobe volume in bipolar patients when compared to schizophrenics, and the amygdala in bipolar cases is actually larger than in normal subjects.[88] Such increase in volume is controversial, since no changes in neuronal or glial densities are seen in amygdala specimens of patients with bipolar disorder.[71] In the hippocampus, nonpyramidal neuronal density is significantly decreased in CA2 of bipolar patients compared to control subjects, with no other differences in the pyramidal or nonpyramidal neurons throughout the Ammon's horn between any groups.[89] In the entorhinal cortex, decreased vesicular glutamate transporter 1 mRNA expression is found, but not in the hippocampus or temporal cortex.[90] Other studies have also reported decreased neuronal and glial density in the prefrontal cortex of bipolar specimens, as well as enlargement of layer III interneuronal neuropil.[91] In interictal dysphoric disorder, normal magnetic resonance imaging and normal electroencephalogram is found in the majority of cases.[28] Based on what is known about bipolar cases and on TLE with psychiatric comorbidities, it would be expected neuropathological changes underlying interictal dysphoria, whereas no answer to this hypothesis is available up to now.

Evidences from animal models

One of the first described TLE models was electrical kindling, which is characterized by the sustained increase in seizure susceptibility and the absence or minimal extent of neuronal injury, as well as the absence of spontaneous recurrent seizures when the number of kindled seizures is low.[92,93] However, spontaneous motor seizures may appear after sufficient electrical stimulation (*e.g.* ranging from 88 to 293 stimuli in amygdala kindling).[94,95] Systemic[96] or intracerebral[97] administration of pilocarpine or kainate in rodents leads to a pattern of repetitive limbic seizures and *status epilepticus* (SE), which can last for several hours.[98] Neuropathological changes - such as neuron loss - in several hippocampal subfields and reorganization of mossy fibers into the molecular layer of the fascia dentata are observed in both models and are similar to hippocampi from patients with hippocampal sclerosis.[98]

One of the challenges associated with understanding mechanisms of depression in epilepsy has been the lack of validated animal models of this condition.[99] So far, studies

that attempted to develop valuable animal models of comorbidity between epilepsy and depression focused on behavioral alterations in animal models of epilepsy classically linked to depression. As already mentioned, two of the major symptoms in depression are despair and anhedonia. In rodents, the behavioral equivalents to these emotional states are accessed by two classical tests: the forced swim test and the saccharin or sucrose taste preference test. The forced swim test relies in the adaptive behavior of rodents when confronting a stressful situation. Basically, rodents exhibit two patterns of behavior: active escaping and/or exploring behavior or immobility, when their movements are limited to those necessary to keep their heads above the water. An increase in immobility time is regarded and related to the degree of despair. The taste preference evaluates the hedonic state measuring rodent's natural preference for sweets: when given access to tap water and sweet solution they strongly prefer the latter. However, animals submitted to experimental stress have a decrease in consumption of the sweet solution, indicating an alteration of underlying reward mechanisms.[100]

Several studies have shown that rats submitted to SE induced by lithium-pilocarpine, kainate or electrical kindling spent a significantly longer time immobile in the forced swim test and exhibited loss of preference for saccharin solution when compared to non-epileptic animals,[101-105] indicating that rats submitted to seizures show an increase in depressive behavior. Although immobility time is increased in post-SE rats, severity of behavioral, endocrine and biochemical hallmarks of depression seem independent of seizure frequency,[105] similarly to what occurs in humans.[19] However, there is a positive correlation between severity of depression and hippocampal hyperexcitability, suggesting that depressive symptoms may be a net result of limbic dysfunction.[106]

Nevertheless, other studies using pharmacological models of epilepsy were unable to replicate these data. Recent experimental studies have shown that mice submitted to SE induced by pilocarpine, lithium-pilocarpine, focal kainate administration or kindling showed decrease in depression-like behavior.[107-110] Results from our laboratory also indicate that rats submitted to SE induced by lithium-pilocarpine do not present depressive behavior in the forced swim test and in the learned helplessness paradigm during the silent phase of epileptogenesis (unpublished results). These discrepancies can be the result of differences in the protocol used, mainly, (1) rodent's age at the time of the SE induction; (2) time after SE and frequency of recurrent spontaneous seizures; (3) used species and gender.

