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A clinical model for identifying an inflammatory phenotype in mood disorders

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ABSTRACT

Increasingly, clinical research has found inflammatory correlates of psychiatric disorders, particularly mood symptomatology. Biological measures may provide greater precision in many cases and may capture clinically-relevant inflammatory signposts, such as central obesity risk, inflammation-associated co-morbid medical conditions, or proinflammatory lifestyle choices. In order to expand understanding of the role of inflammation in mood disorders, we propose a more inclusive clinical model for capturing an inflammatory phenotype of depression by identifying clinically-relevant inflammatory phenotypes grounded in biology. Our model includes chronic conditions and lifestyle behaviors associated with clinically elevated inflammation in mood disorders. Elements of this "inflamed depression" model include: obesity, low HDL concentrations, elevated triglyceride concentrations, chronically elevated blood pressure, clinical diagnosis of hypothyroidism, migraines, rheumatoid arthritis, adult onset diabetes, inflammatory bowel diseases, inflammatory skin conditions, and lifestyle factors including smoking cigarettes and chronic stress.

1. Introduction

Depression is the leading cause of disability worldwide, affecting more than 300 million people globally (World Health Organization, 2018). Over the past two decades, several studies have established a bidirectional relationship between chronic medical illness and depression (Katon, 2011). The WHO World Health Survey found a greater prevalence of depression in people who had at least one chronic physical condition (9.3–23%) compared to those with none (3.2%) (Moussavi et al., 2007), with each additional chronic medical condition increasing the odds of having a depressive disorder by 45% than those with no chronic physical conditions in one meta-analysis (Read et al., 2017). Inversely, epidemiological (Chang et al., 2010; Walker et al., 2015; Whiteford et al., 2013) and longitudinal studies (Thomson, 2011) have found that those with mood disorders develop chronic illnesses at higher rates and die significantly earlier than those without affective illnesses.

1.1. Defining inflammation

Inflammation has been increasingly examined as a key factor underlying the complex relationship between depression and chronic medical illnesses (Gregory et al., 2018; Rosenblat et al., 2014; Sayuri-Yamagata et al., 2017). In its most basic sense, inflammation is the body's complex, coordinated, and innate physiological response of the body to injury or infection, as well as a fundamental part of normal tissue repair and the body's defense against infection (Feghali and Wright, 1997). In response to a threat, such as a pathogen, the body elicits a rapid, local cellular response (e.g., releasing histamine, leukotrienes, prostaglandins, and chemokines) that lead to the eventual release of inflammatory factors, particularly cytokines, which include interleukins (IL-1a, IL-1b, IL- 2–35), interferons (IFNa, b, g, and v), and tumour necrosis factor (e.g., TNFa). Many of these cytokines are pro-inflammatory (e.g., IL-1a/b, IL-6), although some serve anti-inflammatory (e.g., IL-10, transforming growth factor-b [TGFb]) and anti-apoptotic (e.g., IL- 9) roles (Shelton and Miller, 2010). Depending on the magnitude and/or extent of the inflammatory response, cytokines can enter the peripheral circulation and travel to the liver, inducing up-

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and down-regulation of a large number of acute phase reactants, such as C-reactive protein (CRP) that both activate and suppress the inflammatory response.

However, the body also has an adaptive immune response that serves to create and maintain the immune system's memory through the release of cytokines (primarily IL-2). Over time, instead of fulfilling its acute function of repair and defense, the immune system's response leads to gradual tissue degeneration (McEwan, 1993; Nasef et al., 2017), as well as development of immune-mediated inflammatory diseases (Walker et al., 2011), such as cardiovascular illnesses, metabolic disorders and autoimmune disorders (Caneo et al., 2016).

Dysfunction of the innate immune system leading to neuroinflammation has been increasingly implicated in the pathophysiology of numerous psychiatric disorders (Friedrich, 2014). Extant research indicates that disturbances in peripheral or central pro-inflammatory markers, as well as alterations in inflammasome—the model of the inflammatory genetic architecture—increase risk for psychiatric disorders (McIntyre, 2016). Inflammatory processes have also been observed in mood and cognitive symptoms across psychiatric, neurological, and medical disorders (Swardfager et al., 2016). Chronic neuroinflammation, including maladaptive immune-related processes that occur in the central nervous system, exacerbate development of pathology associated with neurodegenerative diseases and the cognitive decline that often accompanies them (Wohleb and Godbout, 2013).

1.2. Inflammation in mood disorders

Increasingly, clinical psychiatric research has found inflammatory correlates of mood disorders, informing pathogenic models of mood disorders (Gururajan et al., 2016; Han and Yu, 2014; Miller et al., 2011; Rosenblat and McIntyre, 2016; Swardfager et al., 2016). Many of the same cytokines and chemical factors produced during these inflammatory processes have been implicated as etiological factors in mood disorder symtamatology (For a review, see Rosenblat et al., 2014), including the development of both major (Krishnadas and Harrison, 2016) and bipolar depression (Rosenblat and McIntyre, 2016). In mood disorders, it is well established that pro- and anti-inflammatory cytokines (i.e., interleukin (IL)-1β, IL-6, and TNF-α) govern processes at the cellular level that regulate the inflammatory response to perceived or actual stress via lymphocyte, macrophage, and neutrophil activation and deactivation (Dantzer et al., 2011). Stress hormone cortisol peaks when stress activates the hypothalamic-pituitary-adrenal (HPA) axis, which regulates the induction of pro-inflammatory response genes and subsequent production of cytokines (Dantzer et al., 2008). High levels of cortisol temporarily block the pro-inflammatory response (Sapolsky et al., 1987), but in the cases of chronic stress and depression, immune cells may become less responsive to this blunting effect, yielding high levels of both cortisol and pro-inflammatory cytokines (Miller et al., 2002). The resulting excessive inflammation may change the structure of the brain, and in turn, its functioning, in ways that increase susceptibility for mood disorders and symptomatology (Wagner-Smith and Markou, 2011). Furthermore, there is increasing evidence that association between inflammation and mood disorders appears to be bidirectional: inflammation may induce mood symptoms and vice versa, creating a potential positive feedback loop (Rosenblat et al., 2014).

