

Comparing underlying mechanisms of depression in multiple sclerosis and rheumatoid arthritis

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Multiple Sclerosis (MS) and Rheumatoid Arthritis (RA) are common, chronic, autoimmune diseases affecting many people worldwide. While clinically very different in their phenotype, both diseases are thought to have an autoimmune-mediated origin. MS and RA share genetic similarities, and in both diseases, antibodies against host antigens can be found. Aside from the well-known somatic symptoms, many RA patients also show signs and symptoms of psychiatric illnesses, of which depression is the most common diagnosis. In this commentary, both diseases will be introduced and briefly characterized individually and then compared. Depression will be introduced as one of the most frequent psychiatric diseases in the general population. This paper focuses on presenting the possible causes, including psychosocial factors, genetics, and immunologic mechanisms. Hypotheses aimed to explain the higher incidence of depression in these two seemingly different autoimmune diseases will be discussed.

Keywords

Autoimmune diseases; Depression; Multiple sclerosis; Rheumatoid arthritis; Pathophysiology

1. Introduction

There is limited literature discussing depression in the context of autoimmune diseases as a group, specifically MS and RA. MS is a neurological disease affecting the central nervous system and associated sensory motor functions primarily, while RA is a disease of the rheumatoid spectrum, affecting joints and internal organs. However, both diseases are thought to be autoimmune in nature [1, 2]. Depressive symptoms and manifest depression accompanying MS and RA are frequent, yet not well understood. The purpose of this commentary is to compare depression in MS and RA, including underlying pathomechanisms. The prevalence of depression is higher in MS compared to the general population [3], reported to be between 25–50% [3]. Similar findings have been reported in RA with prevalence ranging between 9–68% [4] while the frequency of depression in the general population has been reported to be between 3–7% [5]. Whether this association represents a coincidence or if there are causal factors leading to the higher rate of depression in both, MS and RA is still controversial. However, current research suggests

several explanations, out of which two are discussed most frequently: Either depression in these two autoimmune diseases occurs due to a common neurobiological correlate in the central nervous system (CNS) as part of the underlying disease or depression is simply a reactive component, as both MS and RA are typically incurable and progress over time, causing adverse psychological reactions. Moreover, a minority of researchers have suggested reverse causality, i.e., depression may promote the development of MS or RA.

2. Multiple sclerosis

MS is a chronic, progressive, autoimmune inflammatory disorder of the central nervous system [6]. Patients show a variability of symptoms ranging from sensory problems and motor disabilities to fatigue and cognitive deficits. Not uncommon during the progression of the disease are psychiatric disturbances, for example depression, emotional lability, and bipolar disorder [7]. The origins of MS remain unclear. Multifactorial causes, including genetic predisposition, environmental triggers and infectious agents are discussed [1]. The disease affects mainly young adults. At least 2.5 million adults worldwide are diagnosed with MS, with women affected roughly three times as often as men [1]. For the purpose of this commentary, MS will be discussed regardless of clinical phenotype. Immunomodulatory medication and symptomatic therapy are the two most common therapeutic methods [8]. Depressive symptoms, as well as fatigue are common in patients with MS [9]. The lifetime incidence rate of depression in MS patients is between 40–50%, influencing their quality of life and adherence to treatments as well as the progression of the disease [3, 10].

3. Rheumatoid Arthritis (RA)

RA is an autoimmune and inflammatory disorder, characterized by joint pain, synovial destruction and swelling; also internal organs, for instance lung, blood vessels or the heart can be affected. In later stages joint damage may result in immobility, affecting quality of life severely. While RA is well established as an autoimmune disease, the underlying mechanisms that cause autoimmunity are unknown. Covariates in

the genesis of RA include environmental, genetic, and infectious agents, but their interplay and exact contribution is not known. Behavioral changes are common in RA and include depression, sleep disorders, increased pain sensitivity and affective disturbances [11, 12]. The prevalence of RA is approximately 1% in Caucasians but can vary from 0.1 to 5 percent depending on ethnicity [13]. Annually, approximately 40 out of 100,000 people are affected, with a 2-to-3-time higher risk for women [14]. RA is an autoimmune disease, where autoantibodies against common antigens found in or near joints and some internal organs cause inflammation. Non-steroidal anti-inflammatory drugs (NSAIDs), such as Aspirin, Fenoprofen and Celecoxib are not only pain relievers but also help in reducing inflammation since they reduce the production of prostaglandins which promote pain and fever. Disease-modifying antirheumatic drugs (DMARDs) are also frequently used in the treatment of RA [15]. These immunosuppressives will slow-down damage to joints and help in maintaining remission and reduce the likelihood of peaks (flare-ups).

4. Depression

Major Depressive Disorder (MDD) or depression is a mood disorder where patients are feeling sad and hopeless and lose their interest in activities they previously enjoyed¹.

According to WHO depression is a leading cause of disability and causes considerable morbidity and mortality². Based on substantial evidence from both clinical and biomarker-studies there is a shift towards a dimensional view of depression which is based on the grading of its severity as well as by different associated clinical features. It has been suggested that sedentary lifestyle is one of the contributing risk-factors for developing an MDD. Supporting evidence comes from studies in physically disabled people, where also higher rates of depression compared to the normal population have been found. Both facts point in the direction of inflammation as the key pathological mechanism for depression [16].