Although there are still controversies if animal models of epilepsy can present with behavioral alterations related to depressive symptoms, there is evidence about shared mechanisms. The genetic absence of epilepsy in rats from Strasbourg (GAERS) show depressive and anxiety-like behavior before the onset of seizures, indicating that common biological alterations could be underlying the two neurological conditions.[111] Ferrero et al.[112] showed that chronic treatment with fluoxetine enhances seizure threshold and the basal glutamate release. Interestingly, when rats are submitted to the learned helplessness paradigm, there is no effect of fluoxetine in seizure threshold or glutamate release.[112] In fact, rats bred for susceptibility to depression-like phenotypes present higher mortality than non-depressive rats after SE induction by kainate.[113] Also, rats that spent more time immobile in the forced swim test show faster and more intense hippocampal kindling.[114] Evidences also link stress with seizure susceptibility. Rats treated with corticosterone supplementation are more sensitive to epileptogenesis in the amygdala kindling model of TLE.[115] Also, the genetic model of epilepsy Wistar audiogenic rats (WAR)[116] has increased adrenal gland hyperplasia associated with enhanced pituitary and adrenal responsiveness after hypothalamic-pituitary-adrenal (HPA) axis stimulation.[117] Besides HPA hyperactivity, WARs also display hypertension, tachycardia and increased sympathetic tone[118] as well as a pattern of endogenous anxiety revealed by decreased exploration in both the open arms of the elevated plus maze and in the open field.[119] Thus, the WARs are currently being explored as a genetically developed strain with epilepsy and a variety of neuropsychiatric comorbidities.

Neurotransmitter systems altered in epilepsy and mood disorders

Several experimental cues from the common neurobiological alterations between epilepsy and comorbid depression came from the genetic epilepsy prone rat (GEPR). GRPR-3 and GEPR-9 strains have predisposition to sound-induced generalized seizures and marked kindling acceleration. They also present depressive behavior manifested by decreased sucrose consumption and increased immobility time in the forced swim test.[120] Moreover, GEPR exhibit endocrine alterations - such as increased corticosterone serum levels, deficient secretion of growth hormone, and hypothyroidism[121] - in accordance to what is found in depressive patients, such as elevated concentrations of circulating cortisol and corticotrophin.[122] In addition to that, GRPR-3 and GEPR-9 strains are marked by noradrenaline and 5-HT neurotransmission deficits, resulting from impaired arborization of noradrenergic and serotonergic neurons arising in the locus coeruleus and raphe nuclei.[123] Likewise, substances that interfere with synthesis or release of noradrenaline or 5-HT have been found to accentuate seizures,[121] and an increase in noradrenergic or serotonergic neurotransmission might prevent seizures.[124-128]

Disturbances in glutamate and GABA

The excitatory and inhibitory misbalance in epilepsy is known for a long time.[64] However, only recently the involvement of GABA and glutamate was recognized in depressive disorders.[129] There is evident relation between glutamatergic and monoaminergic neurotransmission. Glutamatergic neurons projects from the cortex to monoaminergic subcortical nuclei like locus coeruleus, raphe nucleus, and substantia nigra.[129] Also, drugs that augment noradrenaline and 5-HT usually decreases glutamate response.[130,131]

