Systematic Review

Peripheral Inflammatory Markers in Subtypes and Core Features of Depression: A Systematized Review

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Abstract

Introduction: The aim of this work was to summarize relationships between two subtypes of major depressive disorder (melancholic and atypical) and four core features of depression that reflect the domains identified consistently in previous studies of major depressive disorder endophenotypes (exaggerated reactivity to negative information, altered reward processing, cognitive control deficits, and somatic symptoms) on the one hand and selected peripheral inflammatory markers (C-reactive protein [CRP], cytokines, and adipokines) on the other. *Methods:* A systematized review was conducted. The database used for searching articles was PubMed (MEDLINE). *Results:* According to our search, most peripheral immunological markers associated with major depressive disorder are not specific to a single depressive symptom group. The most evident examples are CRP, IL-6, and TNF-α. The strongest evidence supports the connection of peripheral inflammatory markers with somatic symptoms; weaker evidence indicates a role of immune changes in altered reward processing. The least amount of evidence was found for the role of peripheral inflammatory markers in exaggerated reactivity to negative information and cognitive control deficits. Regarding the depression subtypes, a tendency for higher CRP and adipokines was observed in atypical depression; increased IL-6 was found in melancholic depression. *Conclusion:* Somatic symptoms of depression could be a manifestation of a specific immunological endophenotype of depressive disorder. Melancholic and atypical depression may be characterized by different profiles of immunological markers.

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Introduction

Major depressive disorder (MDD) is a widespread disorder that, in 2015, affected approximately 216 million people – 3% of the global population – and was responsible for the second-most years lived with disability, after lower back pain [1]. Only about half of individuals with depression achieve remission with available treatment [2, 3]. Considering the impact of depression on healthcare systems and the relatively high proportion of patients resistant to current therapeutic interventions, searching for more effective treatment methods for this disorder is an important topic both for psychiatric research and public health. However, MDD seems to be an exceedingly heterogeneous disorder, as evidenced by the mixed symptom phenotypes that qualify for the disorder [3–5]. Identify-

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ing further biological and behavioral processes underlying depression and their connections should be a priority and should be taking place in more endophenotypic approaches, as the US National Institute of Mental Health recently recommended in Research Domain Criteria, asking for a shift away from symptom-based diagnoses toward a transdiagnostic neurobiological focus in the study of brain illnesses [6].

Various studies have concluded that inflammation plays an important role in the etiopathogenesis of MDD [7–10]. Inflammatory changes in depression have been described in humoral and cellular immunity and both in innate and adaptive immunity [11–14]. The most available evidence points to increased concentrations of the acute-phase reactant C-reactive protein (CRP) and other markers of inflammation, including the innate immune cytokines: interleukin (IL)-1beta, IL-6, and tumor necrosis factor alpha (TNF-α) in peripheral blood. Their significant elevation was detected in a substantial proportion of patients (approximately 25–45% depending on the sample) and associated with depression severity, treatment resistance, and risk of depression among healthy individuals [15, 16]. The production and secretion of pro-inflammatory cytokines were found to be modulated by activation and polarization of microglia and central nervous system resident macrophages, and this phenomenon led in the early 1990s to the formulation of cytokine/macrophage theory of depression, proposing that activation of innate immune mechanisms mediates external and internal stressors to depressive behavior [17, 18].

Lately, cell-mediated adaptive immunity has started to be considered a key component of MDD immunopathology [11]. The specific immunity in individuals with MDD seems to be predominantly activated in its humoral branch, comprising the B-cell lineage lymphocytes. Moreover, increased Th/Tc cell ratios have been frequently detected in the peripheral blood of the patients, as well as a higher number of B-cell subsets and decreased T-cell proliferation [13, 18]. Nevertheless, although T lymphocytes might have crucial importance in the development of MDD according to animal studies, human studies focused on alterations of Th/Tc lymphocyte ratios in MDD sometimes found different results [11, 13, 19]. Further inconsistencies were observed in studies focusing on cytokine changes in the peripheral blood of MDD individuals and in studies on antidepressants [15, 20–22].

Although there is still uncertainty about the directions of causal relationships between peripheral inflammation, brain inflammatory changes in MDD, and its effects on neural processes relevant to depression (e.g., neuroplasticity, neurotransmitter systems, and neuroendocrine function), it is likely that these processes are interconnected, and changes in one of them are reflected in others [3, 16]. Moreover, the heterogeneity in findings regarding inflammation in MDD suggests that there may be more immunopathological pathways leading to possible multiple immunological phenotypes of this disorder. This idea raises the question of whether diverse immunological backgrounds of depression could reflect the clinical presentation of MDD, its subtypes, and predominant symptom clusters.

Many attempts have been made to subclassify MDD further [23]. The most used classification of depression is into melancholic and atypical subtypes, both currently acknowledged in the DSM-V, which relies on the evidence concerning the different neurobiological mechanisms behind them [24, 25]. These two subtypes are characterized by different functioning of the reward system, vegetative symptoms, disturbance of circadian rhythmicity, and motoric activity disturbances during a depressive episode [24–26].

Another subclassification was recently established by Dooley et al. to broadly reflect the domains identified with the most consistent evidence in previous studies of depression endophenotypes that had been examined in relation to inflammation in human research [27–29]. Dooley et al. [3] postulated four core features of depressive symptoms: (1) exaggerated reactivity to negative information, (2) altered reward processing, (3) deficits in cognitive control, and (4) somatic symptoms [30].

