Fibromyalgia and Bipolar Disorder: Emerging Epidemiological Associations and Shared Pathophysiology

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Abstract: Fibromyalgia (FM) is a prevalent disorder defined by the presence of chronic widespread pain in association with fatigue, sleep disturbances and cognitive dysfunction. Recent studies indicate that bipolar spectrum disorders frequently co-occur in individuals with FM. Furthermore, shared pathophysiological mechanisms anticipate remarkable phenomenological similarities between FM and BD. A comprehensive search of the English literature was carried out in the Pubmed/MEDLINE database through May 10th, 2015 to identify unique references pertaining to the epidemiology and shared pathophysiology between FM and bipolar disorder (BD). Overlapping neural circuits may underpin parallel clinical manifestations of both disorders. Fibromyalgia and BD are both characterized by functional abnormalities in the hypothalamic-pituitary-adrenal axis, higher levels of inflammatory mediators, oxidative and nitrosative stress as well as mitochondrial dysfunction. An over-activation of the kynurenine pathway in both illnesses drives tryptophan away from the production of serotonin and melatonin, leading to affective symptoms, circadian rhythm disturbances and abnormalities in pain processing. In addition, both disorders are associated with impaired neuroplasticity (e.g., altered brain-derived neurotrophic factor signaling). The recognition of the symptomatic and pathophysiological overlaping between FM and bipolar spectrum disorders has relevant etiological, clinical and therapeutic implications that deserve future research consideration.

Keywords: Bipolar disorder, fibromyalgia, inflammation, oxidative stress, brain-derived neurotrophic factor, hypothalamic-pituitary adrenal axis, neuroimaging, pathophysiology, psychiatry, neurology.

1. INTRODUCTION

Fibromyalgia (FM) is a centralized pain syndrome characterized by the presence of chronic widespread pain (CWP) in association with fatigue, sleep disturbances and cognitive dysfunction [1, 2]. Individuals with FM exhibit an increased prevalence of mental disorders as compared to the general population and may have a four-fold increased risk of developing mood disorders [3, 4]. The most consistently reported psychiatric comorbidities are Major Depressive (MDD) and anxiety disorders, which co-occur in up to 80% and 63.8% of individuals with FM, respectively [5]. Chronic pain aggravates the prognosis and course of subjects with mood disorder and has been associated with higher rates of non-remission and recurrences as well as greater disability [6, 7]. The relationship between mood disorders and FM extends beyond the traditional concept of comorbidity, since chronic pain and depression are acknowledged mutual predictors of the development of each other in a complex bidirectional fashion [8]. Notwithstanding the patho-etiological processes involved in these conditions have not been fully elucidated to date, emerging evidence reveals that this large symptomatic overlap could be at least in part explained by identified common shared pathophysiological substrates [9].

While the literature on the association between FM and MDD is vast, the relationship between other chronic psychiatric disorders and FM has received comparatively little attention. However, recent findings suggest that the co-occurrence of BD and chronic pain conditions is probably overlooked [8]. Individuals with

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BD are significantly more likely to complain of chronic pain as compared to subjects with MDD or anxiety disorders. Moreover, self-reported pain has been correlated with functional impairment, notably greater disability and unemployment in populations with bipolar spectrum disorders [10-12]. Accordingly, chronic pain has been reported to affect approximately 50% of individuals with bipolar depression and seems to be related to sleep disturbances and a delayed diagnosis of BD [13]. A large-scale (N = 106 214) meta-analysis indicates that chronic pain may co-occur in 23.7% of individuals with BD [14]. Conversely, subjects with FM from two community-based rheumatology practices in the U.S. had a 12.8% lifetime prevalence of BD [15], which is much higher than the estimated 2.4% lifetime prevalence in the general population worldwide [16].

The pathophysiological overlap of BD and FM is further suggested by notable clinical and phenomenological similarities between these illnesses. For example, both BD and FM have been associated with circadian rhythm abnormalities [17, 18], cognitive dysfunction [19], fatigue [20, 21], as well as an altered stress response [22, 23].

The association between FM and BD has important treatment implications, since the widespread use of antidepressants in FM management may promote mood destabilization, manic switches and episodes with mixed features, complicating the progressive course of BD [24, 25], while other novel therapies may be more feasibly targeted to the comorbidity. Thus, the overarching aims of this article are (1) to review epidemiological and clinical associations between BD and FM and (2) to summarize evidence supporting a partially shared neurobiological and pathophysiological basis between BD and FM leading to relevant potential implications for the prevention and treatment of both diseases.

2. METHODS

A comprehensive search of the English literature was carried out in the PubMed/Medline database, including combinations of the following search terms: “Fibromyalgia”, “chronic widespread pain”, “Bipolar Disorder”, “comorbidity”, “pathophysiology”, “neuro-imaging”, “inflammation”, “oxidative and nitrosative stress”, “hypothalamic-pituitary-adrenal axis”, “neuroplasticity”, “melatonin”, and “vitamin D” through May 10th, 2015. For this narrative review, articles were screened based on overall methodological quality and relevance to the topic. We also considered for inclusion systematic reviews and meta-analyses as well as previous reviews related to the subject. This search strategy was augmented by a review of reference lists of selected articles.

2.1. Epidemiology of Fibromialgia and Comorbidity with Bipolar Disorder

Fibromyalgia is defined according to the American College of Rheumatology (ACR) by CWP (i.e., pain in the axial skeleton plus in the left and the right side of the body and pain above and below the waist for a duration of at least 3 months) in combination with tenderness at 11 or more of 18 specific tender point sites [26]. The alternative 2011 FM survey criteria were intended for use in epidemiological studies and do not rely on the examination and counting of tender points [27]. Furthermore, a screening questionnaire intended for use in large-scale epidemiological studies is also available [28]. Population-based studies of FM report a mean prevalence rate of 3.1% in the Americas, 2.5% in Europe and 1.7% in Asia, as summarized by a recent review [29]. FM is more common in females, with a marked female preponderance considering the alternative criteria [1, 27] and consistently associated with poor socio-economic status and lower educational attainment [30, 31].

Up to 80% of individuals with FM exhibit one or more co-occurring medical or psychiatric disorders [32], including but not limited to mood and anxiety disorders, hypertension, dyslipidemia, diabetes, atherosclerosis, cardiovascular diseases, thyroid dysfunction, asthma, autoimmune diseases and gastrointestinal disturbances [27, 33]. Moreover, other “functional” conditions, such as irritable bowel syndrome and chronic fatigue syndrome are more frequently reported in FM subjects than the general population [34]. Trauma exposure in childhood has been implicated as a risk factor for both FM and BD in adulthood [35, 36]. Concordant with this, early life adversity leads to long-lasting immune, neuroendocrine and metabolic imbalances [37-39], which contribute to more complex somatic and psychiatric comorbidity patterns [40, 41].