In a recent review, Kanner proposes three lines of evidence that support a pathogenic role of glutamate and GABA in depression: (1) dysfunction of glutamate transporter proteins; (2) abnormal concentrations of cortical glutamate and GABA; and (3) antidepressant effects of glutamate receptor antagonists.[129] Glutamate transporters are important to maintain low excitatory extracellular glutamate's levels and consequently regulate the synaptic concentration. Experimental studies have shown reduced expression of

glutamate transporters excitatory amino acid transporters in animal models of depression.[132,133] Also, decreased function of glutamate transporters are related to elevated extracellular glutamate levels, neuronal death, and epilepsy.[134]

The role of the excitatory/inhibitory neurotransmission in mood disorders is strengthened by the antidepressant effects of several glutamate antagonists. NMDA and metabotropic glutamate receptor antagonists (including MK-801, ketamine, mGluR5 antagonist 2-methyl-6-(phenylethynyl)-pyridine (MPEP), and the mGluR2/3 antagonists LY341495 and MGS0039) have antidepressant activity in the forced swim test, tail suspension test and learned helplessness models of depression.[132,135]

Deregulation of Hypothalamus-Pituitary-Adrenal (HPA)

Deregulation of the HPA system is a central feature of depressive disorders. Briefly, hypothalamus secretion of corticotropin-releasing factor (CRF) stimulates synthesis and release of pituitary gland adrenocorticotropin. In turn, the latter stimulates adrenal cortex to secrete glucocorticoids. These hormones are central to successfully coping with a major physical stressor, as they mobilize stored energy, increase cardiovascular tone, and suppress costly anabolism. HPA deregulation occurs when failures in the negative-feedback that controls the level of circulating glucocorticoid are present.[136] Several brain structures regulate this activity, including the hippocampus, which has inhibitory influence on hypothalamic CRF-containing neurons, while the amygdala exert excitatory control.[137] A neurotoxic role for augmented glucocorticoids has been extensively described in experimental data. High levels of glucocorticoids leads to injury of synapses,[138,139] particularly involving CA3 pyramidal neurons, reduction of dendritic branching and spines that are part of glutamatergic synaptic inputs,[136] decrease in BDNF levels, and interference with neurogenesis of granule cells in the adult hippocampal dentate gyrus.[140] All of these effects result in structural changes in the dentate gyrus, pyramidal cell layer of hippocampus, amygdala, and temporal neocortex.[70,140,141] In the frontal lobes, high corticosteroid secretion has been associated with a decrease in glial cell numbers in subgenual, cingulated, and dorsolateral sections of the prefrontal cortex.[54,142-146]

Neuronal alterations are also associated with the development of mood and anxiety disorders.[147] Patients with major depressive disorder exhibit alterations that are linked with hyperactive HPA such as atrophy of hippocampi, and frontal lobes, including cingulate gyrus and orbitofrontal and dorsolateral cortex demonstrated by multiple investigators.[148-150] In fact, neuropathologic consequences attributed to excessive cortisol include: (1) decreased glial densities and neuronal size in the cingulate gyrus; (2) decreased neuronal sizes and neuronal densities in layers II, III, and IV in the rostral orbitofrontal cortex resulting in a decrease of cortical thickness; (3) a significant decrease of glial densities in cortical layers V and VI associated with decreases in neuronal sizes in the caudal orbitofrontal cortex; and (4) a decrease of neuronal and glial density and size in all cortical layers of the dorsolateral prefrontal cortex.[54,142-146]

Furthermore, enhanced glucocorticoids levels can be involved in the disruption of raphe-hippocampal serotonergic transmission found in depressive patients. It's proposed that a mechanism involved in the regulation of 5-HT neurotransmission from raphe, involves somatodendritic 5-HT_{1A} autoreceptors.[99] The activation of raphe 5-HT_{1A} autoreceptors by locally released serotonin inhibits firing of serotonergic neurons and further neurotransmitter release.[151] Clinical and experimental data have suggested that glucocorticoids can cause an up-regulation of 5-HT_{1A} in raphe, therefore, leading to an enhanced autoinhibition of 5-HT.[59,152] So in chronic stress conditions like depression or after SE it is possible that the elevated corticosteroid levels could lead to reduced 5-HT neurotransmission.[99]