Such defined core features partially reflect four out of six domains of the research domain criteria: exaggerated reactivity to negative information – negative valence systems, altered reward processing – positive valence systems, deficits in cognitive control – cognitive systems, and somatic symptoms – arousal and regulatory systems [31]. Furthermore, these clusters also correspond to four "clinical content" depression subtypes (depressed mood, anhedonic depression, cognitive depression, and somatic depression) based on predominant common behavioral characteristics by Sharpley and Bitsika [32]. They subsequently validated these subtypes in several populations [33]. Interestingly, each of these core features is hypothesized to be associated with different neurotransmitter systems, brain networks, and structures:

Exaggerated reactivity to negative information may result from dysregulation of the serotonergic system, leading to increased efficiency in the processing of aversive information in the dorsomedial prefrontal cortex (PFC)

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and enhanced processing of threat-related stimuli in the amygdala, further increased by the dorsal and subgenual anterior cingulate cortex (ACC) [3, 32]. Behavioral representations of exaggerated reactivity to negative information are represented by symptoms of negative emotions (from MDD symptoms, e.g., depressed mood, worry, feelings of sadness, guilt, or worthlessness), and their development is broadly considered to depend on early life experiences, particularly early environmental deprivation [3, 24, 25, 32].

Altered reward processing is hypothesized to result from an imbalance in catecholaminergic systems, principally via postsynaptic reductions of the dopamine receptor sensitivity in the nucleus accumbens [3, 32]. The behavioral manifestation of altered reward processing represents anhedonia, the loss of pleasure or interest in previously rewarding stimuli, that is estimated to be 46% heritable in studies of monozygotic twins [3, 32].

Cognitive control relies heavily on the PFC, the hippocampus, and ACC but also recruits broader neural networks, including subcortical areas, and seems to be affected by hypercortisolemia-induced apoptotic effects on hippocampal and PFC neurons [32]. Deficits in cognitive control manifest in MDD as deficits in various executive functions (e.g., motivation, planning ability, inhibition, attention shifting, working memory, updating, verbal fluency) and have been observed to occur independently of the cognitive bias toward negative interpretations of events [3, 32].

Somatic symptoms were defined as a group of vegetative symptoms pertaining to the regulation of bodily functions: motor functions, wake and sleep cycle, and appetite. Somatic symptoms of MDD include fatigue, sleep disturbance, appetite disturbance, and psychomotor changes [3]. Fatigue is associated with alterations in dopamine and associated frontostriatal regions [3]. Psychomotor slowing includes alterations in dopamine functioning and the basal ganglia circuit [3]. Sleep disturbances affect multiple brain regions, including dorsolateral and medial PFC, amygdala, intraparietal sulcus, the hippocampus, the ACC, and instability within the default mode network [3]. Appetite changes are related to the hypothalamus, mesolimbic circuitry, insular cortex, and the action of several orexigenic and anorexigenic molecules, including but not limited to adipokines [34]. Genetic factors explain up to 74% of individual differences in somatic symptoms in twin studies, supporting the co-occurrence of these somatic symptoms as a depression endophenotype [3]. In comparison to Doley et al. [3], we instead used the term "somatic symptoms" rather than

"somatic syndrome" to avoid confusion with "somatic syndrome" according to ICD-10, which is equivalent to MF-MDD in DSM-V [24, 25].

Hypotheses of putative association between changes in the central nervous system and peripheral immunological markers and the existence of MDD subtypes and core features suggest that stratification of depressive symptoms based on peripheral immunological markers could be a promising approach toward understanding the neuroinflammatory underpinnings of MDD.

Thereby, we decided to investigate the connection between peripheral blood inflammatory markers and subtypes and core features of depression. Identification of MDD symptom clusters associated with distinguishable immunological parameters could be beneficial not only for a better understanding of the processes behind the depression but also for better diagnostics and for new therapeutic approaches, for instance, immunomodulatory therapy [35].

Methods

Aim and Objectives

The aim of this work was to summarize relationships between core features and subtypes of depression on the one hand and selected peripheral immunological and inflammatory parameters on the other in MDD patients without comorbidities. Particular objectives were:

1. To assess whether peripheral immunological and inflammatory parameters play a different role in different subtypes of MDD and the development of different core features and
2. To find whether there are specific peripheral immunological and inflammatory parameters connected to specific subtypes of MDD or specific symptoms.

For this purpose, a systematized review on this topic was conducted. Explored markers included CRP, cytokines, and adipokines.

Description of Selection Process

The database used for searching for articles was PubMed (MEDLINE). The search string included the following terms: ("depression" OR "major depressive disorder" OR "MDD") AND ("endophenotype*" OR "core feature*" OR "subtype*" OR "melancholic" OR "atypical" OR "reactivity to negative information" OR "negative mood" OR "depressed mood" OR "low mood" OR "sadness" OR "anhedonia" OR "loss of interest" OR "cognition" OR "cognitive control" OR "cognitive function*" OR "working memory" OR "updating" OR "inhibition" OR "planning abilit*" OR "shifting" OR "verbal fluency" OR "fatigue" OR "psychomotor slowing" OR "psychomotor retardation" OR "agitation" OR "sleep*" OR "insomnia" OR "hypersomnia" OR "appetite" OR "weight" OR "anorexia") AND ("inflammation" OR "cytokine*" OR "interferon*" OR "interleukin*" OR "tumor necrosis factor" OR "CRP" OR "C-Reactive Protein" OR "adipokine*" OR "leptin" OR "adiponectin" OR "ghrelin" OR "resistin").