Despite consistent evidence of an association between FM and MDD, anxiety as well as trauma- and stressor-related disorders [42, 43], evidence of a relationship between FM and bipolar spectrum disorders is less compelling. However, a growing number of studies have been addressing this topic. Preliminary observational reports indicated a higher than expected risk for treatment-emergent affective switches among FM patients receiving antidepressants [24], which provided initial evidence for a possible association between FM and bipolarity. A cross-sectional study on women diagnosed with FM (N=37) reported a high frequency of self-reported manic symptoms (defined as a Mood Disorder Questionnaire-MDQ score > 6), approximately twice that of controls (N=138) [44]. In a small longitudinal study, the same research group assessed the long-term effects of antidepressant treatments over a 1-year follow-up in a sample of women with FM (N=23) [45]. Approximately 40% of the sample screened positive for a bipolar spectrum disorder regardless of previous exposure to antidepressant treatment. However, the group treated with antidepressants reported more impaired quality of life and greater functional disability – whether this reflects true detrimental effects of antidepressants (e.g. mood instability), or the use of these agents in more ill people requires clarification. In keeping with this evidence, another cross-sectional study on 128 FM patients referred to a tertiary rheumatology practice reported that a quarter of subjects (25.19%) screened

positive for bipolarity [46]. Importantly, in this survey among 100 individuals with FM who self-reported clinically significant depressive symptoms (defined by scores on the Beck Depression Inventory- BDI- >10) nearly a third (32%) screened positive for a bipolar spectrum disorder. Moreover, individuals with FM who screened positive for BD exhibited more severe depression as compared to those with a negative screen [median BDI: 26.0 (19.0, 32.0) versus 15.0 (9.0, 24.0)] [46]. Consistent with this report, several studies reported significantly higher rates of diagnosed BD in cohorts of FM patients compared to general population estimates [47, 48]. This is particularly relevant considering that an underlying bipolar diathesis may portend a poorer response to conventional treatments for FM. In FM treatment with selective serotonin–norepinephrine reuptake inhibitors (SNRIs) (e.g., duloxetine, venlafaxine and milnacipram) is supported by high-quality evidence and is recommended by the U.S. Food and Drug Administration (FDA) [1]. However, the exposure to dual-acting antidepressants has been associated with a particularly high rate of treatment-emergent manic switch and mood destabilization in BD [49]. Therefore, FM patients should be routinely evaluated for a co-occurring bipolar spectrum disorder prior to treatment with antidepressants.

The importance of careful screening for manic/hyphomanic symptoms is further underscored by another cross-sectional study on 167 individuals with FM, in which the number of lifetime manic symptoms, as assessed by the Mood Spectrum Self-Report, positively correlated with more severe pain and worse quality of life [50]. It is possible that an underlying bipolarity among individuals with FM may not be restricted to BD as defined by the current diagnostic criteria. For instance, premorbid “overactivity”, which has been well described in subjects with FM, may be viewed as a core feature of BD [51, 52].

Furthermore, some researchers have hypothesized that the association between CWP/FM and an “intense creative energy- ICE-” behavioral phenotype (defined by high emotional intensity, racing thoughts, artistic temperament and/or presence of diagnosed affective disorder) may be associated with alpha-1-antitrypsin (A1AT) S or Z polymorphism, similarly to individuals with bipolar spectrum disorders, who also exhibit an increased proportion of A1AT polymorphisms as well as significant overlap with the ICE phenotype and FM [53]. The A1AT gene polymorphism is implicated in processes related to the inflammatory response and brain development and has been postulated to exert a potential genetic influence on the pathophysiology of FM, along with genetic polymorphisms related to the monoaminergic pathways, neuroendocrine and autonomic response pathways (vide infra). However, these findings should be interpreted with caution in the light of advances in recent genetic studies demonstrating that BD and FM are genetically heterogeneous conditions to which multiple polymorphic genes appear to confer vulnerability with small single effect sizes and complex gene-environment epigenetic interactions [54].

A growing body of literature indicates that the relevant symptomatic association between BD and FM may be at least in part explained by significant pattern of overlap with regard to shared neurobiological changes in CNS structures involved in the regulation of pain and emotional control. Furthermore, alterations in neuroendocrine as well as in immune/inflammatory pathways, along with cellular/subcellular abnormalities affecting neuroplasticity and neurotransmission seem to overlap both in FM and BD (see Fig. **1**).

3. STRUCTURAL AND FUNCTIONAL NEURO-IMAGING FINDINGS

3.1. Structural and Functional Brain Abnormalities Related to Fibromyalgia

A complete understanding of mechanisms involved in the pathophysiology of FM remains heuristic. Nevertheless, there is a general consensus that FM may be viewed as a product of aberrant pain transmission [9]. Central amplification of pain processing leads to an enhanced transmission of nociceptive information to the brain, expanded receptive fields (resulting in a wider distribution of pain) and augmented stimulus responses (i.e., temporal summation) [55].

Under physiological conditions, nociceptive information is at first transmitted *via* A delta and C fibers of primary afferent neurons to second-order neurons in the dorsal horn of the spinal cord. The activation of N-methyl-D-aspartate (NMDA) glutamate receptors is thought to play a role in “wind-up” sensitization phenomena in dorsal horn neurons [56]. Painful stimuli reach the thalamus *via* spinothalamic and spinoparabrachial tracts and its sensory-discriminative as well as affective-emotional aspects are subsequently processed in the somatosensory cortices I and II and associated structures, such as the insula, the anterior cingulate cortex (ACC) [57], the posterior cingulate cortex (PCC), the amygdala, the hippocampus and the hypothalamus [58]. The periaqueductal gray area (PAG) is implicated in the integration of ascending pain information and regulates the activity of descending modulatory pain pathways [59]. Descending excitatory connections from the PAG reach the rostral ventromedial medulla (RVM) and dorsolateral pons (DLP), which, in turn, send inhibitory projections to the spinal cord, thus modulating nociceptive transmission. The dorsolateral (DLPFC) and the ventrolateral (VLPFC) prefrontal cortices also connects to subcortical structures, which modulate descending pain pathways, leading either to a substantial reduction in pain intensity or a to heightened pain threshold. Therefore, the dysregulation of descending regulatory pathways, as a result of inadequate activity in the inhibitory pathway or excessive activity in the facilitatory pathway has been postulated to play a significant role in hyperalgesia (i.e., increased response to a painful stimulus) and allodynia