Recently, abnormal functioning of HPA comparable to those found in depressive patients has been demonstrated in humans with TLE without depressive disorders[149] as well as in animal models of epilepsy.[104] Again, using the lithium-pilocarpine model, Mazaratti group showed an increase in corticosteroid serum levels in SE rats that is correlated with depressive-like behavior and raphe-hippocampal serotonergic deficit. Furthermore, local raphe treatment with glucocorticoid receptor blocker reversed both enhanced immobility time in the forced swim test and raphe-hippocampal serotonin deficit hallmarks of depression.[104] As cited before, corticosteroid treatment can accelerate amygdala kindling and this process is inhibited by corticosteroid antagonists.[111,153] This mechanism may also be involved in depression associated with epilepsy: in TLE patients with concurrent depression, binding affinity of raphe 5-HT_{1A} receptors is increased, and positively correlated with the severity of clinical symptoms of depression.[154]

Exacerbated HPA function promoted by chronic stress is related with decrease in 5-HT_{1A} mRNA expression and binding in the hippocampus, an effect prevented by tricyclic antidepressants.[155] 5HT_{1A} receptor binding and its mRNA expression are under tonic inhibition by glucocorticoid receptor stimulation. Accordingly, high levels of corticosteroid could underlie the reduced 5-HT_{1A} receptor binding seen in patients with depression.[129]

Furthermore, increased corticosteroid concentrations are associated with decreased levels of BDNF. BDNF is related with plasticity and survival of adult neurons and glia;[156] and reduced BDNF levels might contribute to hippocampal injury. This deficiency is ameliorated by antidepressant treatment and is related to treatment efficacy. Administration of antidepressant drugs increases BDNF expression in several brain structures.[74,157,158] Also, BDNF administration produces anti-depressant effects in rats.[141,159] However, TLE patients have an increased BDNF expression that might either act as a neuroprotector factor promoting cell survival or contribute to modifications in neuronal circuitries related to epileptogenesis.[160]

Hippocampal neuroinflammation is another possible common pathological mechanism in TLE and depression. Interleukin-1 beta (IL-1β) signaling could be underlying these alterations.[99] Clinical and experimental studies have linked increased IL-1β and its receptor activation as a feature of TLE.[161] Also, IL-1β can induce activation of HPA axis and facilitate depressive symptoms.[162] In fact, 2-week intrahippocampal administration of an IL-1β antagonist reduced the biochemical, endocrine and behavioral features of depression

but had no effect in frequency of spontaneous seizures in lithium-pilocarpine SE model.[106]

Synaptic plasticity

Neural plasticity is a key feature in a mammal's brain that could sustain changes in organization and functional dynamics of nervous tissue allowing adaptive behavior to different ecological demands.[163] In accordance, experience can modify brain activity including maladaptive plasticity in response to brain injury. A number of studies have connected neural plasticity with the pathophysiology of mental disorders like epilepsy, mood disorders and schizophrenia. Current theories hypothesize that neuroplastic alterations during development may contribute to structural and functional changes in important circuits, which can have long-lasting effects on adult brain function.[164]

A decrease in plasticity is related to an increase of the threshold for adaptation[165] making the individual more vulnerable to negative input[166]. Reduced spine and synapse density have been shown in *post-mortem* studies of depressed patients[167] and in animal models;[168] also, such features may be restored with antidepressant treatment.[169] In addition to morphological rearrangement, activity-dependent changes in synaptic efficacy (*i.e.* synaptic plasticity) are also affected in depression.[170] This kind of plasticity affects neurotransmission efficiency and might regulate information flow and behavior.[163] Reduction of long-term potentiation (LTP) and enhancement of CA1 long-term depression (LTD) is observed in animal models of depression.[171,172] Illustrating the severity of these plastic modifications caused by stress events, Ryan et al.[173] showed that acute inescapable foot-shock stress - used to study learned helplessness - inhibited LTP in the dorsal hippocampus for at least 4 weeks.