The PubMed search was performed on June 1, 2021. The titles and abstracts of the articles were scanned to see if they met the inclusion criteria. If there were any doubts whether an article should be included, the whole text was read.

Only original articles published between January 1, 1990, and June 1, 2021, and written in English were considered. Previous reviews, meta-analyses, short communications, letters to editors, and editorials were not used for this review, but their reference list was scanned for articles that might have been missed by the PubMed search [34, 36].

Criteria for a study's inclusion in this review were

1. The study must concern the symptomatic phase of MDD diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM), Fifth Edition (diagnostic codes: 296.21–296.24, 296.31–296.34) or equivalents in DSM-IV and International Classification of Diseases, Tenth Revision (diagnostic codes: F32.0–F32.3, F33.0–F33.3) established using structured diagnostic interviews or clinically by a psychiatric specialist [24, 25].
2. The study must report the difference in the levels of examined peripheral inflammatory markers between at least one group of MDD patients with a certain MDD subtype and controls or between at least one MDD core feature and the other core feature(s) of MDD/entire depressive symptomatology/the same depressive symptom in controls after adjustment for depression severity.

Because of other possible interfering factors which could influence the relationship between depressive symptoms and selected molecules, articles that primarily focused on physical illnesses such as cancer, cardiovascular, metabolic, infectious, autoimmune, degenerative, traumatic, and functional disorders with comorbid depression were excluded from the review, as were studies on depression in the elderly, during pregnancy, puerperium, and adolescence. Studies dealing with patients with psychiatric comorbidities were not included either. Both somatic and psychiatric comorbidities can lead to the elevation of peripheral inflammatory markers [16]. An exception to this exclusion criterion was made for MDD with a comorbid anxiety disorder because of the frequent co-occurrence of depressive and anxiety symptoms [37]. Another exception was made for studies conducted on mixed populations of patients with unipolar and bipolar depression if bipolar patients made up less than 10% of the patient group because bipolar depression is frequently misdiagnosed as unipolar MDD and because up to 1 in 5 MDD patients may in fact have undeclared bipolar disorder [38]. Treatment with antidepressants was not an exclusion criterion, although antidepressants may change inflammatory biomarkers [39].

MDD Subtypes and Symptom Clusters
In order to better understand the heterogeneity of MDD, this review focused on two subclassifications of MDD and its symptoms.
A. Two subtypes of MDD: melancholic and atypical subtypes [24, 25].
B. Four core features of MDD as were described by Dooley et al. [3] and which corresponds with four depression subtypes postulated by Sharpley and Bitsika [32]: (1) exaggerated reactivity to negative information, (2) altered reward processing, (3) deficits in cognitive control, and (4) somatic symptoms. Somatic symptoms were further subclassified into fatigue, sleep disturbances, appetite disturbances, and psychomotor changes [3, 32].

These classifications and their theoretical underpinnings were described in detail in the Introduction section.

Results

Based on our search strategy, 5,132 papers were retrieved (shown in Fig. 1); only 262 were considered sufficiently relevant to warrant an abstract review. Fifty-seven publications were excluded because they were reviews or meta-analyses. One hundred seventy-six out of 205 papers were excluded because they did not fulfill the inclusion criteria.

Inflammatory Markers and Depression Subtypes
Twelve studies focusing on inflammatory markers and depression subtypes were identified. Their results are heterogeneous. A summary of the studies comparing inflammatory markers during a concurrent depressive episode of MDD with melancholic, atypical, or non-melancholic features is shown in Table 1.

Most of the studies regarding the acute phase of depressive episodes explored interleukins IL-1, IL-6, CRP, and tumor necrosis factor alpha (TNF-α) [40–49]. In these studies, CRP was elevated in AF-MDD; results regarding CRP in MF-MDD were inconsistent or non-significant [40, 42, 44, 46, 47]. In contrast, IL-6 elevation was found more often in MF-MDD [42, 44, 45, 48, 49]. There is less evidence suggesting different IL-1 and TNF-α levels between depression subtypes than in IL-6 and CRP, and studies reached inconsistent findings [41, 43, 44]. Concerning other cytokines, there is a lack of studies, or the studies lack control groups [50]. One study suggests higher levels of leptin in AF-MDD compared to controls; one study found higher resistin in AF-MDD [51, 52]. Works focused on adiponectin failed to find any significant results [51].

Inflammatory Markers and Core Features of Depression
Eighteen studies focused on cytokine or adipokine changes across core features of depression were identified. An overview of the studies is summarized in Tables 2 and 3.