1.3. Targeting inflammation to target depressive symtomatology

Despite advances in the treatment of mood disorders, evidence increasingly suggests that pharmacological treatments targeting mood disorders are not effective for many patients or may be poorly tolerated due to adverse effects (Geddes and Miklowitz, 2013; Linde et al., 2015; Rosenblat et al., 2019; Vázquez et al., 2015). As the body of research linking inflammation and mood disorders has grown, anti-inflammatory agents have been increasingly investigated as novel treatments for mood disorders. Findings of three meta-analyses have suggested that anti-inflammatory treatments decreased depressive symptoms without increased risks of adverse effects (Husain et al., 2017; Köhler et al., 2014; Rosenblat et al., 2016).

1.4. Methodological challenges to interventional research

Extant research highlights well-established indicators of mechanisms of disease development and maintenance used to identify chronic inflammation in clinical research populations when examining psychological symptom changes as outcome measures. However, there remains a need for a model in clinical psychiatric research that captures this inflamed depression phenotype as researchers continue to explore inflammation mechanisms and targeted interventions aimed at reducing mood symptoms by disrupting these inflammatory contributors, whether through pharmacological or behavioral interventions. However, current approaches to measuring inflammation may be unnecessarily limiting progress.

Notably, C-reactive protein (CRP) peripheral blood concentration is commonly used in clinical and research settings as a biomarker of systemic inflammation, with higher levels indicating a chronic inflammatory state (Avramopoulos et al., 2015). An acute-phase protein produced by the liver in response to inflammation and infection (Macy et al., 1997), CRP provides the body with a first-line defense against pathogens (Ansar and Ghosh, 2013). In healthy individuals, CRP is reported in terms of trace plasma protein, with levels above 10 mg/L representing clinically significant elevations in chronic inflammation (Clyne and Olshaker, 1999).

Despite its widespread use, one challenge to using CRP alone to explore mechanisms and interventions targeting mood disorder symptoms by way of inflammation is that CPR levels may not fully capture the full spectrum of individuals with chronically elevated inflammation in psychiatric research when it is used as the sole gauge of inflammation due to high intra-individual biological variation, even among medically healthy individuals (Bogaty et al., 2013; Hansen et al., 2017). In a study of patients with cardiovascular disease, DeGoma et al. (2012) found one in eight high-risk participants were deemed at average relative inflammation risk based on a single CRP measurement. Furthermore, CRP is vulnerable to environmental and lifestyle factors (Shen and Ordovas, 2009) that may undermine its stability as a measure of chronic inflammation. Dietary factors, such as high intake of refined carbohydrates like sugar, have been found to acutely elevate CRP for a matter of hours due to a temporary increase of postprandial hyperglycemia that may lead to increased circulating levels of pro-inflammatory cytokines that elevate CRP levels (Esposito et al., 2002), leaving investigations vulnerable to false positives at the hands of a starch-laden breakfast.

1.5. Identifying an inflammatory phenotype in patients with mood disorders

There is a need for a succinct model of pro-inflammation in mood disorders for both clinical and research purposes. In addition to traditional peripheral measurements, there is an opportunity to leverage deep, interdisciplinary research findings to inform an inflammatory phenotype in clinical research that can be used to cast a wider net in identifying patients for whom inflammation may be contributing to severity and persistence of mood disorder symptoms (Raison et al., 2013).

We provide an organizational framework by identifying a clinically-relevant inflammatory phenotype grounded in biology. Model criterion inclusion was based on two standards:

1. Strong, repeated associations observed across varied methodologies, scientific disciplines, and populations.
2. Chronic conditions and lifestyle behaviors likely to produce clinically elevated, stable inflammation over the course of an interventional study.

In the proposed model (see Fig. 1), a primary objective is inclusion of a multiple inflammatory characteristics that may have been previously underrepresented in psychiatric research. Our inflammatory phenotype model proposes using both BMI and waist circumference as a conservative, inclusive measure of obesity. It further pairs BMI with factors initially described in Reaven's (1988) description of metabolic syndrome, characterized by obesity, low HDL concentrations, and elevated triglyceride concentration (Dandona et al., 2005). Furthermore, it expands inflammatory definitions to capture the chronic, diagnosed inflammatory medical conditions anchored in persistent inflammation that have also been established to be associated with mood symtomatology, including hypothyroidism, migraines, rheumatoid arthritis, adult onset diabetes, inflammatory bowel diseases, and inflammatory skin conditions. Finally, it relies lifestyle factors including smoking cigarettes and chronic stress that accumulates and triggers inflammatory processes that become stable over time.