Based on DSM-5 criteria, subjects have to experience five or more symptoms (e.g., significant weight changes, cognitive disturbance, psychomotor agitation or retardation, feeling of worthlessness, suicidal ideation, fatigue) during the last two weeks and one of the symptoms to diagnose a depression has to be either a depressed mood or a loss of interest or pleasure to diagnose a depression. All these symptoms have to be clinically significant, leading to a meaningful impairment in everyday activities. They cannot be explained by any other medical condition or substance abuse³. MDD with melan-

cholic features, previously called melancholic depression, is a particular severe form of MDD characterized by anxiety, reduced responsiveness, loss of appetite and sleep-disturbances with symptoms usually ameliorating in the evening.

Patients with MDD with melancholic features have higher cortisol level while patients with atypical depression are characterized by reactive mood, increased appetite, insomnia, leaden paralysis and interpersonal rejection sensitivity. These patients show an increase in abdominal circumference and BMI, and higher circulating levels of C-reactive protein, interleukin (IL)-6 and tumor necrosis factor (TNF)- α . Moreover, their levels of plasma triglycerides and glucose are higher and their levels of high-density lipoprotein cholesterol is lower than in MDD patients with melancholic features [17].

5. Depression and MS

Depression is very common in MS patients and is one of the most significant predictors of low quality of life. Furthermore, suicide rates are increased in depressed MS patients [3]. Depression influences the response to treatment and can accelerate the progression of the disease [10]. It is therefore important to understand the link between both diseases. Perhaps the obvious view is that patients suffering from MS due to increased motor disabilities, cognitive dysfunctions or other symptoms realize that this chronic, autoimmune disease threatens to severely impact their quality of life. This view would lead to identifying depression as “reactive” to impact the primary disease has on the patients. Another perspective tries to understand whether there are shared features in the pathophysiology of MS and depression without necessarily attributing a causal link between them. Is depression caused by MS or are there underlying shared pathological mechanisms in both diseases?

5.1 Incidence and prevalence

Some authors report lifetime prevalence rates of depression between 25–50% in MS patients [3]. In a longitudinal study of more than 5000 patients with MS Hoang and colleagues [18] found depression to occur in more than half of their subjects (54%) during an overall observation period of 4 years, split between 2 years before and after diagnosis. Incidence rates are rarely reported. One study found an annual incidence of depression in MS patients between 4% in one year up to 34.7% over five years [19]. The 12-month period prevalence of MS patients is 15.7% [20]. These results indicate that rates of depression amongst patients with MS are substantially higher than in the general population.

5.2 Hypotheses explaining the link between depression and MS

Evidence for distinct causes for depression in MS is insufficient [8]. Comorbid features, psychosocial factors, genetic predispositions, and immunologic mechanisms have been discussed.

¹ World Health Organization. International statistical classification of diseases and related health problems. 2020; 11th edition

² World Health Organization. World health statistics 2013. 2013; World Health Organization

³ American Psychiatric Association (APA). Depressive Disorders in Diagnostic and Statistical Manual of Mental Disorders (DSM-5). 2013; Fifth edition

5.2.1 Psychosocial factors

Psychosocial factors have been associated with depression in MS patients and include feelings of hopelessness, reduced social participation, reduced enjoyment of activities and maladaptive coping strategies [10]. Kneebone and colleagues [21, 22] found a significant association between negative attributional styles and depressive symptoms in MS patients. Furthermore, young people diagnosed with MS are at risk due to their natural wish for interpersonal relations and careers that result in additional stressors contributing to depressive symptoms [23]. Limited autonomy in normal activities in patients diagnosed with MS are associated with decreased well-being, lower mood and psychological adaptations. Mohr and colleagues [24] argued that MS-derived disability might be a predictor to develop depression, especially in the first year after diagnosis. Alghwiri and colleagues [25] conclude that depression significantly predicts balance impairments in MS patients and should therefore be treated accurately.

5.2.2 Comorbid factors

Chronic pain has been discussed as a comorbidity that contributes to the association between MS and depression. Pain and depression have been shown to amplify each other in MS patients but causal and temporal relationship remains elusive [26]. Fatigue has also been considered to influence the link between MS and depression, however the relationship is quite complex. Fatigue could arise independently of depression or could be secondary to insomnia. If depression is treated appropriately in MS patients, fatigue symptoms should improve [27, 28]. However, other authors have suggested that due to the neuropathic correlate of MS rest alone may not relieve fatigue and treating insomnia or depression without treating the underlying inflammatory causes of MS will not lead to an improvement in fatigue [29]. In addition, symptoms of anxiety, generalized anxiety disorder, panic disorder, obsessive-compulsive disorder and social phobia are three times higher in depressed MS patients compared to the general population [30]. When depression is accompanied by anxiety, patients experience increased thoughts of self-harm, more somatic complaints, and greater dysfunction than when anxiety is present alone [31]. Depressed patients with MS also suffer from cognitive impairment which occurs in about 40–50% of patients. They have greater difficulties with their working memory abilities, executive functioning, and information processing speed [32]. Solaro and colleagues [10] argued that MS-derived disability could be a predictor of depression since patient's autonomy is lowered including decreased well-being, lower quality of life and lower mood. Importantly, the same group and others concluded that while psychosocial factors are important, they only predict 15.7% of variance.

5.2.3 Genetics

Studies show no correlation between genetic predisposition and depression in MS patients. Family history shows inconsistent findings, while most studies could not find a link [7]. However, one study found a higher prevalence of depression in females with a family history of depression [23]. Apolipoprotein ϵ^2 has been attributed to have a protective role since this allele has been found to correlate with less depressive symptoms [33], but these findings have not been validated further. A recent study investigating the relationship between depression and MS using mendelian randomization came to conclusion that there is no causal contribution between depression genetic liability and MS susceptibility and vice versa [34].