Also, antidepressant drugs as well as electroconvulsive therapy (ECT) effectively modulate synaptic plasticity in the hippocampus and other brain structures.[169,174-176] For example, escitalopram restored CA1-LTP and monoamine levels in neonatal clomipramine-exposed rats.[177] Additionally, tianeptine, a selective serotonin reuptake enhancer, counteracted the negative effects of acute stress on synaptic plasticity.[178] Lithium, a well-known drug used in bipolar disorder related to cell survival and neurogenesis, enhances LTP induction in the hippocampus' dentate gyrus.[179,180]

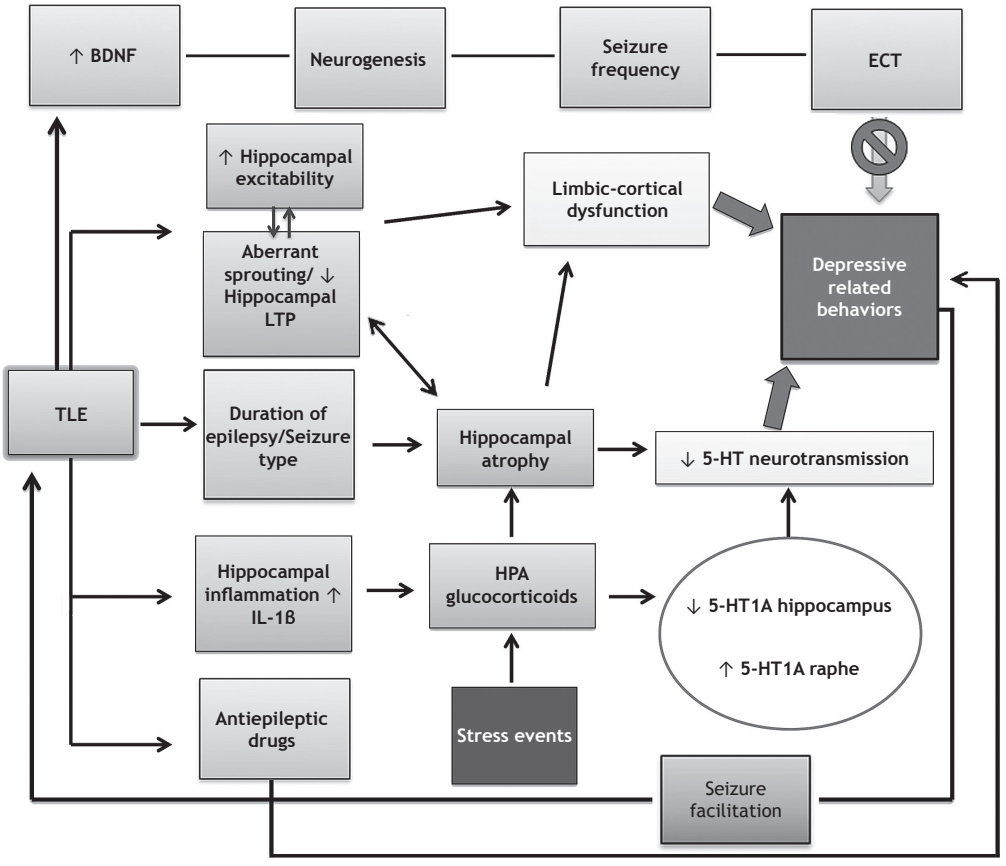
The existence of a continuum between plasticity and pathology is an appealing hypothesis sustained by some authors.[181] Synaptic efficiency is constantly regulated on a dynamic equilibrium, maintaining the balance between excitation and inhibition. In a pathological situation this normal process could be deregulated, which might result in an increase in excitation and a decrease in inhibition. This unbalanced condition could lead to an epileptic focus and subsequent seizure activity. The mechanisms underlying these types of changes would presumably be very long-lasting forms of plasticity resistant to reversal and/or LTD.[181,182] In addition, morphological changes independent of LTP could be responsible for the development of pathology.[183] However, LTP itself is associated with morphological changes similar to those seen as a result of kindling.[184] In fact, LTP and kindling share similar mechanisms such as the requirement of high-frequency stimulation, glutamatergic transmission and an increase in the intracellular calcium. Moreover, LTP and kindling involve changes in gene expression, protein synthesis, morphology and the activity of metabotropic glutamate receptors.[181,182]