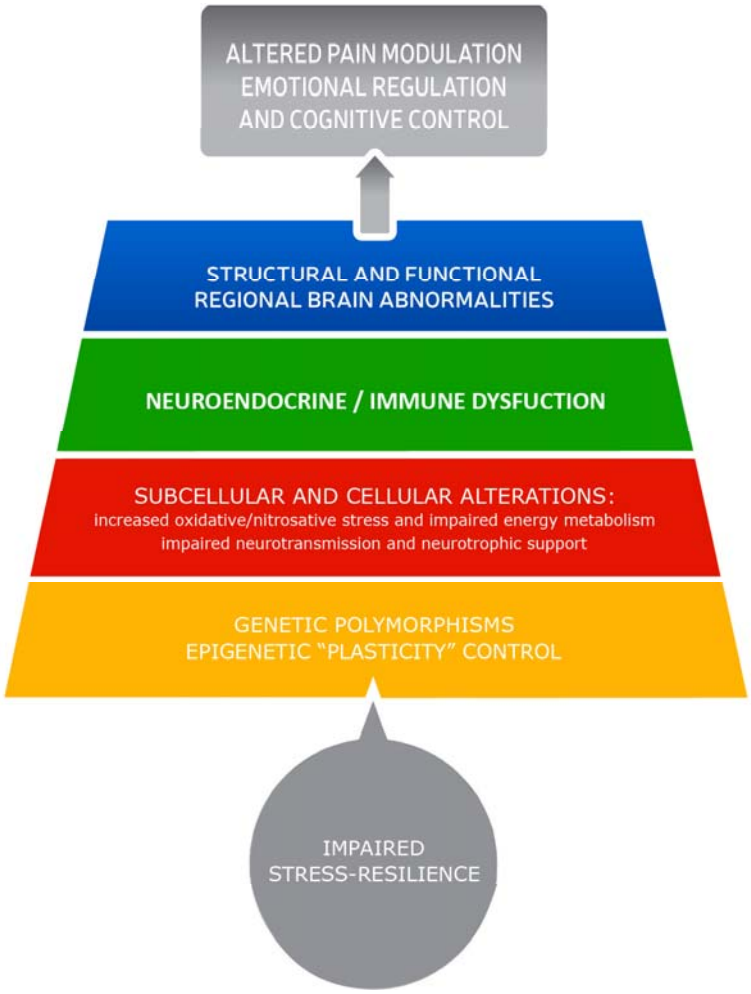

Fig. (1). Shared pathophysiological mechanisms may underpin the substantial epidemiological and clinical overlap between FM and BD.

(i.e., increased response to an innocuous stimulus), which are thought to underlie FM painful manifestations (see Fig. **2**) [60].

Structural magnetic resonance imaging (MRI) studies have documented a decrease in grey matter density in areas involved in pain transmission and processing including the medial frontal cortex, the ACC, the insula as well as the amygdala and the parahippocampal gyri in FM patients as compared to healthy controls [61, 62]. These findings have been confirmed in a recent systematic review, which indicates a moderate correlation between central sensitization and gray matter volume decrements in the medial prefrontal network, notably the ACC and the PFC, the insula, the thalamus and the parahippocampal gyri [63]. These brain areas are implicated not only in the affective discrimination of painful stimuli, but also in the anticipation and amplification of self-perceived pain in response to an apparently innocuous stimulation [64]. Additionally, abnormalities in the medial frontal cortex and ACC have been correlated with impairments in working memory performance, possibly representing structural correlates of pain-cognition interaction [65].

Functional magnetic resonance imaging (fMRI) studies have reported a greater activation in "pain matrix" areas, including but not limited to the DLPFC, PCC ACC, insula, superior temporal gyrus and inferior parietal lobule in individuals with FM as compared to healthy controls [66, 67]. Temporal summation of pain stimuli in subjects with FM has been associated with increased activity of the somatosensory cortex, the ACC and the thalamus as well as with altered connectivity between these interrelated areas [67]. Furthermore, fMRI studies provided evidence of a decreased functional connectivity in the descending pain-modulating system in FM patients as well as a significant connectivity imbalance within the pain network also at rest [63, 68]. A growing base of evidence supports specific differences in brain activation patterns in resting and pain-evoked states, which confirms associations between hyperalgesia and impaired inhibitory descending systems, as well as integrated cognitive-affective influences on painful

experiences, leading to augmented pain-processing [69].

Alterations in the activity of the insula, the cingulate cortex, the amygdala and the nucleus accumbens (Nacc) in FM subjects when compared to controls have also been reported using magnetic resonance spectroscopy (MRS) [70]. In addition, a meta-analysis of MRS studies assessing the hippocampal content of N-acetylaspartate (NAA) as a marker of neuronal structure and function revealed a significant decrease in NAA in FM patients *vs* controls, supporting a role for hippocampal neuronal abnormalities in the pathophysiology of FM [71]. Moreover, these studies reported high concentrations of glutamate in these brain areas, possibly suggesting a role for excitotoxic neuronal damage and neuroplasticity disruption in FM [72]. Morphometric and functional changes in the mesolimbic areas of the brain appear to be more pronounced after a longer exposure to FM-related pain, as well as in association with more severe co-occurring depressive symptoms [73]. Taken together, evidence from both structural and functional neuroimaging studies supports the involvement of integrated neurocircuitries subserving emotional regulation, cognitive functioning and pain modulation/processing in the pathophysiology of FM.

3.2. Structural and Functional Brain Abnormalities Related to Bipolar Disorder

Notwithstanding a significant heterogeneity of BD samples with regard to the stage and duration of illness as well as treatment status confounded the replication of many neuroimaging studies in BD [74], converging evidence indicates that the progressive course of BD is associated with substantial structural and functional brain abnormalities [75]. Global structural changes and the enlargement of lateral ventricles are replicated findings and seem to correlate with the cumulative number of mood episodes [76]. Cortical thickness reduction across frontal and limbic areas has also been found to correlate with affective symptom severity, cognitive dysfunction and age of disease-onset in BD [77].

Structural and functional abnormalities are also reported in the PFC of individuals with BD, including alterations in the ventromedial PFC (VMPFC), VLPFC and DLPFC [78-80]. Replicated findings from functional neuroimaging studies also confirm evidence of diminished prefrontal cortical activity in the DLPFC, the VLPFC and the dorsomedial (DMPFC) in bipolar depression [81-83]. Given the consistent pattern of reciprocal projections between the VMPFC and the ACC, the amygdala and the hypothalamus, it has been posited that the VMPFC may exert a pivotal role in the regulation of autonomic and neuroendocrine responses to emotional states [84]. The VLPFC has been indicated as the origin point for executive control network and appears to be involved in the "top-down" affective modulation leading to the suppression of maladaptive emotional responses [81]. In addition, striatal-VLPFC connections are implicated in the reward-processing circuitry, the "overactivity" of which seem to contribute to the characteristic behavioral abnormalities associated with BD, including emotional dysregulation and as well as heightened reward sensitivity [85]. Abnormalities in DLPFC activity have been implicated in executive-cognitive network dysfunction *via* disturbed connectivity with the ACC and limbic structures [86]. These later disturbances may translate into deficits in sustained attention, working memory and executive functions.