5.2.4 Immunologic mechanisms

Immunologic mechanisms linked to depression in MS patients remain controversial. Some studies show an association between depression and an increasing level of proinflammatory substances, such as Tumor Necrosis Factor- α (TNF- α), Interleukin-1 (IL-1) and IL-6 [3]. Elevated levels of proinflammatory cytokines can induce depressive symptoms due to a decreased presynaptic serotonin release and a malfunctioning of serotonergic and adrenergic neurotransmitters. MS pathology is also marked by neurodegeneration. Post-mortem studies found an increase in hypothalamic-pituitary-adrenal (HPA) axis activity in MS patients that coincided with increased neurodegeneration, possibly suggesting a link between the biochemical expression found in some patients with depression, evidenced by a decreased activity of the adrenocorticoid hormones and MS [35]. Rossi *et al.* [36] explored inflammatory processes and their contribution to psychiatric factors associated with MS. In a study of 450 patients with RRMS, inflammatory activity levels were evaluated by MRI. Psychiatric symptoms were assessed by the Beck Depression Inventory II (BDI-II) and State/Trait Anxiety Inventory (STAI-Y). In the MRI part of the study the authors found that inflammatory activity in the brain correlated with anxiety scores even in patients that at the time of MRI had no apparent signs and symptoms of active MS. The authors postulated that subclinical inflammatory activity is expressed by mood and psychiatric disorders, perhaps even predicting later active MS. In a subset of 111 patients that had a minimum of three months without anti-inflammatory drugs against MS, CSF levels of proinflammatory cytokines were also determined. In this part of the study higher scores in BDI-II were correlated with increasing levels of IL-1 β and TNF- α in the CSF (IL-1 β : $r = 0.52$, $p < 0.001$; TNF- α : $r = 0.50$, $p < 0.001$). Other inflammatory cytokines, namely IL-2 and IL-8 were not correlated with BDI-II score [36]. Overall, the study provides evidence that patients with MS during symptom-free intervals show evidence of inflammation that correlate with psychiatric symptoms.

It is plausible that the same immunological pathways that is involved in the progression of MS-pathology may also be responsible for developing depression in MS.

5.2.5 Endocrine factors

A possible link between major depression in MS and changes in the circadian cortisol levels has been studied. Small studies showed an attenuation of the circadian cortisol secretion with normal morning levels and elevated evening levels of cortisol, resulting in a flattened curve of cortisol secretion. A role of HPA-axis in depression and MS has been suggested. As with other findings in this review, causality or direction of causality is by no means established [37, 38]. Evidence for an increase in HPA-activity has been found in different bioprobes showing elevated glucocorticoid levels, such as saliva, CSF, blood-samples and urine [39]. There is growing evidence towards a contribution of inflammation to neuroendocrine abnormalities through either direct or indirect effects. Direct effects are exerted via the cytokine induced glucocorticoid receptor (GR) nuclear translocation, GR-protein-protein interaction, GR-isoform shifts towards less active isoforms and GR-binding to response elements – all of them leading to GR-resistance, thus promoting inflammation. Indirect effects of cytokines on glucocorticoid signaling are mediated through an inhibition of 11 beta-hydroxysteroid dehydrogenase, an enzyme responsible for glucocorticoid metabolism, by inhibiting the p-glycoprotein pump which removes glucocorticoids and by inhibiting corticosteroid-binding globulin which under physiological circumstances prevents diffusion into cells [40]. Finally, though these findings (elevated proinflammatory cytokines and HPA-axis hyperactivity producing an anti-inflammatory effect) seem to produce conflictive effects, they both have negative influence on monoamine metabolism, neuro-degeneration and neurogenesis and thus may give rise to cumulative damage.

Although these inflammatory and neurohormonal mechanisms may not be either necessary, nor sufficient to cause depression, they may nevertheless exert a previously underestimated role in the development of affective disturbances.

5.3 Pathophysiology, structural findings, and neurobiology of depression in MS

The structural and functional link between pathological findings in MS and depression is difficult to study as both diseases do not have any pathognomonic features that would easily distinguish them from healthy subjects, or from each other. There are, however, several hints pointing to a possibly different brain pathology in depressed MS subjects compared to those without depression. Still, as there are no clearly reproducible findings yet, all imaging and pathology findings need to be interpreted with caution as they may not be representative. In a review of the matter, Solaro *et al.* [10] reported on several structural and functional MRI studies (fMRI) that generally show a loss of gray matter volume in different brain regions. In one of the largest studies, Gobbi *et al.* [41] found the frontal, parietal and occipital lobes in depressed MS patients linked to depression and fatigue and the left middle frontal and right inferior frontal gyrus in depressed MS patients to be mostly affected. Kiy *et al.* [42]

found an increased temporal horn volume in MS patients which was correlated with depressive symptoms. They suggest the link between MS and depression may be a hippocampal atrophy due to the same neuroanatomical localization in the brain and in similar functional impairments. Stuke *et al.* [43] reported an association between depressive symptoms and grey matter loss in the left temporal lobe, advocating for the assumption that grey matter loss in the right middle cingulate and middle frontal gyrus at baseline predicted the increase of depressive symptoms. Moreover, Pravata *et al.* [32] reported grey matter volume thinning, involving the cerebral cortex in the left middle orbito-frontal, right inferior frontal and entorhinal cortex in addition to the temporal pole in depressed and cognitively impaired patients with MS. Several other groups have studied the subject and associated different brain regions with the co-incidence of depression and MS.