Our search found only two studies focusing on cytokine and adipokine changes in relation to more depressive symptom clusters. Because the symptomatic clusters used in one of the studies were defined differently from the concept of our review, these studies are listed separately here. The first study was by Duivis et al. [53] and observed the association of depressive symptoms with higher levels of CRP, IL-6, and TNF-α, driven mainly by somatic symptoms (weight loss or gain, insomnia or hypersomnia, psychomotor agitation or retardation, and
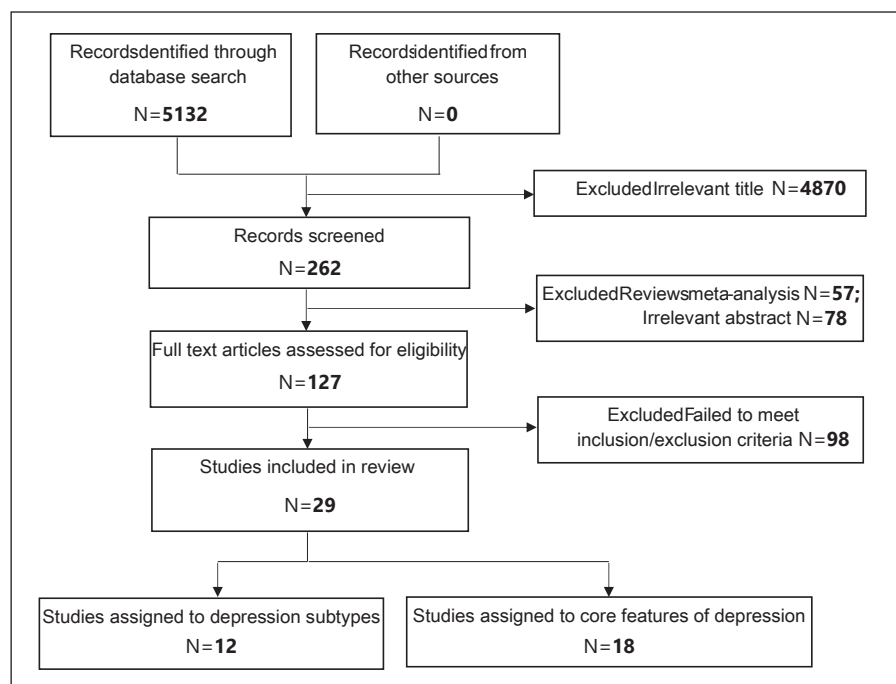
Fig. 1. Research strategy.

loss of energy or feeling tired) and less by other symptoms (anhedonia, feeling depressed, feelings of worthlessness, concentration problems, and recurrent thoughts of death). The second was by Milaneschi et al. [52] which found leptin positively correlated with mood related to time of the day, increased appetite, increased weight, reduced energy level, aches and pains, other bodily symptoms, and leaden paralysis; it negatively correlated with decreased appetite.

Exaggerated Reactivity to Negative Information

Few studies have addressed the role of inflammation in exaggerated reactivity to negative information. As mentioned above, Milaneschi et al. [52] found higher leptin levels related to depressed mood. Prossin et al. [54] observed an association between levels of IL-18 and exaggerated reactivity to negative information in women with MDD only indirectly through activation of opioid system induced by sadness.

Altered Reward Processing

Focusing on altered reward processing, the most significant results were reached in the study by Jha et al. [55], which found higher levels of IL-17, Th1 cell markers (IFN-γ and TNF-α), Th2 cell markers (IL-4, IL-5, IL-9, and IL-13), and non-T cell markers (IL-1β, IL-1 receptor antagonist, IL-6, IL-8, macrophage inflammatory proteins

1alpha, and macrophage inflammatory proteins 1beta) associated with greater severity of anhedonia in MDD. Tang et al. [56] observed higher levels of IL-6 in MDD patients with anhedonia than in those without anhedonia. Felger et al. [16] found an indirect correlation of blood CRP with anhedonia.

Deficits in Cognitive Control

To our knowledge, only two studies of inflammatory markers and deficits in cognitive control reached significant results. Grassi-Oliveira et al. [57] found a significant association of IL-6 levels with verbal memory in depression, even after controlling for depression severity. A study by Felger et al. found higher CRP led indirectly to deficit in motivation [16].

Somatic Symptoms

No studies focusing on somatic symptoms as a whole symptom group were found except those exploring depression subtypes and the report by Duivis et al. [53] finding an association of somatic depressive symptoms with higher levels of CRP, IL-6, and TNF-α. Nevertheless, several studies examining specific somatic symptoms reached significant results and are listed below.

Fatigue. Pedraz-Petrozzi et al. [58] found fatigue in MDD associated with TNF-α levels. According to Maes et al. [59], IL-1 and TNF-α were higher in depressed