2. Central obesity risk index

Obesity is a convincing clinical proxy for elevated inflammation, increasingly conceptualized as an inflammatory condition (Dandona et al., 2005; Das, 2001). Hotamisligil et al. (1996) first proposed this association, in which TNF- α was shown to be constitutively expressed by adipose tissue, hyperexpressed in obesity, and a mediator of insulin resistance in major animal models of obesity (Dandona et al., 2005). Visceral adipose tissue is a metabolically active organ that secretes pro-inflammatory cytokines, leading to a state of chronic low-grade inflammation (Gregor and Hotamisligil, 2011; Lauridsen et al., 2017). As a result, individuals categorized as obese often have reliably higher concentrations of inflammatory biomarkers than their normal-weight counterparts (Ferrante, 2007; Kantor et al., 2013). Excess weight, particularly abdominal adipose tissue specifically secretes cytokines IL-6 and TNF-a, which have been associated with depressed mood (Shelton and Miller, 2010). Notably, in a study of depression symptoms in individuals with obesity, mediation analyses revealed that CRP levels explained 20% of the increase in depression scores (Daly, 2013).

2.1. BMI with waist circumference

Body Mass Index (BMI) is a clinical index of a person's weight in kilograms divided by the square of height in meters. It does not measure body fat directly but is moderately correlated with more direct measures of body fat, such as skinfold thickness measurements or bioelectrical impedance (U.S. Centers for Disease Control and Prevention, 2017). Elevated BMI has been found to be a significant contributor to inflammation in comorbid psychiatric disease, such as bipolar depression, even moreso than recent mood illness severity (Bond et al., 2016). Even a gradual increase in BMI may be associated with discrete signs of altered gene expression, including reduced mRNA expression of IL10, and anti-inflammatory cytokine, in the prefrontal cortex of neurologically and psychiatrically healthy human brains (Lauridsen et al., 2017). Both overweight and obese adults classified using BMI alone have been found to have elevated CRP serum levels (Das, 2001).

However, using BMI as a sole measure of obesity may fail to fully capture the full spectrum of inflammation in mood disorders. Specifically, BMI may not be generalizable across different ethnic groups as the amount of body fat-BMI ratio is variable across ethnic groups (Luke, 2009). For example, discrepancies between BMI and expected waist circumference have been especially large in both Mexican-American and non-Hispanic Whites (Albrecht et al., 2017). Walls et al. (2011) caution that this disproportionate increase in waist circumference suggest that the adverse health consequences associated with obesity may be increasingly underestimated by trends in BMI alone. Despite being the primary means to assess obesity since the mid-19th century, in 2013, the U.S. Centers for Disease Control and Prevention (CDC) reclassified BMI, noting it was not clinically appropriate for diagnosing adiposity or the health of an individual (Kaluski et al., 2007; Locke et al., 2015). Recent findings suggest that fat distribution may be more important than total body fat (Bozeman et al., 2012; Koster et al., 2008; Lackner et al., 2014; Walls et al., 2011; World Health Organization, 2008), with abdominal fat positively associated with metabolic disease risk independent of overall adiposity (Janssen et al., 2004). Waist circumference is strongly related to visceral fat depot and is therefore a measure of abdominal obesity (Bozeman et al., 2012; Janssen et al., 2002). Recommendations from the National Heart, Lung, and Blood Institute (NHLBI, 2013) advise complementary use of waist circumference as a better indicator of co-occurring inflammation-related illnesses (Nainggolan, 2013). Furthermore, the World Health Organization (2008) delineates ethnically-defined waist standards, with generally obesity cutoff levels of 40 + inches for men and 35 + inches for women with lower cutoff points for some ethnic groups (i.e., Asians).

2.2. Blood pressure

Elevated blood pressure, or hypertension, has also been associated with inflammation (Nosalski et al., 2017; Dinh et al., 2014; Rabinovitch et al., 2014), and multiple inflammatory mechanisms have been shown to be amplified in hypertension (Caillon and Schriffrin, 2016). Several studies have suggested that as CRP levels increase, the presence or risk of hypertension also increases (Bautista, 2003; Sung et al., 2003). It is unclear whether inflammation precedes and contributes to hypertension, or whether inflammation is the result of chronically elevated blood pressure (Ghanem and Movahed, 2007). However, inflammation has often been associated with chronic hypertension (Sesso et al., 2003; Niskanen et al., 2004). In turn, hypertension is strongly linked to mood disorders, with the co-occurrence of hypertension and depression suggesting a less favorable medical prognosis (Scalco et al., 2006). A meta-analysis of 41 studies found a high (28.8%) prevalence of depression among hypertensive patients (Chen et al., 2015), more than three times the prevalence of depression (6.7%) in the general population (NIMH, 2018).

2.3. Lipid profile

A lipid profile is a common clinical screening tool for abnormalities in lipids, such as cholesterol and triglycerides, and elevated results may also serve as a clinical proxy for inflammation. Aberrant lipid levels are associated with various inflammatory disorders, such as diabetes, and have been associated more directly with increased inflammatory response, with the strongest available evidence supporting elevated triglyceride concentrations and elevated low-density lipoprotein (LDL) cholesterol (Connelly et al., 2016).