In summary, no clear pattern of affected regions in MRI studies has emerged, possibly due to the lack of standardization in imaging and the small series that have been studied, rarely exceeding more than 50 subjects per study. Patients with MS and depression display a wide range of neuroimaging abnormalities. It is clear, however, that patients with MS who display symptoms of depression present with different neuroimaging profiles compared with MS patients who are depression-free [44].

Increased rates of peripheral inflammation, notably elevated interleukin IL-6 and CRP, appear to differentiate MS patients suffering from comorbid depression from those who do not [45].

Oxidative and nitrosative stress has been reported in both diseases individually and augmented when they occur together, suggesting shared pathophysiological mechanisms in both diseases. Low levels of antioxidants have also been found in patients with depression and MS compared to those that were depression-free [46]. Morris *et al.* [44] conclude that many abnormalities common to MS and depression likely have their origins in the presence of chronic inflammation and concomitant oxidative stress.

6. Depression and RA

Since both depression and RA are common diseases in adults it is not surprising that in many patients both diseases co-occur. However, this correlation does neither preclude causality nor direction of causality. Nonetheless, a robust and clinically significant association between RA and depression has been suggested in several studies [47, 48].

6.1 Incidence and Prevalence

Unlike literature on prevalence of depression in RA, data on incidence rates are scarcely reported, perhaps owing to the relatively high co-occurrence of both conditions. A retrospective study using Taiwanese health record data has reported an incidence risk ratio of 2.06 of depression between individuals with RA and otherwise healthy subjects [49]. However, the temporal relationship when RA and depression occur relative to each other remains elusive. Literature

on depression rates in the general population varies considerably. Most studies assume prevalence rates of depression to be 3–7% [5]. Depression in RA has been reported to be substantially higher, with prevalence rates of depression in adult patients with RA ranging between 9 and 68% [4, 50, 51]. In a metaanalysis based on 72 studies with more than 13,000 patients Matcham and colleagues [4] established a depression prevalence of 16.8% in RA patients when including those studies using clinical gold standards.

6.2 Hypotheses explaining the link between depression and RA

The causes of why RA patients develop depression remain unclear. As in MS, the causes for an overall elevated rate of depression in RA also remain to be further elucidated. In the following, we will present some findings psycho-social factors, comorbid features, genetic predispositions, and possible immunological mechanisms.

6.2.1 Psychosocial factors

Covic and colleagues [52] found in a study that included 134 patients with RA twelve predictors that classified 80% of their subjects into non-depressed and depressed subgroups, leaving 20% unclassifiable. In this study, the strongest predictors for developing depression were high tension ($r = 0.65$) and low self-esteem ($r = 0.63$), followed by perceived impact of RA ($r = 0.46$) and passive coping strategies ($r = 0.5$). Similar findings were reported by Jacob and coworkers [53] demonstrating that the aforementioned variables together with further comorbidities all increased the likelihood of developing depression in RA.

6.2.2 Comorbid features

A simple and straightforward explanation for the elevated rate of depression in RA is based on the finding that patients with RA suffer from increased pain and fatigue and hence experience a reduced health-related quality of life [4]. This assumption is corroborated by several studies that have investigated this relationship further. Kwiatkowska and colleagues [48] assessed in a cohort of 120 patients with RA whether depression correlated with symptom severity of RA. The authors found that symptoms of depression were reported more often in professionally inactive (not working/retired) patients. They also found an association between depression and pain symptoms. Furthermore, longer disease duration was a factor influencing symptoms of depression in RA patients. When biologics (rituximab, etanercept, infliximab, abatacept) designed to interrupt the inflammatory pathway were administered to patients, the level of proinflammatory cytokines was reduced which could have exerted a benefit in reducing the severity of depressive symptoms. A study by Eusden and colleagues [54] found a bidirectional link between depression and RA: while pain from RA can worsen depression, the latter in turn exacerbates RA symptoms impeding thereby disease-management. In an earlier study [55] a mere 20% of depression was explained by 'changes in clinical variables', interpretable as signs and symptoms of exacerbating RA.

6.2.3 Genetic predispositions

Both depression and RA are poorly understood in regards to their genetic correlates. No single gene defect was found for depression in RA that increased the likelihood of both diseases occurring together. One large study of 520 patients with RA suffering from depressive episodes found that the genetic risk for developing depression was a significant predictor of Mental Health [56]. Jones and colleagues [56] were not able to identify genetic causes for the association between RA and depression. They reported little consistent evidence of association between RA and depression at age 18 years, negative symptoms at age 16 years, psychotic experiences at age 12 or 18 years, or Development and Well Being Assessment bands predicting a 15% or greater probability of developing depression at a later age. The study found some evidence that symptoms of hyperactivity and inattention at younger age occurred more frequently in patients that later developed RA suggestive of a possible polygenetic shared origin of somatic and psychiatric symptoms that co-occur in RA. Taken together, however, no convincing genetic evidence has been identified thus far that could explain the co-occurrence of the two diseases.