Table 1. Description of studies focusing on depression subtypes

Author(s) (year)	N (C/MDD/MF/nMF/AF/nAF)	Age: mean (SD) in C/MDD/MF/nMF/AF/nAF	Cytokines measured	Significant results
Rothermundt et al. (2001) [40]	86 (43/43/22/21/–/–)	44.5 (10)/44.5 (10)/–/–/–/–	IL-1β, CRP	**CRP:** nMF < C
Kaestner et al. (2005) [41]	74 (37/37/21/16/–/–)	44.6 (13.9)/–/51.4 (12.0)/36.8 (12.4)/–/–	IL-1β, IL-1ra/IL-1β ratio	**IL-1β:** nMF > MF, nMF > C; **IL-1ra/IL-1β ratio:** nMF > MF
Lehto et al. (2010) [51]	140 (70/70/–/–/–/–)	54.2 (9.2)/D/–/–/–/–	Adiponectin, resistin	**Resistin:** AF > C
Karlovic et al. (2012) [42]	73 (18/55/32/–/23/–)	45.0 (9.5)/–/48.6 (8.1)/–/50.9 (8.3)/–	CRP, IL-6, TNF-α	**IL-6:** MF > C; **CRP:** MF > C
Maes et al. (2012) [43]	57 (20/37/12/25/–/–)	42.1 (12.8)/42.0 (11.0)/–/–/–/–	TNF-α, IL-1	**TNF-α:** MDD > C; MF > nMF; **IL-1:** MDD > C; MF > nMF
Lamers et al. (2013) [44]	776 (543/233/111/–/122/–)	41.3 (14.6)/–/40.2 (12.1)/–/39.6 (12.1)/–	IL-6, TNF-α, CRP	**IL-6:** AF > C; AF > MF; **TNF-α:** AF > C; AF > MF; **CRP:** AF > C; AF > MF
Dunjic-Kostic et al. (2013) [45]	86 (39/47/29/–/18/–)	49.90 (4.99)/–/50.28 (7.41)/–/52.26 (7.29)/–	IL-6, TNF-α	**IL-6:** MF > C
Glaus et al. (2014) [46]	3,355 (3,059/296/198/–/98/–)	All: 50.9 (8.8)	IL-6, IL-1β, TNF-α, CRP	**CRP:** MF < C
Hickman et al. (2014) [47]	1,791 (1,682/109/–/–/16/93)	29.0 (5.8)/–/–/29 (5.1)/30.1 (6)	CRP	**CRP:** AF > nAF; AF > C
Rudolf et al. (2014) [48]	56 (24/32/24/–/8/–)	30.8 (9.5)/–/35.1 (10.9)/–/34.0 (12.5)/–	IL-6	**IL-6:** AF > C
Spanemberg et al. (2014) [49]	87 (54/33/13/20/–/–)	47.4 (9.97)/–/52.8 (10.7)/48.4 (7.7)/–/–	IL-4, IL-6, IL-10, TNF-α, IFN-γ, IL-17	**IL-6:** MDD > C; MF > C; **IFN-γ:** MF < C, MF < nMF
Milaneschi et al. (2017) [52]	1,559 (497/1,062/–/–/–/–)	40.6 (14.8)/40.7 (12)/–/–/–/–	Leptin	**Leptin:** AF > C

">", biomarker levels were significantly higher in this group ($p < 0.05$); "<", biomarker levels were significantly lower in this group ($p < 0.05$); AF, patients with atypical depression; C, controls; CRP, C-reactive protein; IFN-γ, interferon gamma; IL, interleukins; IL-1ra, interleukin-1 receptor antagonist; MDD, patients with depression; MF, patients with melancholic depression; N, number of participants; nAF, patients with non-atypical depression; nMF, patients with non-melancholic depression; SD, standard deviation; TNF-α, tumor necrosis factor alpha.

Table 2. Overview of findings in depression core features – exaggerated reactivity to negative information, altered reward processing, and deficits in cognitive control

Author(s) (year)	Exaggerated reactivity to negative information	Altered reward processing	Deficits in cognitive control	
			motivation	memory
Grassi-Oliviera et al. (2011) [57]				↑ IL-6
Prossin et al. (2011) [54]	↑IL-18 (in women only)*			
Milaneschi et al. (2017) [52]	↑ Leptin			
Jha et al. (2018) [55]		↑ IL-17, Th_1 markers, Th_2 markers, non-T markers		
Felger et al. (2020) [16]		↑ CRP*	↑ CRP*	
Tang et al. (2021) [56]		↑ IL-6		

"*", indirect association; "↓", decrease of the marker(s); "↑", elevation of the marker(s); CRP, C-reactive protein; IL, interleukins; TNF-α, tumor necrosis factor alpha. Non-T markers: interleukin-1β, interleukin-1 receptor antagonist, interleukin-6, interleukin-8, macrophage inflammatory protein 1alpha, and macrophage inflammatory protein 1beta. Th_1 markers: interferon gamma and tumor necrosis factor alpha. Th_2 markers: interleukin-4, interleukin-5, interleukin-9, and interleukin-13.

Table 3. Overview of findings in depression core features – somatic symptoms

Author(s) (year)	Fatigue	Psychomotor slowing	Insomnia	Decreased appetite	Increased appetite
Esel et al. (2005) [68]				↑ leptin (in women only)*	
Motivala et al. (2005) [63]			↑ IL-6		
Maes et al. (2012) [59]	↑ IL-1, TNF-α*				
Duivis et al. (2013) [53]	↑ CRP, IL-6, TNF-α	↑ CRP, IL-6, TNF-α	↑ CRP, IL-6, TNF-α	↑ CRP, IL-6, TNF-α	↑ CRP, IL-6, TNF-α
Rethorst et al. (2015) [64]			↑ IL-1β*		
Cho et al. (2017) [62]			↑ CRP		
Lamers et al. (2018) [65]					↑ CRP, TNF-α
Milaneschi et al. (2017) [52]	↑ Leptin			↓ Leptin	↑ Leptin
Milaneschi et al. (2017) [67]					↑ CRP, Leptin
Pedraz-Petrozzi et al. (2020) [58]	↑ TNF-α				
Shi et al. (2020) [60]		↑ CRP			
Simmons et al. (2020) [66]					↑ CRP, leptin; ↓ ghrelin
Belge et al. (2021) [61]		↑ IL-6			

"*", indirect association; "↓", decrease of the marker(s); "↑", elevation of the marker(s); CRP, C-reactive protein; IL, interleukins; TNF-α, tumor necrosis factor alpha.

patients with fatigue symptoms than in controls; there were no significant differences between MDD patients without fatigue symptoms and controls. Milaneschi et al. [52] observed leptin elevation in connection with fatigue in MDD patients.