Excess circulating cholesterol and low-density lipoprotein (LDL) promote a low-grade pro-inflammatory state that can lead to further activation of the pro-inflammatory response (Haas and Mooradian, 2011). Cytokines IL-1beta, IL-6, IL-8, and TNF-alpha expression have been found to be significantly associated with elevated HDL cholesterol (50.4 ± 11.0 mg/dl)(Menzaghi et al., 2017). Furthermore, metabolic syndrome, which is characterized by a low HDL in association with an elevated triglyceride concentration, has been associated with elevated C-reactive protein levels (Dandona et al., 2005). Atherosclerosis, once regarded simply as excessive accumulation of lipids in the artery wall, is now considered to be a chronic inflammatory disorder characterized by the presence of macrophages and other inflammatory cells in the arterial intima (Hansson, 2005; Tabet and Rye, 2009). Notably, a reverse dose effect has been observed between plasma concentrations of HDL cholesterol and depressive symptomatology (Almeida et al., 2014).

3. Inflammation-associated Co-occurring medical conditions

Chronic inflammation has been linked to a broad range of chronic

diseases, both through direct and indirect mechanisms (Nasef et al., 2017). Chronic disease may be triggered by either a primary defect in the regulation of an inflammatory pathway or a pathologic autoimmune cascade (Tabas and Glass, 2013). Furthermore, the inflammatory response itself may amplify the production of disease-specific damage-associated molecular patterns that accelerate the underlying disease process (Kanters et al., 2003).

Chronic, inflammatory diseases not directly induced by an autoimmune process are the most common diseases of aging and represents some of our greatest health threats, such as most forms of cardiovascular disease, type 2 diabetes, and nearly all neurodegenerative diseases (Tabas and Glass, 2013). However, autoimmune disorders, in particular, provide an excellent model of a stable, heightened inflammatory state (Rosenblat et al., 2014). Symptoms present when the immune system that falsely recognizes certain cells or tissues as foreign, triggering both local and systemic inflammatory response that results in illness symptoms (Abbas et al., 2012). Because of this, the role of inflammation in autoimmune disorders can inform a clinical inflammasome model.

3.1. Thyroid disorders

Thyroid diseases have been closely associated with inflammation (Bozec et al., 2010). In fact, Provatopoulou et al. (2014) found altered expression levels of pro-inflammatory serum interleukin cytokines (namely IL-6, IL-7, IL- 8, IL-10, and IL-13) were associated with both malignant and non-cancerous thyroid diseases, with IL-13 and IL- 8 serving as highly efficient predictors of thyroid disorders generally. Kobawala et al. (2011) found both serum IL-8 levels and TNF-α cytokines were significantly higher in patients with both thyroid cancer, goiter, and autoimmune thyroid diseases, even suggesting serum levels of these proinflammatory cytokines could be used to clinically detect thyroid disease.

Chronic hypothyroidism, in which the thyroid gland under-functions, is especially compelling as a clinical sign of chronic inflammation. Clinical hypothyroidism is characterized by a serum TSH level—the single-best screening test for primary thyroid dysfunction—above the upper reference limit (Garber et al., 2012). An elevated TSH, usually above 10mIU/L characterizes subclinical hypothyroidism; in combination with a subnormal free thyroxine (T4) hormone serum level characterizes overt hypothyroidism (Garber et al., 2012). Mechanistically, Gavin et al. (2008) hypothesize that chronic TSH elevation stimulates lymphocytes to produce pro-inflammatory cytokines. Interestingly, Marchiori et al. (2015) found a significant, positive correlation between TSH level and serum interleukin levels, but no changes in CRP related to TSH, providing further evidence that using CRP alone as a clinical indicator of inflammation may limit understanding of inflammation by excluding other inflammatory presentations. In the most common cause of primary hypothyroidism, chronic autoimmune thyroiditis (also known as Hashimoto's thyroiditis) (Gavin et al., 2008), TNF-α is excessively secreted by intra-thyroidal lymphocytes (Aust et al., 1996), contributing to its characteristic inflammatory immune system reaction against thyroid antigens in which thyroid epithelial cells are progressively depleted and replaced by fibrosis (Bozec et al., 2010).

Depressive symptoms often co-occur in hypothyroid disorders. In fact, they are often used as a clinical indicator of elevated TSH by patients in their management of the disorder.

Taken together, these findings suggest that chronic hypothyroidism has been significantly associated with elevated inflammatory proteins and may serve as a clinical indicator of elevated inflammation in mood disorders.

3.2. Migraines

Although there are many subtypes (Franceschini et al., 2013), migraine is a complex neurological disorder characterized by headaches, and inflammation in the broad trigeminal nerve (Friedman, 2004). The etiology of migraine pain remains poorly understood because the exact cause of headache onset, and its predisposing factors, remains etiologically unclear (Franceschini et al., 2013). However, it is presumed that migraine arises within the brain as a consequence of simulation of nerve terminals of trigeminal ganglion neurons (Farinelli et al., 2008). Notably, anti-inflammatory agents, such as NSAIDs, have been commonly used to treat migraine pain, although it is unclear whether mechanistically it is relieving associated pain alone.