It is proposed that seizure activity causes an indiscriminate and widespread induction of long-term potentiation, consuming and thereby reducing overall hippocampal plasticity available for information processing. In fact, repeated seizures reduce the ability to induce LTP and impair spatial learning in animals.[185] The amount of learning deficits seen in animals is similar in time course as the transitory cognitive impairment seen following ECT in humans treated for severe affective disorder.[185] Further, the effects of ECT in humans or electroconvulsive seizures in animal models on LTP can be blocked by the NMDA antagonist ketamine.[185] This suggests that seizures "saturate" the synapses with long-term facilitation that decreases the capacity for plasticity including LTP and memory. Kindling also suppresses LTP,[186] and lithium-pilocarpine induced SE promotes a severe reduction of LTP in the hippocampus, which is related to impaired fear memory formation.[187] Neonatal seizures in animals can induce long-term loss of LTP, impair spatial learning, and alter NMDA protein expression.[188] Also, LTP is markedly reduced in the epileptogenic hippocampus of humans with TLE, but LTP is quite normal in the hippocampus, which is not the primary seizure focus.[189]

Most of the works have investigated changes in synaptic plasticity in the pathological hippocampus. Studies that investigate changes in more expanded circuitry including thalamus, prefrontal cortex and amygdala, for instance, are of great importance to better understand the pathophysiology of the disease and the genesis of a comorbid condition. For example, a recent work by Sloan and Bertram[190] shows that epileptic rats present a significant reduction in the thalamically-induced responses in the prefrontal cortex, reducing thalamo-cortical communication. Importantly, some studies have shown that the effects of depression on LTP impairment and cognitive deficits may be mediated via profound alterations in neural information flow in the thalamus-cortical pathway.[191] In addition, thalamocortical dysrhythmia is found in a series of pathological conditions such as neurogenic pain, tinnitus, Parkinson's disease and depression.[192]

Conclusions

As summarized in the Flowchart, emerging results from a variety of clinical and experimental paradigms suggest that epilepsy and mood disorders have shared and also antagonistic mechanisms. Cytoarchitectural and neuropil disarray are seen in these conditions, and such changes are indicative of robust circuitry dysfunction. Both mood disorders and epilepsy present marked changes in hippocampal synaptic plasticity. The most evident is a reduction in the ability of LTP induction, which is reflected in the cognitive deficits shown in both conditions, since LTP represents a cellular mechanism underlying memory and learning. Defining whether these plastic changes are possible causes or simply a consequence is still a matter of debate. Studies conducted in TLE experimental models such as amygdala kindling, SE (pilocarpine, kainate), as well as research with genetically developed strains (GAERS, GEPRs, WARs) indicate that changes in the dynamics of information processing caused by genetic



Flowchart Some of the cooperative and antagonistic mechanisms that underlie the close association between TLE and depressive symptoms. Not shown in the scheme are genetic features such as those present in familiar epilepsies and mood disorders, and those modeled in the genetically developed strains. They are obvious components of the complexity of these comorbidities.

susceptibility and the experience of repeated seizures can produce behavioral alterations related to depressive states. However, to better understand these complex interactions, it will be necessary to investigate possible changes in synaptic plasticity (electrophysiology, gene and protein expression) in models of TLE and comorbid depression.

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** Modest*
*** Significant*
**** Significant. Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.*

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