6.2.4 Immunological mechanisms

Explanations focusing on the immune-inflammatory axis have frequently been assumed to account for the association between depression and RA. Namely, pro-inflammatory cytokines, like IL-6, sIL-2R, TNF- α and many others were found to be elevated in patients suffering from both diseases compared to patients with RA only. A meta-analysis and meta-regression reported significantly higher rates of proinflammatory cytokines in depressed RA patients compared to healthy individuals [56]. A role of cytokines in depression is supported by the phenomenological similarities between the symptoms of cytokine induced sickness behavior and depression such as behavioral inhibition, anorexia, weight loss, anhedonia, psychosomatic symptoms, anxiety and neurocognitive symptoms [57]. Kojima *et al.* [58] showed a positive correlation between CRP levels and depression severity in RA patients. In a review Patel [59] the crucial role of cytokines in the pathogenesis of depression, including also alterations in neuroendocrine functions, synaptic plasticity and expression of neurotransmitters. However, even with these mechanistic explanations it still remains unclear what causes inflammation and what is the direction of causality, if any, between RA and depression.

6.2.5 Endocrine factors

Changes in the hypothalamic-pituitary-adrenal axis have been reported to be associated with RA and in some cases resulting in mood changes and depression. Specifically, adrenal insufficiency may lead to RA as a result of an impaired ability to react to inflammatory signals. However, a clear association between developing depression in RA and cortisol deficit is not established. In a study from Taiwan hyperthyroidism

has been identified in a multivariate analysis as a factor linking depression and RA. Hyperthyroidism is known to cause mood changes and, in some cases, MDD [49, 60].

6.3 Pathophysiology, structural findings, and neurobiology of depression in RA

Unlike with MS, only few studies have examined brain changes in patients with RA and we could not identify any focusing specifically on patients with depression and RA. In order to study how the peripheral inflammation that is a hallmark of arthritis affects the structure and connectivity of the brain Schrepf and colleagues [61] used functional and structural MRI in 54 participants aged 43–66. Brain scans were taken both at the beginning of the study and 6 months later. The study participants had a history of RA for an average period ranging between 2.85 years and over 20 years. They found altered patterns of brain connectivity in RA patients with higher peripheral inflammation. Moreover, they found evidence of distinct inflammation-associated subnetwork reorganization. The authors suggested that treatments for RA that successfully control peripheral inflammation should be investigated to determine whether they normalize brain network activity or have a neuroprotective effect.

7. Cognition in depressed MS and depressed RA patients

An interesting study focusing on cognition was published by Whitehouse *et al.* [62]. While the main point of their research did not focus on depression, substantial number of patients in the study either had MDD or other symptoms of depression.

The authors studied whether there is an association between cognitive impairment and autoimmune diseases by assessing different cognitive domains in RA ($n = 154$) and MS ($n = 255$). Four dimensions of cognitive impairment were assessed in RA and MS as well as two autoimmune diseases. The domains for cognitive impairment studied were processing speed, working memory, verbal learning and delayed recall memory. Participants also completed a structured psychiatric interview and underwent anxiety and depression assessment. Results were adjusted according to age, sex and education. Both groups exhibited higher rates of cognitive impairment which were more profound in patients with MS, though the only statistically significant difference between MS and RA was found for processing speed ($p \leq 0.001$) [62]. Besides confirming the well-known association between cognitive impairment and MS, the authors extended our knowledge about the cognitive effects of autoimmune diseases by showing a similar pattern of cognitive deficits in RA.

8. Discussion

To our knowledge, this is the first approach to compare Multiple Sclerosis (MS) and Rheumatoid Arthritis (RA) in regards of depression.

Depressed MS and RA patients share many similarities, i.e., sex, median age of onset and incidence and prevalence

rates are comparable. While the causes for both autoimmune diseases remain unclear, it is assumed that the combination of genetic, immunological, and psychosocial factors contribute to the development of depression in both MS and RA. Table 1 (Ref. [4, 10, 12, 21, 35, 55, 56, 60, 62]) gives an overview of similarities and differences of depression in MS versus RA patients. Many publications have dealt with studying the association of mental disorders with chronic diseases, such as MS and RA. MS and depression commonly occur together, a conservative estimate suggests a prevalence for both diseases together to be 16% [63]. In RA, the co-occurrence is estimated to be 17% [4]. Of note, it has been suggested that these numbers severely underestimate the occurrence of depression due to lack of consistent screening tools and inconsistent application of “gold-standard” interview questionnaires, as evidenced by some individual studies suggesting prevalence rates up to 45% in RA [64]. This contrasts to incidence figures of depression reported in the general population in the US of 7.1%⁴. The WHO estimates that in 2019, approximately 264 million people of all ages suffered from depression, which corresponds to 3.4% of the global population [5]. It is therefore evident that depression is at least 2–3 times more common in patients with MS and RA than in the general population. For both MS and RA, the exact etiology and pathophysiology is poorly understood, yet it is well documented for both diseases that immune inflammatory processes play a major role. This is further illustrated by the fact that treatment for both diseases, while different due to the target structures affected (CNS in MS, peripheral joints and organs in RA) is largely focused on curbing or eliminating inflammation and autoimmune reactions by means of immunosuppressants, immunomodulatory and anti-inflammatory drugs.

There is still a debate whether in both conditions depression is a corollary due to disease-associated symptoms, such as pain, physical limitations, fatigue and many other consequences, or whether depression co-exists and shares a common pathophysiology with MS and RA. In several studies and also in a metaanalysis of the available evidence it is however suggested that a purely downstream association, i.e., MS and RA are causing depression due to difficulties in coping with the hardship of these diseases, is unlikely. For MS it has been suggested that a mere 15.7% of depressive episodes or depression could be explained by a psychosocial reaction to the underlying disease [10]. To complicate the issue further, specifically for RA it has been found that depression may play an etiopathogenetic role in developing RA [65].