Psychomotor Changes. Shi et al. [60] found plasma levels of CRP associated with psychomotor slowing in MDD patients. Belge et al. [61] observed IL-6 levels positively correlated with higher psychomotor retardation scores in individuals with MDD.

Sleep Disturbances. Cho et al. [62] found a connection between increased CRP and sleep disturbance in currently depressed patients. According to Motivala et al. [63], nocturnal elevations of IL-6 was associated with sleep disturbance in patients with MDD. Rethorst et al. [64] observed an indirect correlation of high IL-1β with insomnia and hypersomnia in MDD.

Appetite Disturbances. According to Lamers et al. [65], increased appetite in depressed patients was positively associated with CRP and TNF-α. Simmons et al. [66] found increased appetite in MDD patients associated with higher levels of CRP and leptin and lower levels of ghrelin. In one study, Milaneschi et al. [67] observed higher levels of CRP and leptin in a subgroup of depressed patients with increased appetite and/or weight. In another study, Milaneschi et al. [52] found an association between leptin elevation and increased appetite and weight and between low levels of leptin and decreased appetite. Elevated leptin levels in connection with decreased appetite in depression in women were found by Esel et al. [68].

Discussion

This systematized review was conducted to summarize the current body of research into the relationship between peripheral immunological parameters and subtypes of depression or its core features. The most important finding of this review is that peripheral inflammatory markers seem to be associated with almost all examined MDD symptom clusters; however, the most evidence is available for the role of immunological changes in somatic symptoms of depression. Moreover, examined studies suggest that MF-MDD and AF-MDD may be characterized by different profiles of peripheral immunological markers. That being said, the available evidence points toward only a limited specificity of examined markers for specific symptom clusters. Therefore, current knowledge does not allow us to ascribe functional roles between peripheral inflammation and brain function in MDD.

Major Findings

According to our search, most immunological markers associated with MDD are not specific to a single depressive symptom group but instead appear in more than one. The most evident examples are increased levels of CRP, IL-6 and TNF-α, which are associated with all core features of depression [16, 43, 53, 55, 57, 65, 68]. According to a study by Bryleva et al. [69], which did not pass our inclusion criteria and which was performed on a mixed

group of MDD patients and controls, another non-specific marker may be serum amyloid A. Interestingly, all these molecules are considered either acute-phase proteins (CRP, serum amyloid A) or have a role in their regulation (IL-6, TNF-α) [70]. The low specificity of these markers toward specific symptoms of depression suggests that the inflammation detectable by peripheral markers reflects more general changes in brain functions and morphology affected by MDD.

There are several proposed connections between peripheral inflammatory or immunological alterations, changes in brain function or morphology, and clinical symptoms that would be more general: inflammation may influence endothelial function, leading to increased blood-brain barrier permeability or neurovascular dysfunction and effect of inflammatory markers on neuroplasticity [71, 72]. Conversely, theories about more localized effects of inflammation include a direct effect on brain parenchyma and an influence of inflammation on neurotransmitter systems relevant to reward and threat sensitivity [72, 73].

That being said, there is evidence that one symptom cluster is more closely associated with peripheral inflammation and immunological reactions than other features: somatic symptoms. Results of studies included in this review are further supported by the research letter of Jokela et al. [74] that did not pass our inclusion criteria. In this report, data from three cross-sectional studies suggested an association of CRP with all symptoms of MDD; however, after adjustment for the other depression symptoms, only the association with somatic symptoms remained significant. None of these findings are surprising given the role of inflammatory markers in sickness behavior that resembles some of the somatic symptoms of depression [75].

Apart from non-specific markers mentioned above, there are several more specific markers associated with somatic symptoms. One of them is the IL-1 family of cytokines, which appears to be the main mediator of behavioral changes during illness [43, 64, 75]. Another more specific marker appears to be adipokine leptin associated with changes in appetite and fatigue [52, 67, 68]. Levels of leptin were usually increased in MDD patients, with a single exception being a study by Esel et al. [68]. The importance of leptin in these somatic symptoms is in line with leptin's role in regulation of energy homeostasis [76]. Interestingly, increased levels of leptin were also found to be associated with exaggerated reactivity to negative information, further supporting the hypothesis of leptin's importance in the pathophysiology of MDD, which is not surprising given the expression of leptin receptors in the ventral tegmental area [52, 76].

Presented evidence may suggest that an increase in peripheral inflammatory markers may represent a putative immunological subtype of MDD with a more significant role for peripheral inflammation as reflected by more prevalent somatic symptoms. This subtype of MDD would correspond with somatic depression defined by Sharpley and Bitsika [32].