In addition to abnormalities in the PFC, morphological studies have documented significant decrements in the volume of the subgenual ACC in BD [87]. The subgenual ACC and the insula are pivotal structures of the "salience" network, which influences the assessment of the relevance as well as the selection of behavioral responses related to environmental stimuli [88]. Furthermore, the ACC exerts an important role in the regulation of autonomic and neuroendocrine responses to stressors [89].

Structural and functional neuroimaging studies have also reported increased amygdala volumes in BD as well as heightened activity, notably during mania [81, 90]. Furthermore, increased activity of the thalamus, hypothalamus and insula has also been reported in bipolar depression compared to healthy controls [91, 92].

Diffusion tensor imaging studies report patterns of altered connectivity between the subgenual ACC and the amygdala, the frontal and occipital cortices, the insula and the thalamus in individuals with BD as compared to healthy controls [93, 94]. In addition, BD is associated with significant abnormalities in subcortical cytoarchitecture as evidenced by alterations in the hippocampus, thalamus and caudate nucleus [95]. Impairments in the connectivity between the PFC and the amygdala, thalamus and striatum may serve as a neuroanatomical correlate of global deficits in prefrontal control over limbic and paralimbic structures [96]. Other findings include changes in functional connectivity within the hippocampal network as well as volumetric reductions and altered white matter fiber integrity in BD patients as compared to healthy controls [97].

3.3. Summary of Shared Structural and Functional Findings in Fibromyalgia and Bipolar Disorder

In FM as well as in BD, structural and functional neuroimaging studies document abnormalities in cortical areas involved in pain processing and emotional control including the medial frontal cortex, the DLPFC, the VLPFC and the VMPFC and the ACC. In particular, the DLPFC and the VLPFC are implicated in the control of descending modulatory pathway, the dysregulation of which is thought to play a significant role in hyperalgesia and allodynia in FM. On the other hand, the medial frontal cortex, the ACC and the PFC are implicated also in emotional regulation and inhibitory control, providing a basis for the understanding of behavioral abnormalities such as emotional overreactivity both in FM and BD. Therefore, the significant overlap between neuroanatomical

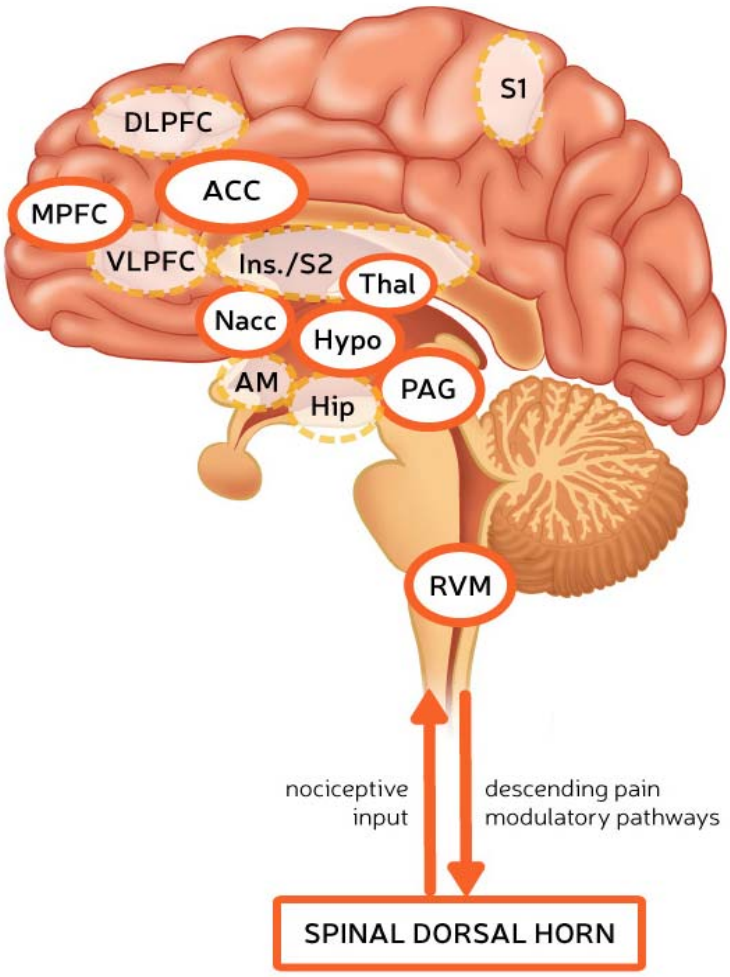

Fig. (2). Cortical and subcortical structures relevant to pain processing. Structural and functional abnormalities of the PFC, the insula and the ACC are the most replicated cortical abnormalities in FM. DLPFC, dorsolateral prefrontal cortex; MPFC, medial prefrontal cortex; VLPFC, ventrolateral prefrontal cortex; Ins., insula; S1/2, somatosensorial cortex 1/2; Thal, thalamus; Nacc, nucleus accumbens; AM, amygdala; Hip, hippocampus; Hypo, hypothalamus; PAG, periaqueductal gray; RVM, rostral ventromedial medulla.

interconnected circuits, both involved in the regulation of pain and emotional/cognitive control may support a shared organic basis for overlapping symptomatology in BD and FM.

Furthermore, structural and functional imaging in BD and in FM provides evidence for an impairment of prefrontal-limbic networks in the pathophysiology of both illnesses. For instance, decreased volume in the amygdala and decreased connectivity with the PFC are linked to an increased perception of emotional salience to non-emotional contexts. Abnormalities in the ACC and the insula, observed both in FM and BD, may contribute to a dysregulated "salience" network relevant to the pathophysiology of both disorders. Disturbed connectivity between the prefrontal cortex, the amygdala, the hippocampus as well as striatal structures may translate into neurocognitive deficits in the domains of executive functions, attention and memory. Lastly, disturbed connectivity among the VMPFC and the ACC, the amygdala, the hypothalamus and the hippocampus may influence neuroendocrine and autonomic responses in both disorders.

4. NEUROENDOCRINE DYSREGULATION

4.1. Neuroendocrine Dysregulation in Fibromyalgia

Evidence of a disturbed stress response in FM is provided by replicated studies demonstrating an imbalance in hypothalamic-pituitary-adrenal (HPA) axis activity. Notwithstanding several studies providing evidence of basal hypocortisolism in individuals with FM as compared to healthy controls [98], a meta-analysis of 85 studies involving individuals with functional somatic syndromes *versus* healthy controls indicates that the findings across studies remain inconclusive [99]. Separate investigations have also reported a flattened circadian secretion of cortisol with an attenuated cortisol increment following awakening [100, 101], as well as enhanced feedback sensitivity to dexamethasone [102], although this may manifest at

the adrenal level [103]. However, these findings must be interpreted with caution as other studies documented reduced feedback sensitivity to dexamethasone in FM at least in part mediated by comorbid depression (for example, see Ref. [104]). It has been posited that hypocortisolism may ensue in FM after a prolonged period of hyperactivity of the HPA axis [105]; this "exhaustion" could explain hypocortisolism in FMG despite possible resistance of glucocorticoid receptors (GRs) (vide infra).