Since incidence rates of depression in RA patients have not been reported it is therefore difficult to understand whether RA induces depression, or the latter facilitates de-

⁴ Adams K. *et al.* Results from the 2017 National Survey on Drug Use and Health: Detailed tables. 2017. Retrieved from <https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHFFR2017/NSDUHFFR2017.pdf> (Accessed: 10 April 2021).

Table 1. Similarities and Differences of depression in Multiple Sclerosis (MS) versus Rheumatoid Arthritis (RA).

Depression	MS	RA
Association	a robust and clinically significant association between depression and proinflammatory cytokines	a robust and clinically significant association between rheumatoid arthritis and depression
Incidence	4% in one year, up to 34.5% over five years [21]	Incidence rates of depression in RA not reported
Prevalence	varies from 4.27–59.6% [10]	variations, 38.8% using the PHQ-9 and between 14.8% and 48% using the HADS [4]
Age	higher in younger patients [10]	higher in younger patients [12]
Sex	women > men, particularly if women or patients were younger than 45 years of age [10]	women > men
		HR 1.6 [55]
Neurobiology	altered neurotransmission, HPA axis abnormalities involved in chronic stress, inflammation, reduced neuroplasticity, and network dysfunction [12]	
(f)MRI	structural and functional link between MS pathology and depression, loss of gray matter volume in frontal and temporal lobes. T2 weighted lesion load higher [10]	altered patterns of brain connectivity in RA patients with higher peripheral inflammation [62]
Genetic	no clear correlation yet Potential protective role of apolipoprotein ε*2 [10, 35]	no single gene was found multifactorial genetic risk had significant, albeit modest impact on mental health in general and also depression [56]
Immune- inflammatory factors	T4 helper/inducer lesions, proinflammatory cytokines [10]	positive correlation between CRP levels and depression severity in RA patients [60]
Psychosocial factors	psychosocial factors remain unclear significant association between negative attributional style and depressive symptoms, feelings of helplessness, reduced social participation and enjoyment of activities, stress, maladaptive coping styles correlated with depression in MS patients [10]	psychosocial factors remain unclear association between depression and the following: high tension, low self-esteem, perceived impact of RA, fatigue, passive coping, pain, physical disabilities, comorbidities [55]

PHQ-9, Patient Health Questionnaire –9; HADS, Hospital Anxiety and Depression Scale; HR, hazard ratio; HPA, Hypothalamic-pituitary-adrenal axis; CRP, c-reactive protein.

Highlights:

- MS and RA are very common autoimmune disorders that have very distinct and different phenotypes.
- The pathogenesis of RA and MS share communalities in T-cell dysfunction and imbalances in somatic reaction to trigger events.
- Depression is at least twice as common in both diseases compared to the general population.
- There is ample evidence that depression is not just *reactive*.
- The association between depression in MS and RA is, however, potentially bidirectional and poorly understood with more research needed.

velopment of RA. The immune-inflammatory nature of both MS and RA early on came into focus and it has been studied extensively how inflammatory signals (such as IL-1 β , IL-6, TNF- α , etc.) are more prevalent in depressed patients with MS or RA [66]. Meanwhile there are multiple lines of evidence emerging from both animal as well as human studies suggesting that inflammatory processes might contribute to the pathogenesis of depression, either via direct actions on the CNS or indirect pathways connecting the brain with the peripheral organs. Studies have documented that individuals with major depression, as a group, have increased inflammatory activity. Elevated peripheral blood chemokine levels and increased stress-induced nuclear factor - κ B levels have been reported in several studies. Moreover, there is growing evidence pointing to the contribution of inflammatory cytokines in the development of mood disorders in both medically ill and medically healthy individuals. Cytokines may exert their behavioral effects by activating cerebral inflammatory signaling pathways, thus leading to monoamine, glutamate,

and neuropeptide imbalance, and attenuating neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), thereby adversely influencing neurogenesis and neuroplasticity. More precisely, peripheral cytokines are able to trespass the CNS-barrier thereby upregulating the production of local inflammatory mediators such as cyclooxygenase-2 (COX-2), prostaglandin E2 (PGE2), nitric oxide (NO), cytokines, and chemokines by endothelial cells, perivascular macrophages, and microglia. They are also associated with an increased oxidative stress and generation of reactive oxygen (ROS) and reactive nitrogen species (RNS). As a consequence, increased ROS and RNS contribute to oxidation of tetrahydrobiopterin (BH4), a co-factor required for monoamine-synthesis.

Another pathway influencing the monoamine metabolism is their role in signal transduction pathways such as p38 mitogen- activated protein kinases (MAPKs). There is both in vivo and in vitro evidence showing that a stimulation of the p38 MAPK pathways increases serotonin transporter expression and activity. Moreover, inflammatory cy-

tokines may decrease expression or function of the vesicular monoamine transporter 2 (VMAT2) and/or increase expression or function of serotonin and dopamine transporters (5-HTT/DAT). The glutamatergic system is also affected by inflammatory cytokines. This is done by activation of the enzyme, indoleamine-2,3-dioxygenase (IDO), that is required to catabolize tryptophan, the primary amino-acid precursor of 5-HT, into kynurenine [67].

In addition to the direct influence of some proinflammatory molecules discussed so far, the HPA axis and GR alterations seem to play a major role in depressed individuals with MS [37, 38, 49, 60].