Similar to thyroid disorders, there is strong evidence that pro-inflammatory cytokines implicated in mood disorders symtomatology, (i.e., TNF-α and IL-6) are released in the trigeminal neurovascular system, mediators implicated in pathogenesis of migraine attacks (Borkum, 2015; Farinelli et al., 2008; Sobaniec et al., 2009; Yilmaz et al., 2010; Yu and Aksakal, 2006). Inflammation and oxidative and nitrosative stress seem to play a role as mediators in the cross-sensitization between bipolar disorder and migraine (da Costa et al., 2016), suggesting their role as a clinical indicator of inflammatory depression. Furthermore, migraines are often co-morbid with mood disorders, particularly bipolar disorders in which they have been associated with increases in number of depressive episodes, depression severity, suicidality, rapid cycling, and morbidity (da Costa et al., 2016).

3.3. Rheumatological disorders

Rheumatoid arthritis (RA) is an autoimmune disease in which the body's immune system mistakenly attacks synovial joints (Di Paola and Cuzzocrea, 2008), causing pain, redness, stiffness, and swelling due to inflammation around the joint and associated damage over time (Mobasheri et al., 2011). RA is driven by pathogenic inflammation (Ansar and Ghosh, 2013; Chandrashekara and Sachin, 2012). Cytokines are directly implicated in many of the immune processes that are associated with the patho-genesis of rheumatoid arthritis. Numerous cytokines are expressed and are functionally active in synovial tissues. Accordingly, cytokine modulation alters the outcome in many rodent models of arthritis. Importantly, tumour-necrosis factor (TNF) is now targeted in the standard treatment of patients with rheumatoid arthritis. RA serves as a useful clinical proxy for inflammation since the disease itself is self-perpetuated by chronic inflammatory processes.

Individuals with RA have been found to be at a greater risk of mood symptomatology. A meta-analysis of 72 studies found an increased prevalence of depression among those with RA (Matcham et al., 2013). Furthermore, a longitudinal cohort study recently found a bidirectional relationship between RA and depression: not only were those with RA more likely to develop depressive symptomatology, but even after adjusting for confounding variables, those with depressive disorders were found to have a greater incidence of RA compared with those without depression (2.07 vs. 1.21 per 1000 persons) (Lu et al., 2016).

3.4. Type II diabetes mellitus

In Type 2 diabetes mellitus (T2DM), which typically onsets in mid-adulthood, activated innate immunity and an acute-phase inflammatory are pathogenically implicated in disease development and maintenance (Crook, 2004). Mechanistically, raised concentrations of proinflammatory cytokines lead to pancreatic β-cell apoptosis and insulin resistance, and predict onset of type 2 diabetes in initially non-diabetic patients. The relationship between diabetes and inflammation may also be mediated by obesity, with the pro-inflammatory state of adipose tissue setting the conditions for the systemic disruption of insulin sensitivity and glucose homeostasis that is characteristic of type 2 diabetes (Stuart and Baune, 2012).

Depression has been found to be almost twice as common in people with T2DM as in the general population (Anderson et al., 2001). Evidence is growing that depression and type 2 diabetes share biological

origins, particularly overactivation of innate immunity leading to a cytokine-mediated inflammatory response, and potentially through dysregulation of the hypothalamic-pituitary-adrenal axis (Moulton et al., 2015). The relationship between type 2 diabetes and depression observed across longitudinal studies has been bidirectional, with both biological and lifestyle factors contributing etiologically (Moulton et al., 2015).

3.5. Inflammatory gastro-intestinal disorders

Inflammatory bowel disease (IBD), which encompasses both ulcerative colitis (UC) and Crohn's disease (CD), is an auto-immune disorder characterized by the chronic relapsing inflammation of the small and large intestines (Kim and Cheon, 2017). Pathogenically, a complex interplay between environmental, multigenic, and microbiologic etiological factors contribute to the IBD (Danese and Fiocchi, 2011). Mucosal inflammation, the hallmark feature of IBD, is characterized by an imbalance between pro-inflammatory and anti-inflammatory cytokines (Neurath, 2014), leading to the perpetuation of inflammation and tissue damage. Pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α, are universally increased in individuals with IBD. (Danese and Fiocchi, 2011). Click et al. (2015) found that 20% of individuals with asymptomatic CD had elevated CRP levels. Furthermore, asymptomatic patients with elevated CRP were found to be twice as likely as asymptomatic patients without elevated CRP to require disease-related hospitalization within two years (Click et al., 2015). Sands (2015) observed similar rate of individuals with UC or CD who did not have elevated inflammation, however, this may reflect limitations of CRP as a stable measure of inflammation given that anti-TNF therapies, including infliximab, currently represent the first-line treatment for IBD.

The etiology of subthreshold IBD, dubbed Irritable Bowel Syndrome (IBS), is similarly multifactorial, involving physical stressors like infection, as well as genetic, immunological, and psychosocial components (Spiller et al., 2007; Camilleri et al., 2012). CRP levels have been found to be higher in individuals with IBS (Hod et al., 2011). However, low grade inflammation contribute to and perpetuates IBS (Hod et al., 2011; Ford and Talley, 2011), and anti-inflammatory treatments often yield reductions in IBS symptom severity (Ohman and Simren, 2010).

Mood disorders have been shown to occur more frequently in individuals with IBS than similar groups of general medical patients (Marrie et al., 2017). Inversely, IBD has been found to be strongly associated with depressive episodes, especially during flare-ups (Graff et al., 2009; Mikocka-Walus et al., 2015; Walker et al., 2011). Although there is some evidence of a bidirectional relationship, data supporting IBS as a risk factor for depression have been found to be more robust than data supporting depression as a risk factor for IBD (Gregory et al., 2018). Notably, however, antidepressants have been found to have a beneficial effect on the course of the IBD, suggesting similar mechanisms may be at work (Macer et al., 2017).