Nevertheless, converging evidence points out to the functional nature of HPA axis hypoactivity in FM [106]. A host of studies documented a significant reduction in glucocorticoid receptor (GR) sensitivity as well as a reduced GR expression in peripheral mononuclear cells in individuals with FM compared to healthy controls [107, 108]. Importantly, the aforementioned HPA axis disturbances in FM may in part be attenuated after successful treatment of the disorder. For instance, a good clinical response (i.e., reduction in pain intensity) to a multidisciplinary treatment program combining physical activity and cognitive behavioral therapy was associated with increased GR mRNA expression [109]. Noteworthy, a diminished sensitivity to glucocorticoids may lead to an unopposed production of pro-inflammatory mediators (e.g., cytokines), which may contribute FM-related pain and fatigue [110].

4.2. Neuroendocrine Dysregulation in Bipolar Disorder

A dysfunctional hypothalamic-pituitary-adrenal (HPA) axis may play a key role in the pathophysiology of BD and related neuroprogression [111, 112], but the precise mechanisms leading to this dysregulation remain incompletely elucidated. In contrast to what has been reported for FM, replicated evidence, although not unequivocal, indicates that BD is associated with HPA axis hyper-activation. Subjects with BD exhibit higher cortisol levels as compared to healthy controls [113], as well as non-suppression to dexamethasone [114]. HPA axis hyperactivity appears to be more pronounced in late-stages of BD and correlates with the number of previous affective episodes as well as with cognitive deterioration [114], suggesting that HPA axis dysfunction may be 'neurotoxic' [111].

While these findings may support differential patterns of HPA axis dysfunction in FM and BD (i.e., hypoactivity *vs* hyperactivity, respectively), a closer look at the functional implications of impaired glucocorticoid signaling in both illnesses is warranted. For example, similar to FM, BD has been associated with GR hypo-responsiveness and glucocorticoid resistance, *via* increased expression of inactive receptors isoforms (GR β subunit) partly as a result of cytokine signaling [115]. Furthermore, environmental insults may also influence GR hypo-responsiveness through epigenetic mechanisms. For instance, increased DNA methylation of the FK506-binding protein 51 gene, which codes for a co-chaperone involved in GR desensitization, has been recently associated with GR hypo-responsiveness in BD [116]. These findings are consistent with etiologic models of BD that implicate disturbed stress-response pathways established in the early development as a pathophysiological substrate for the disorder [117]. Furthermore, glucocorticoid resistance may contribute to the activation of cell-mediated immunity, which leads to cytokines-induced glucocorticoid secretion with a detrimental effect on hippocampal neurogenesis [118, 119].

4.3. Summary of Shared Neuroendocrine Abnormalities in FM and BD

Taken together, the aforementioned results indicate that BD is associated with a hyper-activation of the HPA axis, impaired GR-mediated signaling as well as a blunted cortisol response to dexamethasone. Conversely, reported neuroendocrine disturbances in FM have been less consistent. Nevertheless, evidence indicates that both disorders are associated with abnormalities in GR responsiveness, which may contribute to impaired resilience to stress as well as to the over-activation of innate and cellular immunity in both disorders (vide infra). In this view, HPA axis dysregulation and inflammation possibly contribute in a vicious circle to the progressive nature of BD and FM.

5. IMMUNE DYSFUNCTION AND OXIDATIVE/ NITROSATIVE STRESS IN FIBROMYALGIA AND BIPOLAR DISORDER

5.1. Immune System Dysfunction and Oxidative/ Nitrosative Stress in Fibromyalgia

The extent literature regarding the levels of inflammatory mediators in individuals with FM provides discrepant results. Several methodological limitations and potential confounders limit between-study comparisons, including small sample sizes and heterogeneous sample composition, as well as insufficient control for factors influencing the levels of inflammatory mediators including gender, illness duration, BMI, co-occurring depression and concomitant medications [120]. Nevertheless, a growing body of evidence indicates that FM is associated with a pro-inflammatory status as well as oxidative and nitrosative stress (O&NS).

Several studies reported increases in cytokines serum levels, including tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6) and IL-8 [121-123], as well as elevated peripheral levels of macrophage chemoattractant protein-1 (MCP-1) [124]. In parallel, a reduction in the levels of anti-inflammatory cytokines in FM may contribute to a chronic low-grade inflammatory state. For instance, reductions in IL-4 and IL-10 levels have been reported in chronic widespread pain [125]. Data from a meta-analysis and systematic review indicate elevated serum levels of interleukin (IL)-1 receptor antagonist, IL-6 and IL-8 in individuals with FM as compared to controls [126]. The cross-talk between peripheral immune cells and immune cells within the CNS, including but not limited to the microglia, may induce the central production of cytokines, chemokines

as well as reactive oxidative and nitrogen species [127]. Preclinical studies using the continuous-stress rat model provided evidence that the activation of microglia cells in the dorsal horn are involved in the development of abnormal pain with allodynia and hyperalgesia [128]. This pro-inflammatory status may contribute to HPA axis activation and stress-induced autonomic responses, characterized by enhanced sympathetic activity and dampened parasympathetic activity [129]. In addition, it may intensify pain experience *via* increased substance P release from primary afferent nerve terminals leading to a facilitation in the transmission of painful signals [130]. Higher levels of substance P along with serotoninergic dysfunction may promote hyperagesia and sleep disturbances in FM [131]. Furthermore, although FM is classically viewed as a non-autoimmune rheumatic disease, some evidence indicates that FM may be associated with higher serum levels of autoantibodies. For example, higher serum autoantibodies to 5-TH [132], anti-thyroid autoantibodies [133] have been reported in individuals with FM as compared to healthy controls.

Similarly to BD, accumulating evidence implicates a dysfunctional tryptophan-kynurenine pathway associated with neuroplasticity impairment and oxidative stress as a pathogenic factor in FM [134]. Tryptophan catabolites (TRYCATs) (e.g., kynurenine and quinolinic acid) derived from cytokines-induced and glucocorticoid-induced activation of the indoleamine 2,3-dioxygenase (IDO) mainly in microglial cells, exert neurotoxic effects that contribute to neurodegeneration [135]. Moreover, the activation of the TRYCATs pathway leads to tryptophan depletion, leading to serotonin (5-TH), N-acetylserotonin and melatonin reduction [136].