This notion is supported by the fact that inflammation was demonstrated credibly to play a role in the development and maintenance of somatic symptoms not only in MDD but in exogenously induced depression as well [3]. Furthermore, inflammatory markers are associated with symptoms resembling depressive somatic symptoms in other disorders. For example, Mills et al. [77] found an association of IL-6 with increased sleep and REM latency without any major medical condition, sleep or psychiatric disorders. Another somatic symptom, fatigue, was often explored in the context of chronic fatigue syndrome, in which fatigue is one of the defining symptoms [78]. Recently, a review by Yang et al. [79] reported on an association between fatigue and TNF-α, IFN-γ, IL-6, IL-1, and weaker evidence exists for a role of elevated CRP [80]. The inflammatory response in chronic fatigue syndrome appears to be similar to that in MDD but more pronounced [59]. To summarize, based on available evidence, it is possible to hypothesize that inflammation and immune alterations in somatic symptoms may represent an important transdiagnostic feature between various disorders and conditions.

While discussing somatic symptoms, the topic of depression subtypes should not be neglected. The two most examined subtypes of MDD episodes, melancholic and atypical (MF-MDD and AF-MDD, respectively), are partially defined by the existence of specific somatic symptoms: insomnia and loss of appetite in MF-MDD and "reverse vegetative syndrome" as hypersomnia and hyperphagia in AF-MDD. On the other hand, the differences between those subtypes are not limited to somatic symptoms since mood reactivity, feelings of guilt, or a long-term interpersonal rejection sensitivity are other important distinguishing factors [24]. Considering the depression subtypes, two questions arise: does available evidence support findings regarding somatic symptoms of depression, and if so, are there any differences between markers associated with MF-MDD and AF-MDD?

Several studies have been conducted concerning inflammatory markers and depression subtypes. Nevertheless, only a limited range of cytokines has been examined. In addition, the reviewed studies often focused on a different spectrum of cytokines. Despite that, a certain tendency for CRP elevation in AF-MDD and higher IL-6 in MF-MDD were found; increased adipokines were observed in AF-MDD. Changes of adipokine levels detected in AF-MDD are not surprising considering a weight gain or increase of appetite being one of the defining features of AF-MDD and the role of adipokines in a regulation of feeding behavior and obesity-related metabolic alterations [52].

More interestingly, CRP and IL-6 differences between depression subtypes could reflect one of the most consistently reported findings in MDD that MF-MDD and AF-MDD differ mainly in hypothalamus-pituitary-adrenal axis activity [26]. Considering that cortisol was demonstrated to trigger IL-6 release into circulation, higher levels of IL-6 in MF-MDD could therefore be caused by relatively higher cortisolemia in MF-MDD compared to AF-MDD, whereas increased CRP in AF-MDD could be related to lower cortisolemia in AF-MDD because CRP and cortisol in MDD may show an inverse correlation through a negative feedback loop between the hypothalamic-pituitary-adrenal axis and the inflammatory response system [26, 81, 82].

That being said, it is important to note that the results of existing studies on depression subtypes and inflammatory markers often vary, sometimes fundamentally. This inconsistency might reflect that although melancholic and atypical depression may differ in their neurobiological underpinnings, most of the depressive patients showed mixed features of MF-MDD and AF-MDD [26]. According to Gold and Chrousos, the proportion of patients with pure MF-MDD or AD-MDD was low – only 25–30% and 15–30%, respectively [83]. The discrepancies raise the question of how stable the cytokine profiles of MF-MDD or AF-MDD are. In terms of time, CRP, considered a possible marker of AF-MDD, remained higher even with mean follow-up periods of more than 5 years in patients who experienced AF-MDD or combined MDD [84]. Moreover, many patients with MDD experience fluctuations between melancholic and atypical episodes over time, and thus it remains a question whether CRP elevation at follow-up visits is still associated with a singular subtype [85]. To put it into context, it is possible that general dysregulation of immunological reactions may represent a trait of a certain immunological subtype of MDD associated with somatic symptoms, while differences between markers found in MF-MDD and AF-MDD may represent current states during specific depressive episodes.

Other Findings

Compared to somatic symptoms, there is less evidence for the role of inflammatory markers in reward processing and reactivity to negative stimuli, and the least amount

of evidence of all points to a role for immune changes in cognitive control deficits. Considering the involvement of immunological changes in reactivity to negative information and altered reward processing, studies included in this review again show an association with non-specific markers (CRP, IL-6, TNF-α). More specific results were only a finding of increased IL-18 associated with exaggerated reactivity to negative information and increased IL-17 associated with altered reward processing [54, 55]. These results are supported by reports in mixed or non-depressed populations not meeting inclusion criteria for this review. For example, Suarez and Sundy [82] found that premorbid dysregulation of the neuro-immune relationship, characterized by an insufficient release of cortisol in conjunction with higher CRP, plays a role in negative affect reactivity in humans with elevated levels of depression symptoms. According to Fagundes et al. [86], bereaved individuals with a higher grief severity had higher levels of IFN-γ, IL-6, and TNF-α than those with less grief severity. On the other side, Brydon et al. [87] found optimism inversely related to IL-6 responses to stress condition. Felger et al. [88] demonstrated a direct association between increased CRP and anhedonia and observed indirect association of anhedonia with high IL-6 and IL-1β. Furthermore, Haroon et al. [89] found increased plasma CRP associated with anhedonia.