Conversely, it has been shown that patients with depression respond less well to the treatment of their MS and RA in terms of functional progression and treatment responses [67], suggesting that successful treatment of depression may positively influence the overall treatment success of the underlying diseases. This again, speaks in favor of a bidirectional relationship between inflammatory processes and neuropsychiatric mood disturbances. Keeping in mind that cytokines can induce both neurotrophic and neurotoxic effects it becomes evident that the effects depend on their concentration and condition, which might vary according to the disease progression. This complicates a causal interpretation since there is a huge variability in the methods how depression in MS and RA is diagnosed, including which symptom scores are used and how long patients are followed. Most studies that looked at the association between MS or RA and depression are cross-sectional while longitudinal and/or prospective studies are still scarce. Yet such studies would be helpful in determining causality and also in understanding the effect of interventions over a longer period. This, and the different assessment methods when structural (MRI) or functional (fMRI) brain studies that have been implied to understand morphologic and functional changes add to the complexity of understanding the association between depression and MS or RA. This is further complicated by the fact that in MS the target organ is the brain, with frequent changes in the white and gray matter and in several specific regions, such as the hippocampus, while this is not the case in RA. Nevertheless, for both diseases, no conclusive link between structural findings in brain imaging or in functional studies (fMRI) has yet been identified that would allow for a clear association between depression and RA or MS.

Depression is viewed as a complex disease involving psychosocial, symptomatic effects and immuno-neuroendocrine factors. All of these factors play a role in both MS and RA, but likely they represent the downstream inflammatory response of the body rather than a specific manifestation of a yet to be determined underlying disease explaining the association between MS and depression or RA and depression. It is, however, still remarkable that two diseases that are phenotypically very different share almost identical rates of depression that are at least 2–3 higher than in the general population, and that imaging studies as well as neurobiology findings re-

veal similar pathophysiological pathways associated with the immune-inflammatory axis in both diseases. Finally, both MS and RA are highly complex diseases in their pathophysiology and are still insufficiently understood when it comes to underlying genetic or environmental factors that cause them, and the same is true for depression. Hence, we can assume that an elevated rate of depression in both, RA and MS is a consequence of a cascade of events in which several factors are interwoven and whose downstream-effects might be best explained assuming a biopsychosocial stance: the same genetic susceptibility that makes a person more prone to develop an autoimmune disease might promote a shift towards a proinflammatory immunotranscriptome which influences body as well as brain structures and function by their bidirectional pathways involving immune and endocrine systems. This might then, together with a negative lifestyle and poorly understood environmental factors, lead to behavioral alterations (i.e., mood disturbances) which are further pandered and maintained by adverse psychosocial circumstances and an unpropitious personality makeup (Fig. 1).

9. Future perspectives

Though MS and RA are based on different pathologies, targeting different structures, both diseases are thought to be autoimmune in nature and hence are associated with an elevated inflammatory activity which, together with a hyperactive HPA-axis may lead to a monoaminergic imbalance causing sickness-behavior and mood disturbances. While there is compelling evidence speaking in favor of a mutual interdependence between depression and inflammation it is still difficult to define a clear cause-effect-relationship from the available studies, for several reasons: first, most of the studies that approached this issue have applied a multitude of definitions of RA and/or MS, both in terms of severity and in terms of subtypes under study. Second, the definitions of depression adopted in these studies have not been applied consistently and, in most studies referring either to RA or MS, depression has not been further sampled according to pertinent subentities (e.g., other types of depression vs MDD with melancholic features). Moreover, many studies only included clinical samples which favors a selection bias that might explain the high prevalence rates of both depressed MS and RA patients [19]. Third, while most studies compared people with MS with or without depression, only few studies with small sample size compared people with MS and depression with people that only had depression without having MS. Finally, to further elucidate the question of causality, it is indispensable to adopt long-term approaches. To improve research in this field, it would be helpful if future studies apply a rigorous definition of MS/RA and depression. It is indispensable to compare MS and RA (and possibly other autoimmune conditions) in the same study, as to avoid reporting bias and also validate more consistently the similar and/or different underlying mechanisms or findings. Since available risk estimates for mood disorders in autoimmune diseases are sub-