A substantial involvement of oxidative stress in the pathophysiology of FM is supported by reports of an increase in peripheral oxidative stress, DNA oxidative damage, an increase in protein carbonyl content, as well as increased plasma levels of malondialdehyde (MDA) and prolidase activity in FM patients as compared to healthy controls [137-139]. In addition to a more elevated oxidative stress index, a significant reduction in total antioxidant capacity is noted in the pathophysiology of FM [140]. For instance, diminished activity of antioxidant enzymes like superoxide dismutase, glutathione peroxidase and catalase have been consistently documented in FM patients compared to controls [138, 141]. Furthermore, lower serum levels of antioxidant vitamins (e.g., vitamins E and A) have been reported in women with FM as compared to age and gender-matched healthy controls [142]. Oxidative stress results in elevated lipid peroxidation as well as mitochondrial dysfunction, which have been associated with symptom severity in FM [143]. Interventions capable of restoring the dysregulated bioenergetic status and cellular metabolism, including oral coenzyme Q (10) (CoQ (10)) supplementation, have been associated with symptomatic improvement in FM and may hold promise as potential novel treatment targets [144, 145].

Increases in peripheral nitric oxide synthase (NOS) activity, along with higher serum NO levels have also been reported in FM as compared to healthy controls [141; 142], albeit inconsistently [146]. Furthermore, an association between NO levels and pain intensity is a replicated finding in FM [141, 146]. Taken together, notwithstanding the need for further studies with appropriate sample sizes and a prospective design in order to establish the role of immune-inflammatory dysfunction and O&NS, the foregoing data support the involvement of these factors in the pathophysiology of FM of the disorder.

5.2. Immune System Dysfunction and Oxidative/ Nitrosative Stress in Bipolar Disorder

In parallel, the role of inflammation in the pathophysiology and illness-related comorbidity patterns in BD is now established. For example, several studies reported elevated levels of the acute-phase protein C-reactive protein (CRP) in mania as compared to healthy controls, while CRP levels have been also inversely correlated with cognitive performance in BD [147, 148]. In addition, elevated levels of high sensitivity-CRP have been associated with reduced volume of the orbitofrontal cortex in a MRI study in euthymic BD patients [149]. With regard to cytokines' levels in BD, two separate meta-analyses integrated the conflicting results of many studies performed across different affective states. Both reported elevated levels of soluble the interleukin-2 receptor (sIL-2R), sIL-6R, IL-4, TNF-α and soluble TNF-α receptor 1 (sTNFR1) [150, 151], while elevated levels of IL-1β, IL-1 receptor antagonist (IL-1RA) and IL-10 were documented by one (the larger) of these meta-analyses [151].

These results point out to an over-activation of both innate and adaptive immunity in BD [152]. It has been postulated that increased levels of anti-inflammatory cytokines (e.g., IL-4 and IL-10) may be a compensatory mechanism related to the stage of illness (i.e., observed in earlier but not later stages of BD) [153]. Thus, an inflammatory state could be aggravated in advanced stages of BD as a result of the failure of adaptive homeostatic mechanisms, thus paving the way to neuroprogression [112]. In addition, increased levels of several chemokines have been reported in individuals with BD as compared to controls, including MCP-1 [154], CXCL-8 [155], CXCL-10 [156]. Increased expression of MCP-1 mRNA by isolated monocytes has been documented both in BD patients as well as in the offspring of individuals with BD, thus possibly representing a trait-marker for BD [157]. A higher activity of matrix metalloproteinases in BD has also been reported and could amplify the effect of pro-inflammatory cytokines and chemokines through increments in blood-brain barrier permeability [158]. Emerging evidence supports the notion that the activated microglia may contribute to neuro-inflammation and neuroprogression associated with BD [159]. Lastly, compelling evidences indicate a higher prevalence of autoimmunity in BD (reviewed in Ref. [160]).

These alterations as a whole are intimately linked to O&NS, which contributes to glutamate excitotoxicity and disturbances in mitochondrial energy metabolism

(e.g., in the activity of enzymes of the electron transport chain) in BD [161]. In a meta-analysis on oxidative/nitrosative stress markers of BD, increased levels of lipid peroxidation, DNA/RNA damage and nitric oxide (NO) were evident in all phases of the illness [162] and may persist in euthymic elderly BD patients [163]. DNA damage appears to correlate with the number of manic episodes in BD [164]. Higher peripheral oxidative metabolites as well as lower total serum antioxidant capacity, along with lower serum glutathione peroxidase activity have been reported in individuals BD as compared to healthy subjects [165, 166]. Furthermore, elevated levels of carbonyl proteins, a putative marker of oxidative stress, have also been reported in early-stage BD [167], in euthymia [168] and in the postmortem PFC [169]. Lastly, increased levels of thiobarbituric acid reactive substances (TBARS), a surrogate of lipid peroxidation, have been reported in mania and bipolar depression, regardless of psychotropic treatment [170]. Importantly, treatment with lithium has been demonstrated to decrease TBARS levels in mania [171] and in euthymia [172], as well as in subjects with BD II depression [173], and antioxidant therapy appears to have promise in the disorder [174]. Taken together, these data indicate that a chronic low-grade inflammatory state accompanied by O&NS occurs in BD.

5.3. Summary of Shared Immune Abnormalities in Fibromyalgia and Bipolar Disorder

Taken together, the foregoing data indicate that both FM and BD are characterized by chronic low-grade inflammation indicated by higher levels of pro-inflammatory cytokines. Higher levels inflammatory cytokines in the periphery as well as in the CNS may lead to the activation of the TRYCATs pathway in both illnesses, which may compromise 5-HT neurotransmission. Furthermore, tryptophan catabolites are neurotoxic, anxiogenic and depressogenic and are linked to O &NS. Neuro-immune alterations (e.g., activated microglia) may contribute to phenomenological similarities between FM and BD, including malaise, fatigue, and cognitive disturbances.

However, there are also significant differences between FMG and BD regarding neuro-immune mechanisms. For example, evidence points to increased levels of IL-6 and its soluble IL-6 receptor (sIL-6R) without significant changes in sgp130 levels in BD, suggesting increased IL-6 signaling [161, 175]. In FMG, however, there is a significant increase in sgp130, which may down-regulate IL-6-trans-signaling [176].

6. NEUROPLASTICITY DYSREGULATION IN FIBROMYALGIA AND BIPOLAR DISORDER

Disturbances in neurotrophic regulation along with immune alterations and O&NS are increasingly associated with impaired neuroplasticity and altered cellular metabolism in FM [177]. Elevated serum [178, 179], as well as plasma [180] and cerebrospinal fluid [181] BDNF levels have been consistently reported in subjects with FM as compared to controls, possibly secreted by microglial activated cells. Furthermore, BDNF serum levels have been inversely correlated with pain pressure threshold in FM [182] and positively correlated with the severity of depressive symptoms [179]. Interestingly, the SNP Val66Val in the BDNF gene has been shown to be associated with a FM subgroup phenotype characterized by higher hs-CRP and BMI [183].