3.6. Inflammatory skin disorders

Psoriasis is a chronic, systemic inflammatory disease affecting the skin that is charactrised by plaques on the skin (Davidovici et al., 2010; Weigle and Mcbane, 2013). It has been strongly associated with elevated levels of CRP and other inflammatory cytokines (Siegel et al., 2013). In a recent meta-analysis of 78 studies and more than 7800 individuals with moderate to severe psoriasis symptoms, psoriasis was associated with significantly elevated serum levels of pro-inflammatory cytokines and a moderate pooled effect size, indicating that a history of severe psoriasis may be a useful clinical marker of an inflammatory phenotype (Dowlatshahi et al., 2013). Clinically, individuals who suffer from psoriasis often have an increased risk of developing other co-occurring inflammatory diseases, including cardiovascular disease, diabetes, Crohn's disease, depression, and obesity (Boehncke, 2015; Davidovici et al., 2010; Di Meglio et al., 2014; Siegel et al., 2013; Hamminga et al., 2006; Harrington et al., 2017; Reich, 2012; Staniak et al., 2014).

Similarly, eczema, also referred to as atopic dermatitis (AD), is well established as a chronic, inflammatory condition (Eichenfield et al., 2014), affecting multiple organs and systems (Darlenski et al., 2014) and associated with genetic and immunological pathogenesis (Bieber and Novak, 2009; Guttman-Yassky et al., 2011; Peng and Novak, 2014). It often co-occurs with other chronic inflammatory conditions (Leung et al., 2004; Zheng et al., 2011). In a large study of more than 1900 adults, atopic eczema was associated with low grade inflammation, even after adjustment for confounding factors, such as BMI and systemic diseases (Sinikumpu et al., 2018). Furthermore, in a large cohort study, individuals who had a childhood onset of eczema (before age ten) were significantly more likely to have elevated IL-6 and have a mood episode in adulthood.

Individuals with inflammatory skin conditions, such as psoriasis, have been found to be at an increased risk of mood disorders. In a large cohort study, those with psoriasis were found to have an increased risk of depression, particularly suicidality (Kurd et al., 2010). However, there is also evidence the relationship may be bidirectional. In a cohort study of more than 50,000 nurses, depression was independently associated with increased risk of psoriasis (Dommasch et al., 2015).

4. Lifestyle factors

Both physical and mental disorders cause distress and disrupt daily life functioning, which can undermine general health habits (Jaarsma et al., 2017; Michopoulos et al., 2016). Several lifestyle factors have been found to activate inflammatory pathways associated with chronic inflammatory response, including tobacco use and chronic high levels of stress (Aggarwal et al., 2012; Michopoulos et al., 2016).

4.1. Tobacco use

Active tobacco use appears to be a reliable behavioral indicator of inflammation and a stable proxy for estimating elevated inflammation in clinical populations, with cigarette smoking being the most common usage (Yanbaeva et al., 2007). Cigarette smoking has been well-established as a mechanism by which inflammation is increased (Aldaham et al., 2015; Gonçalves et al., 2011; Rom et al., 2013; Yanbaeva et al., 2007). Furthermore, smoking is a major risk factor for an array of medical diseases, contributing to an estimated 40% of all cancer deaths in the United States (Lortet-Tieulent et al., 2016; Rom et al., 2013). Many of the adverse consequences of chronic smoking may be explained by its effects on the immuno-inflammatory system (Gonçalves et al., 2011). Bazzano, He, Muntner, Vupputuri and Whelton (2003) found a strong independent dose-response relationship between cigarette smoking and clinically significant CRP serum levels and presence of fibrinogen, a key regulator of inflammation in chronic disease (Davalos and Akassoglou, 2012).

Cigarette smoking is an intriguing behavioral indicator of inflammation in clinical research because inflammatory response in smokers is characterized not only by an increase in the number of circulating pro-inflammatory cells, but also by more stable, phenotypic changes (Yanbaeva et al., 2007), such as an increase in numbers of circulating band cells, a hallmark of early bone marrow release of polymorphonuclear neutrophil (PMN) counts, and an increase in L-selectin expression, a cell adhesion molecule, constitutively highly expressed on maturating PMNs (van Eeden and Hog, 2000). Furthermore, since tobacco smoking is a potent and prevalent addictive habit (Yanbaeva et al., 2007), it is likely to be a sustained behavior perpetuating stable levels among users. Although most of smoking-induced changes are reversible after quitting, some inflammatory mediators like CRP continue to be consistently raised in ex-smokers for as long as 10–20 years after quitting, suggesting an ongoing low-grade inflammatory response persisting in former smokers (Yanbaeva et al.,

2007). CRP is substantially higher in smokers than in either former- or non-smokers. In a randomized trial, Aldaham et al. (2015) found that IL-6 levels were significantly associated with smoking, especially among current smokers. These findings both provide evidence of the association between active smoking and inflammation and affirm the need for more robust clinical indicators of inflammation.