Interestingly, some of the markers associated with reactivity to negative information and altered reward processing were also shown to influence brain structures involved in regulation of mood and reward circuitry. For example, peripheral IL-6 elevation was associated with an increase of activity in the amygdala, anterior insula, and dorsal ACC and reduction of functional connectivity of the subgenual ACC to the amygdala and other medial prefrontal cortical regions, as well as the nucleus accumbens and superior temporal sulcus [73]. Higher levels of TNF-α may cause changes in the hippocampus, striatum and amygdala, which could be the result of glutamate release induction by activated microglia, leading to excitotoxic damage [72, 73]. IL-1β has been shown to decrease neurogenesis in hippocampal progenitor cells, through activation of the kynurenine pathway [72]. Some of these possible influences may be indirect due to changes in blood-brain barrier permeability [72].

Due to minimal evidence of an association between immunological markers and cognitive control deficits, it seems that the role of inflammatory changes in this symptom group is limited. Only studies showing a possible role of markers also associated with other symptom groups (CPR, IL-6, TNF-α) passed the inclusion criteria for this review. Nevertheless, studies with a different focus also report significant results. Charlton et al. [90] observed high levels of IL-6 significantly contributed to memory performance in individuals with late-life depression compared to healthy older adults; however, increased levels of IL-6 alone were not sufficient to account for cognitive difficulties. Concerning cognitive decline prediction, Chang et al. [91] found that attention shifting and psychomotor speed of patients with high baseline CRP levels might remain impaired even if their mood symptoms improve after treatment. Gallagher et al. [92] concluded that high CRP plays a role in the relationship between depressive symptoms and impairment in delayed recall and verbal fluency after a 4-year follow-up period, and Gimeno et al. [93] found that CRP and IL-6 predicted cognitive symptoms of depression even after a 12-year follow-up period. Overall, it is important to note that associations between cognition and inflammation have also been reported in psychiatrically healthy adults, where levels of IL-6 predicted future cognitive decline; however, it seems that depression might cause the deterioration to accelerate [91, 94–96]. These results, however, suggest that the associations of peripheral immune changes with cognitive control deficits are not specific and are rather part of the wider array of dysregulations found in MDD.

Limitations of Conducted Studies

Studies included in this review did show several limitations that may be problematic for the generalization of their findings and complicate comparison of their results. The first limitation of this work is that it did not evaluate central nervous system markers but peripheral markers, whose effect on the brain is still uncertain in several steps [3, 16].

The second limitation is inconsistent methodologies of included studies, especially the use of various questionnaires for establishing depressive subtypes, symptomatic clusters, or specific symptoms, as well as different cut-offs for distinguishing between depressed and non-depressed individuals [42, 44, 45, 53, 69]. Lack of consensus was, for example, found regarding definitions of MDD subtypes: some authors distinguished between typical and atypical depression, whereas others used categories of melancholic and non-melancholic depression that include not only "combined atypical and melancholic" and "unspecified" but also atypical depression according to the DSM classifications [24, 36, 97–100].

Other complicating factors were the low sample size of some of the groups and differences in included covariates among studies (e.g., sex, age, educational level, current

smoking, physical activity, body mass index, depression severity, and medication use) [16, 40–49, 51–68]. In the light of recent findings, notably several approaches to the role of sex should be considered carefully when immune-mood changes might significantly vary between women and men as Moieni et al. [101] observed in a study of inflammatory and depressive reactions to an endotoxin challenge, and Qu et al. [102] confirmed IL-6 modulation of cognition among individuals with MDD, although no differences were observed between male and female in CRP and IL-1β levels. Higher body mass index (BMI) may substantially contribute to the elevation of peripheral inflammatory markers [16, 44]. Several studies in MDD subtypes did not consider differences in BMI between groups [40–43, 48]. However, even the works which corrected for BMI did not reach fundamentally different results and sometimes even reported clearer associations between increased CRP in AF-MDD and elevation of IL-6 in MF-MDD [44, 45, 47, 49, 51, 52]. Of the studies assigned to core features of depression, BMI was considered in all of them except one [59]. Three studies' results became insignificant after BMI adjustment [53, 65, 67]. In the remaining study, the association of higher CRP and cytokines with increased appetite became weaker, while the effect of adipokines remained the same. These relations suggest a potential tridirectional relationship between adiposity, inflammation, and depression [44].

Finally, some of the works proved associations of selected biomarkers with core depression features only indirectly. For example, Felger et al. [16] found a connection between plasma inflammatory markers and anhedonia and reduced motivation through cerebrospinal fluid inflammatory markers, and Prossin et al. [54] observed IL-18 associated with sadness-induced emotional responses through sadness-induced opioid system activation in the subgenual anterior cingulate, ventral basal ganglia, and amygdala.

Conclusions

Because of the limited number of eligible studies and inconsistent results, the examined peripheral inflammation markers have currently limited value for distinguishing specific immunological subtypes. The role of immune changes appears to be more general. There is, however, the notable exception of associations between specific immunological markers and various somatic symptoms of depression. These findings could suggest that depression with marked somatic symptoms could be a phenotypic manifestation of specific endophenotypes of a depressive disorder in which immunological and inflammatory processes play a significant role. This is consistent with repeated findings of immunological alterations in melancholic and atypical depression, which are partly defined by specific somatic symptoms. Further lines of research on the neurobiology of MDD should include longitudinal studies examining concurrent MDD subtypes, a wider range of core depression features, and a large number of depressive symptoms using a broader panel of inflammatory markers and taking into account multiple variables.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Author Contributions

Conceptualization, methodology, and data curation: all authors. Investigation: Pavel Křenek. Writing – original draft: Pavel Křenek. Writing – review & editing: Jana Hořínková, Elis Bartečků.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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