With regard to BD, recent data on BDNF levels provide conflicting results (reviewed in Ref. [184]). For instance, elevated plasma BDNF levels have been reported in BD during euthymic, depressive, manic and hypomanic states as compared to healthy controls [185]. On the contrary, other findings include decreased serum BDNF levels in manic, hypomanic and depressive stages of BD [186] as well as BDNF levels comparable to those of healthy controls during euthymia [187]. A recent meta-analysis indicated that BDNF levels are significantly decreased in patients with an acute depressive episode (d=−1.16, 95% CI −1.79 to −0.54, p=2.5E-04, 6 effect sizes, n=117) or an acute manic episode (d=−0.77, 95% CI −1.10 to −0.44, p=1.9E-05, 8 effect sizes, n=156), but not in euthymic patients when compared with controls (d=0.05, 95% CI −0.42 to 0.43, p=0.098, 9 effect sizes, n=426) [188]. Furthermore, other studies reported that serum BDNF levels inversely correlate with age and duration of illness, possibly representing a marker of neuroprogression [153], while some reports suggest that a successful response to treatments is associated with restored plasma BDNF levels in BD [189].

Lastly, studies have also been inconsistent about the relation between BD and the Val66Met polymorphism of BDNF gene. The Val/Val genotype of the Val66Met BDNF gene SNP has been associated with earlier age of onset [190], rapid cycling [191], and higher levels of anxiety in BD offspring [192]. On the contrary, other studies linked the Met allele to the age of onset, a more severe course of the disorder [193] as well as to cognitive dysfunction in BD subjects with history of childhood abuse [194]. While the BDNF genotype is likely to be relevant in the regulation of anxiety, mood and cognition, further studies are warranted to elucidate the relationship between BDNF genotype, affective states and environmental influences.

7. POTENTIAL SHARED GENETIC SUBSTRATES FOR FIBROMYALGIA AND BIPOLAR DISORDER

The experience of pain results from complex interactions among several genetic variants involved in different steps of neuronal processing of nociceptive information, with additional multiple gene-environment interactions. Further complexity arises from the heterogeneity among different pain conditions and emotional aspects of the pain experience. Nevertheless in population studies, a host of genetic polymorphisms seemingly influence pain experiences [195]. Genetic polymorphisms in the serotoninergic, dopaminergic and

catecholaminergic systems have been implicated in the etiology of FM and mood disorders and may reflect the overlapping neurobiology of both illnesses [196]. For instance, several studies documented an increased distribution for the C/C genetic variant of the serotonin 2A receptor (5-HT2AR) gene polymorphism in FM as well as BD populations [197]. In a study on individuals with FM a decrease in T/T and an increase in both T/C and C/C genotypes of 102T/C single-nucleotide polymorphism have been observed as compared to controls, although higher pain scores correlated with the T/T genotype [198]. Some studies of individuals with BD reported an increased frequency of allele C102 at the 102T/C SNP in the serotonin 2A receptor gene as compared to healthy controls [199], although other studies have not replicated this finding [200].

Similarly, the S/S genotype of the serotonin transporter promoter region (5HTTLPR) has been associated both with FM and BD [201, 202], although this result is not consistently confirmed in all studies [203]. This finding seems particularly relevant when considering the impact of 5HTTLPR gene polymorphism on stress responses. A meta-analysis pointed out to a 5HTTLPR "S" allele moderated association between exposure to stressors and worse developmental psychopathological outcomes in Caucasian samples of adolescents, suggesting a significant contribute of S/S genotype in conferring vulnerability to psychiatric conditions under adverse environmental circumstances [204]. Recently, some authors referred to 5HTTLPR as a "plasticity" rather than a "vulnerability" gene, also underscoring the potential beneficial effect of supportive conditions [205]. Similarly, also the dopamine receptor D4 polymorphism can be conceptualized as a "plasticity" gene, responsible for differential susceptibility to environmental influences. Some investigations reported significant associations between the 48-bp repeat polymorphism in exon III D4 receptor gene and FM [206]. In parallel, the same polymorphism were associated with high novelty-seeking scores and low harm-avoidance scores in individuals with BD [207].

Finally, COMT (catechol-O-methyl-transferase) polymorphism are among the most studied candidate genes associated with mood disorders as well as with cognitive dysfunction in BD [208, 209]. A possible influence of Met/Met genotype of the val158met COMT SNP on pain modulation *via* decreased mu-opioid system responses has also been postulated in chronic pain conditions and FM [210]. More recently, the Met/Met genotype has been associated with an abnormal stress response in FM characterized by an autonomic activation and immune dysregulation [211].

In summary, different SNPs in genes related to monoamine neurotransmission pathways may be implicated in the pathophysiology of both FM and BD. Common 'plastic' gene-environment (e.g., epigenetic) interactions may also underpin the patho-etiology of both illnesses. However, these interesting findings deserve replication in larger studies involving ethnically diverse populations.

8. OTHER SHARED PATHOPHYSIOLOGICAL MECHANISMS

8.1. Melatonin

The activation of the TRYCATs pathway is related to decreased tryptophan availability and consequently to diminished levels of N-acetyl-serotonin as well as melatonin [161]. Melatonin drives circadian rhythm regulation and provides powerful antioxidant and anti-inflammatory effects, optimizes mitochondrial functioning and modulates pain transmission [212]. Decreased levels of circadian melatonin have been reported in individuals with BD [213] and there is also evidence that melatonin supplementation could attenuate weight gain and metabolic disturbances associated with antipsychotic treatments [214]. However, adjunctive treatment with the melatoninergic antidepressant agomelatine failed to exert beneficial effects in subjects with bipolar depression [215], suggestive preliminary reports notwithstanding [216]. Similarly, decreased levels of 6-sulphatoxymelatonin (6-SMT) (i.e., the principal metabolite in urine of melatonin) have been observed in subjects with FM compared to healthy controls [217]. Melatonin supplementation resulted effective in facilitating the inhibitory endogenous pain-modulating system, thus reducing pain experience in FM [218]. Additionally, some reports support the potential of agomelatine in reducing pain severity and depressive symptoms in FM [219, 220].

8.2. Vitamin D

Vitamin D is implicated in the regulation of affective and cognitive states as well as pain perception through the regulation of melatonin synthesis, glucocorticoid signaling and neurotrophin release, and exerts neuroprotective effects *via* increased antioxidant and anti-inflammatory defenses [221]. Furthermore, vitamin D deficiency has been associated with inflammation, alterations in cellular development and neurotransmission linked to altered monoamine metabolism [222]. There is equivocal evidence of the utility of Vitamin D supplementation in mood symptoms [223].