4.2. Chronic psychosocial stress

Although not traditionally targeted as a health behavior, chronic psychosocial stress is a behavioral factor that may clinically predict chronic inflammation. It is generally accepted that different types and sources of psychological stress may cause identical inflammatory reactions in the body (Tian et al., 2014). Psychosocial stressors such as marital strain (Kiecolt-Glaser et al., 2010), financial stress (Sturgeon et al., 2016), and interpersonal stress (Miller et al., 2009), have been associated with higher levels of systemic inflammation. Psychological stress has been robustly associated with an acute inflammatory response (i.e., elevations in IL-6, IL-1β,TNF-α, and CRP) (Steptoe et al., 2007).

Chronic stress associated with physical and mental disease and disorders has also been hypothesized to contribute to associated inflammation. Using hair cortisol levels as a biobehavioral marker of chronic stress, Groer et al. (2015) reported evidence that chronic stress associated with depression, PTSD, and war zone experiences may be related to inflammation in active duty soldiers. Experiencing chronic stressors can influence inflammatory responses by impacting the release of cytokines that, in excess, have been implicated in the development of mood disorders (Kemeny & Schedlowski, 2007).

Tian et al. (2014) note that sustained stress leads to a cascade of changes in pro-inflammatory cytokines across the body and brain, in three distinct biological stages. Initially, chronic stress activates the hypothalamic-pituitary-adrenal (HPA) and sympathetic nervous system (SNS) systems, leading to upregulation of l glucocorticoids and catecholamines, inhibiting the secretion of pro-inflammatory cytokines, and promoting the secretion of anti-inflammatory cytokines. Over time, sustained stress may lead to HPA axis “fatigue” in which glucocorticoid receptors down-regulate, reducing the immune system's sensitivity to the stress hormone cortisol, with inflammatory cytokines mediating a negative feedback regulation on themselves: increasing pro-inflammatory cytokines and decreasing anti-inflammatory cytokines (Rohleder, 2012). In the third stage, continued stress further increases pro-inflammatory cytokines and ultimately results in inflammation, which may induce various diseases. These findings suggest that chronic stress, measured in a systematic way, such as a life stress inventory, may capture an inflammatory phenotype in a population also found to have higher rates of psychopathology.

5. Clinical implications

In recent years, inflammation has been examined as an important etiological factor in mood disorders (McNamara and Lotrich, 2012). Meta-analyses have repeatedly shown elevations in pro-inflammatory cytokines in depressed individuals when compared to non-depressed groups (Dowlati et al., 2010; Hiles et al., 2012). Given widespread interest in inflammation, there has been a rapid proliferation of research exploring mechanisms that account for the relationship between chronic inflammation and mood symptomatology and, subsequently, novel therapeutic interventions that target mood symptoms by disrupting inflammatory processes (McNamara and Lotrich, 2012; Rosenblat et al., 2014). Since many patients with depression are not currently benefiting from psychopharmacological treatment regimens (McIntyre et al., 2015), our model attempts to stretch clinical thinking about inflamed depression in both novel treatment studies and clinical practice, particularly in cases of treatment resistant depression.

Similar to many comorbid medical conditions associated with inflammatory processes, such as autoimmune disorders, mood disorders are increasingly conceptualized as systemic diseases (Sotelo and Nemeroff, 2017), in which mood symptomatology both contributes to and is exacerbated by chronic inflammation (Rosenblat et al., 2014). What has been less evident until aggregated has been the mounting evidence of a bidirectional relationship between inflammatory medical illness and mood symptomatology. Yet, across studies cited in the proposed model, a bidirectional relationship has been observed, suggesting that the biological processes underlying diagnosed inflammatory medical conditions can not only also contribute to mood symptomatology, but may also develop secondary to a mood disorder.

One challenge to advances within this field has been the wide variability used to define clinically useful levels and indicators of inflammation. There is clinical need to systematize the definition of inflammation to aid collaboration across research and allow for comment on the relationships between various components of inflammation and their role in psychopathology. Although CRP is a widely used clinical measure of inflammation, high intra-individual biological differences observed in CRP level (Bogaty et al., 2013; Hansen et al., 2017), as well as frequent empirical findings of individuals who present clinically with pro-inflammatory conditions without clinically elevated biological measures (e.g., normal-range CRP serum levels), suggest that defining inflammation solely in terms of CRP may not be capture the full spectrum of individuals with chronically elevated inflammation in psychiatric research. Furthermore, CRP is vulnerable to even temporary environmental, dietary, and lifestyle influences that may undermine its stability, limiting the stability necessary to observe patterns over time that are clinically vital to insights necessary to draw mechanistic conclusions and tailor interventions.

Furthermore, lessons learned from inflammatory research in other medical disciplines suggest that not all inflammation is created equally. Similar pro-inflammatory mechanisms may be at play across different medical and lifestyle conditions, but clinical presentations and responses to treatment vary. Over the past two decades, mood disorders research has largely focused on exploring the establishing relationships between inflammation and mood symptomatology, as well as investigating how anti-inflammatory treatments might combat mood symptoms by intervening in these inflammatory processes. Further investigation in years to come will likely elucidate phenotypic differences between inflammatory states and their impacts on mood symptomology, allowing for greater precision in interventions.

Applying a clinically-informed inflammatory phenotype that has potential to incorporate a broad range of presentations may facilitate research that extends beyond a bidirectional relationship of inflammatory marker and mood disorders. Instead, probing specific psychiatric similarities and differences reflects a clinical shift across all fields of medicine that increasingly priorities personalized medicine (Wium-Andersen et al., 2017). Pragmatically, the proposed model offers researchers investigating a broad range of mood disorder interventions the opportunity to parsimoniously identify probable inflamed depression, without the cost or burden of biological analysis, by elucidating differences observed in clinical populations with established inflammatory medical diagnoses.