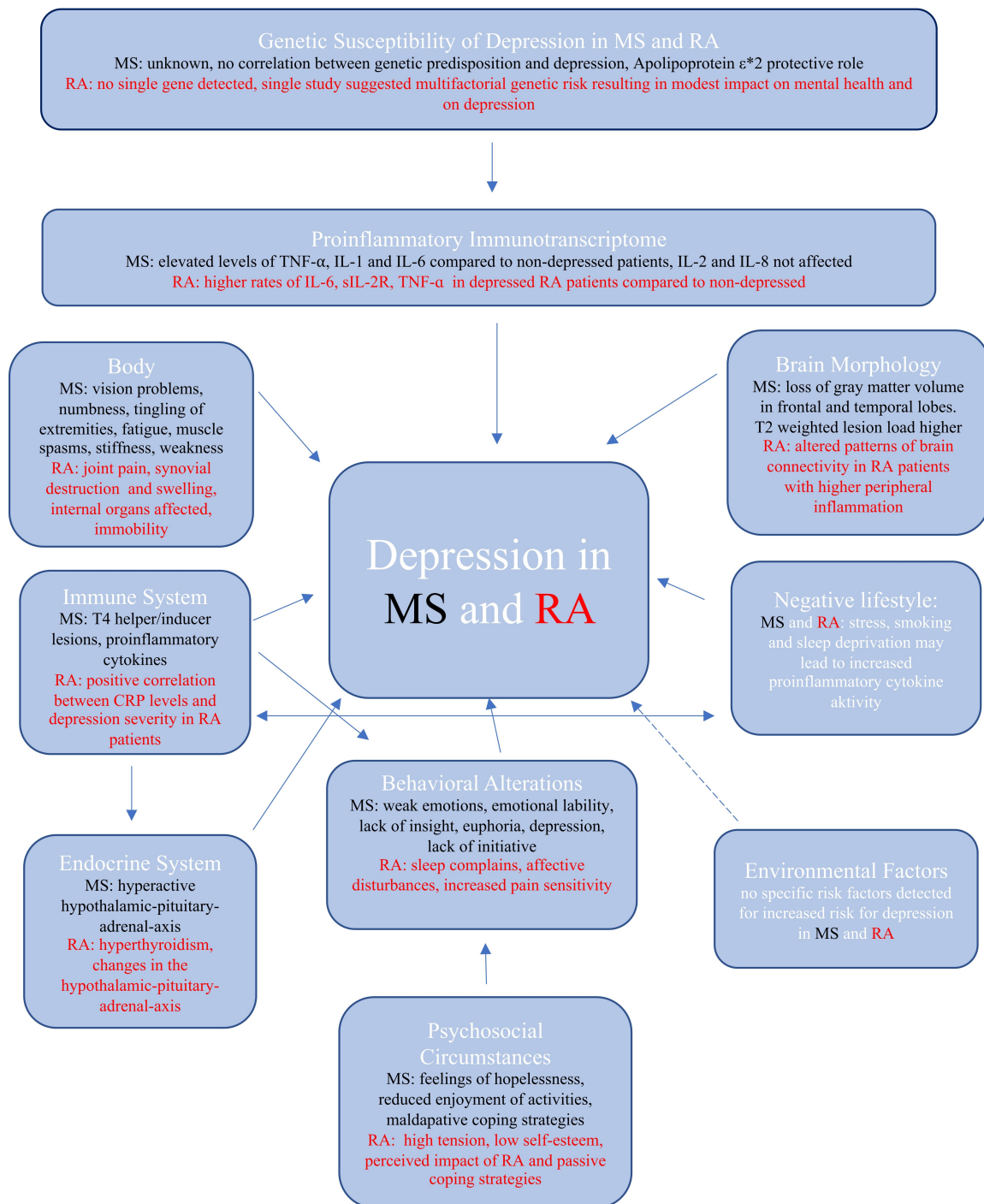


Fig. 1. Overview of the complex and multifactorial association between depression in Multiple Sclerosis and Rheumatoid Arthritis. It is evident that similar patterns exist between these two autoimmune diseases. Causality and direction of causality is poorly understood.

stantially elevated compared to the general population without such illness it is mandatory to routinely screen MS and RA patients for signs of depression [68]. Many studies suggest that depression is severely underreported, and, consequently, also not treated. Furthermore, even in those where a diagnosis of depression is established, too often it is not

treated appropriately, following the idea it is purely “reactive” and symptoms may attenuate by treatment of the underlying disease [32]. A case-control-approach to better understand the overlapping and contrasting risk factors of depression amongst patients with MS and depression in RA should be considered in future studies.

The upregulation of the immune system causes proinflammatory cytokines to bind through the vagus nerve to receptors in the brain that are responsible for emotion regulation occurs both in MS and RA. This shared immunologic pathway in both conditions can be assumed to be predestined for the development of affective disorders.

In summary, it could be demonstrated that several similarities exist between depression in RA and depression in MS, perhaps more than appear obvious when viewing these phenotypically very different diseases. The underlying pathogenesis is poorly understood, but biochemical findings, imaging, and psychosocial studies point to the idea that depression is not purely a psychological consequence in reaction to a life-threatening disease but also might represent a downstream consequence of similar underlying neurohumoral and neuroimmunological mechanisms that are pertinent to both, MS and RA. Whether this may lead to clinical utility, e.g., extending the use of anti-inflammatory drugs proven to be effective in one diseases at this point purely speculative and remains to be further elucidated.

Abbreviations

BDI-II, Beck Depression Inventory II; BDNF, brain-derived neurotrophic factor; BMI, Body Mass Index; CNS, central nervous system; COX-2, cyclooxygenase-2; CRP, c-reactive protein; CSF, cerebrospinal fluid; DMARDs, disease-modifying antirheumatic drugs; DSM-V, Diagnostic and Statistical Manual of Mental Disorders (5th edition); (f)MRI, functional magnetic resonance imaging; GR, glucocorticoid receptor; HPA, hypothalamic-pituitary-adrenal; 5-HTT/DAT, serotonin and dopamine transporter; IL, interleukin; MDD, Major Depressive Disorder; MRI, Magnetic Resonance Imaging; MS, Multiple Sclerosis; NO, nitric oxide; NSAIDs, non-steroidal anti-inflammatory drugs; PGE₂, prostaglandin E₂; RA, Rheumatoid Arthritis; RRMS, relapsing-remitting multiple sclerosis; sIL-2R, soluble form of interleukin 2-receptor; STAI-Y, State/Trait Anxiety Inventory; TNF, tumor-necrosis factor; VMAT2, vesicular monoamine transporter 2; WHO, World Health Organization.

Author contributions

AW and PC conceived and designed the review; AW performed the literature analysis and overview; AW and PC wrote the paper.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

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