Recent evidence supports the role of low vitamin D levels for heightened central sensitivity and augmented pain processing in chronic pain conditions [224, 225]. Separate population based and case-control studies reported an association between chronic widespread pain and low serum cholecalciferol levels [226, 227]. Interestingly, in a preliminary randomized placebo controlled study on individuals with FM, oral supplementation with cholecalciferol resulted in a significant reduction of pain perception [228]. A community-based study suggested a role for vitamin D in influencing personality traits and reported a positive correlation between 1,25 hydroxyvitamin D (i.e., the active form of vitamin D) and extroversion and openness on the Five-Factor Inventory [229]. On the contrary, vitamin D deficiency has been associated to age–related cognitive dysfunction and depressive symptoms [230]. These studies provide an epidemiological basis to

further assess the potential of vitamin D supplementation both in mood disorders and FM.

8.3. Mitochondrial Dysfunction

Many studies in patients diagnosed with FM report evidence of mitochondrial dysfunction. Decreased mitochondrial function resulting in lowered levels of ATP are reported in leucocytes of people with FM, linked to decreased citrate synthase content, which reflects mitochondrial number [231, 232]. Decreased activity of mitochondrial complexes as well as decreased number of mitochondria is reported. Differences in mitochondrial enzyme activity compared to a matched control group, and decreased mitochondrial content are noted. Deletions of redox genes in mitochondrial DNA are also documented [233, 234]. Mitochondrial dysfunction is also evidenced by altered synthesis of ATP and increased concentrations of lactate [235]. Equally, there is a substantial literature showing that in bipolar disorder, a primary abnormality of bioenergetics is present. Phenomenologically, depression is a state of decreased energy, and mania of increased energy. In abstract, this evidence is supported by brain imaging data showing decreased glucose utilization in depression, and increased VO2 max and resting energy expenditure in mania [236]. Similarly there is abundant evidence of altered expression of the electron transport chain in the disorder [237]. Lastly, agents that are of value in the therapy of bipolar disorder share effects on mitochondrial bioenergetics [238].

9. CONCLUDING REMARKS AND PERSPECTIVES

FM is a prevalent, chronic and disabling condition that is associated with sleep disturbances, psychological distress, fatigue, cognitive impairment and reduced health-related quality-of-life [239]. Sleep dysfunction as well as depressive and anxiety symptoms are predictors of greater functional impairment and increased risk of suicide in FM [240]. This review indicates that bipolar spectrum disorders frequently co-occur in among patients with FM. Several studies pointed out to an elevated prevalence of positive screening for BD in FM samples, although it is worthy to note that this finding does not substantiate the diagnosis of BD [241]. Nevertheless, these epidemiological associations and clinical similarities invite clinicians to evaluate FM patients for the possible co-occurrence of a bipolar spectrum disorder. A diagnosis of BD in a patient with FM may have important clinical implications. For example, the prescription of SNRIs to this patient population may induce treatment-emergent affective switches and cycle acceleration, whereas consequences to FM-related outcomes remain to be established.

Recent advances in the understanding of biological underpinnings relevant to the development and progression of FM and BD indicate that shared pathophysiological processes may at least in part explain the symptomatic overlap between these disorders. First, abnormalities in overlapping neurocircuits subserving emotional control, cognitive regulation and pain processing anticipate the similarities among symptomatic patterns in FM and BD. Second, functional aberrations in the HPA axis (e.g., impaired GR-mediated signaling) and a dysregulated stress response are core features of both FM and BD. Third, alterations in monoamine neurotransmission pathways appear relevant to the patho-etiology of both diseases and may in part be driven by epigenetic control. Fourth, FM and BD are characterized by a low-grade inflammatory state with a heightened production of pro-inflammatory cytokines, over-activation of microglia cells, as well as a pathological activation of the TRYCATs pathway leading to a diminished production of 5-HT and melatonin. These shared pathways may contribute to impaired neuroplasticity (e.g., altered BDNF signaling) in both illnesses. Fifth, disturbed cellular energy metabolism mitochondria dysfunction also characterize both FM and BD. Noteworthy, immune imbalances, O&NS, and disturbances in energy metabolism may also contribute to the observed higher prevalence of co-occurring metabolic and cardiovascular disturbances in FM and BD as compared to the general population [242-244].

This review also opens important directions for further research. For example, large-scale collaborative epidemiological studies may shed more light on the relationships between FM and BD. Second, the characterization of intermediate phenotypes (e.g., temperamental traits) related to both disorders may contribute to the elucidation of shared biological mechanisms. Third, the effects of first-line treatments for BD on FM-related outcomes in patients with co-occurring FM and BD deserve further investigations. Finally, increased knowledge of shared biological underpinnings may guide research efforts towards the identification of novel targets with transnosological potential applications.

ABBREVIATIONS

5-HT = Serotonin

5HT2AR = Serotonin 2A receptor

5HTTLPR = Serotonin transporter promoter region

6-SMT = 6-sulphatoxymelatonin.

A1AT = Alpha-1-antitrypsin

ACC = Anterior cingulate cortex

BD = Bipolar disorder

BDI = Beck Depression Inventory

BDNF = Brain derived neurotrophic factor

BMI = Body mass index

CNS = Central nervous system

COMT = Catechol-O-methyl-transferase

CoQ(10) = Coenzyme Q (10)

CRP = C-reactive protein

CWP = Chronic widespread pain

DLPFC = Dorsolateral prefrontal cortex
FAST = Functioning Assessment Short Test
FDA = Food and Drug Administration
FM = Fibromyalgia
fMRI = Functional magnetic resonance imaging
GR = Glucocorticoid receptor
HPA = Hypothalamic-pituitary-adrenal
IL = Interleukin
MCP-1 = Macrophage chemoattractant protein 1
MDD = Major Depressive Disorder
MDQ = Mood Disorder Questionnaire
MRI = Magnetic resonance imaging
MRS = Magnetic resonance spectroscopy
NAA = N-acetylaspartate
Nacc = Nucleus accumbens
NMDA = N-methyl-D-aspartate
PAG = Periaqueductal gray area
PCC = Posterior cingulate cortex
RVM = Rostral ventromedial medulla
SF-12 = 12-item short form health survey
sgp130 = Soluble glycoprotein 130
sIL-R = Soluble interleukin receptor
SNP = Single nucleotide polymorphism
SNRIs = Serotonin–norepinephrine reuptake inhibitors
TBARS = Thiobarbituric acid reactive substances
TNF = Tumor necrosis factor
TRYCATs = Tryptophan catabolites
VLPFC = Ventrolateral prefrontal cortex
VMPFC = Ventromedial prefrontal cortex

CONFLICT OF INTEREST

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