6. Conclusion

In order to expand understanding of inflammation in mood disorders, we have introduced a more inclusive clinical and research model for capturing an inflammatory phenotype in mood disorders. Inflammation is hypothesized to be a pathological mechanism contributing to treatment resistance in depression (Raison et al., 2013) and continues to be a promising horizon of mood symptom intervention (Rosenblat et al., 2016; Rosenblat and McIntyre, 2016). Although biological measures provide greater precision in many cases, alone they may not adequately capture clinically-relevant inflammatory signposts, such as central obesity risk, inflammation-associated co-morbid medical

conditions, or proinflammatory lifestyle choices. Taken together, these clinical factors enable tracking of mood relative to biological and psychological measures of inflammation.

Conflicts of interest

Ms. Kramer: None.
Dr. Cosgrove: None.
Dunlop
Ms. Subramaniapillai: None.
Dr. McIntyre: None.
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Contributors

*Ms. Kramer*was the primary literature reviewerand content author.

Dr. Cosgrove served as the primary content editor, inflammatory research scientific advisor, and as research mentor to Ms. Kramer and Ms. Dunlop.

Ms. Dunlop provided research and writing support.

Ms. Subramaniapillai provided research and editorial support.

Dr. McIntyre and *Dr. Suppes* guided development of the clinical model and provided editorial review and feedback.

All contributors have contributed to and approved the final article.

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Appendix

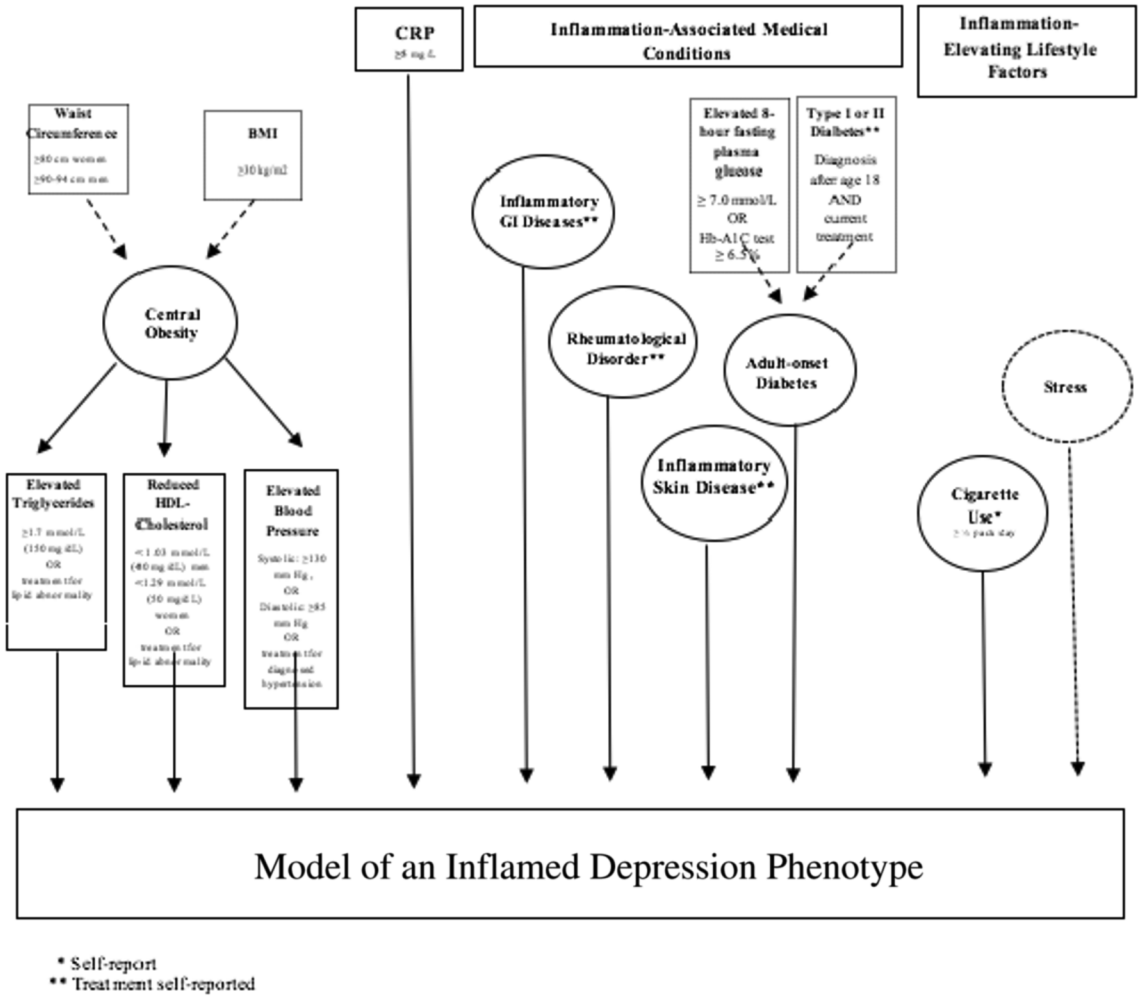

Fig. 1. Clinical model of an inflamed depression phenotype.

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