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Neuroinflammation and neuroprogression in depression: Effects of alternative drug treatments

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A B S T R A C T

Given that available antidepressant pharmacotherapies are not optimally effective, there is a need for alternative treatment options that are rooted in a comprehensive understanding of the illness's pathophysiology. Major depressive disorder (MDD) has been historically attributed to monoamine, i.e., serotonin (5-hydroxytryptamine, 5-HT) imbalance and some brain morphological pathologies that have directed treatment towards particular medications that are only minimally effective. MDD pathophysiologies have now been regarded as linked to chronic inflammation and MDD can be treated with compounds that have anti-inflammatory properties. Individuals vulnerable to MDD have increased baseline neuroinflammatory response that is exacerbated by psychogenic stress. When pro-inflammatory mechanisms are chronically hyperactive, dysfunction of brain-related processes occur. We propose that inflammation is one of the primary mechanisms that trigger biological changes leading to MDD. Inflammatory resolution occurs when homeostasis is achieved after an inflammatory response. However, cascading biological events are likely to prevent resolution from occurring and worsen both inflammation and MDD. Novel and alternative pharmacotherapies—e.g., ketamine, cannabinoids, and psychedelics—provide a richer mechanistic perspective on the role of neuroinflammation and neuroprogression by means of rapid, short-term, and long-term symptom relief potentially based on their anti-inflammatory properties. These drugs ultimately decrease proinflammatory cytokine levels that correspond with improved symptoms. However, it is unclear what differentiates these compounds from others in their mechanistic efficacy. Thus, a closer investigation into their anti-inflammatory effects is imperative in order to better elucidate the link between MDD and inflammation, as well as uncover the mechanisms involved in long-term symptom reduction of MDD.

1. Introduction

Major depression disorder (MDD) is a prevalent and debilitating mental illness that comes with cognitive and affective impairments and decreased quality of life (Tran et al., 2021). Its core diagnostic features are depressed mood and the blunting of reward sensitivity (anhedonia). Other symptoms include hopelessness, loss of motivation, issues with sleep, feelings of worthlessness, comorbid anxiety; and in its severe form, suicidality (Mayo Clinic, 2018). Almost 800,000 people die of suicide each year (World Health Organization, 2020). MDD is the world's leading cause of disability, and over 264 million people suffer from it (World Health Organization, 2020). While there are a number of treatments available, there are several barriers that stymie many people from receiving treatment, such as low income and living in rural areas (World Health Organization, 2020). Moreover, the efficacy and outcome of conventional medications are mixed, leading to a convoluted discussion on the best treatment options for sufferers (Howland, 2008).

The pathogenesis of MDD is complex. While many hypotheses circulate the scientific community, research lacks consistency in isolating biomarkers of MDD's origin. Therefore, our understanding of treatment mechanisms and the development of conventional medications may be inadequately premised on the role of a single factor and precludes the contribution of others. One of the factors that may have been downplayed is neuroinflammation. Indeed, fairly new research has made a strong link between MDD and enhanced inflammatory processes, and it has been suggested that treating inflammation can result in significant symptom relief (Menke, 2019; Bai et al., 2020). Historically, MDD has been loosely linked to monoamine imbalance and neural morphological abnormalities not well understood (Schildkraut, 1965; Miguel-Hidalgo and Rajkowska, 2002). However, disruption of

monoaminergic activity and irregular brain development have been observed to occur after chronic inflammatory responses (Miller and Raison, 2016). Thus, inflammation provides earlier mechanistic insights into the development of MDD.

This review presents a critical synthesis of findings obtained from the growing literature on several aspects of the role of neuroinflammation in the etiology of depressive disorders and how they have upended the trajectory of treatment development and refinement. The medical anthropology and history of mental health has overlooked much of the biological mechanisms and neural changes underlying depressive disorders. The neuroprogression of MDD, i.e., the progressive and protracted brain-based biochemical and neurodegenerative changes in MDD, is now apparent and gives a wider view of how the disorder affects cognitive, affective, behavioral and physiological functions. Second, there are newly understood links between important inflammatory cytokines and cognate proteins and the worsening of depressive symptoms that lends a new impetus to investigate the mechanisms of new alternative pharmacotherapies based on their inflammation-resolving properties. Third, conventional treatments may be supported and amended by these alternatives, and research in the field has opened new possible areas in the development of alternative options that have promising effects on both MDD and inflammation.

2. Linking inflammation with MDD

Throughout the past century, it has been noted that inflammation caused by injury and disease was often accompanied by depressive symptoms. For example, one condition characterized by profound neuroinflammatory changes is traumatic brain injury (TBI). A review of the literature shows that about 31% of those with TBI also exhibit MDD symptoms (Guillamondegui et al., 2011). Inflammation is also implicated in Alzheimer's disease, Parkinson's disease, and multiple sclerosis (Amor et al., 2010). High rates of depression are also seen in each of these conditions (Arnett et al., 2008; Lyketsos and Olin, 2002; Reijnders et al., 2008). Neurodegenerative and brain injury conditions come with changes in quality of life that must be considered when discussing depression. A portion of the explanatory power of depression in these conditions are likely due to decreased quality of life. However, these findings provoked a closer look at the mechanistic influence of inflammation on MDD and lead to studies that suggest a cause of MDD that could be rooted in inflammation (Miller et al., 2009). Some of the indications were that depressed people have increased peripheral levels of cytokines and decreased neurotrophic support (Miller et al., 2009). A key factor in this link was findings of how pro-inflammatory cytokines and cognate proteins behave in the body (Abbott, 2018). It was believed that cytokines were too large and hydrophilic and therefore could not cross the blood brain barrier (BBB), effectively leaving the brain unaffected by their confinement in the periphery. However, earlier animal studies have demonstrated that tumour necrosis factor alpha (TNF-α) did in fact cross the BBB (Gutierrez et al., 1993). Later, Avery et al. (2014) was able to link peripheral and central cytokine activity by demonstrating altered patterns of insula activation and vagus nerve activity as a function of cytokine levels in individuals with untreated MDD. The insula has since been recognized to play a significant role in affect and cognition (Flynn, 1999; Gasquoine, 2014). For example, anterior insular regions are believed to play a role in evaluating stress from cognition and interoception as negative emotional experiences (Reiman, 1997). In addition, other areas of the insula are responsible for self-generated emotional states and regulating homeostasis (Tataranni et al., 1999; Damasio et al., 2000). Importantly, activity of both the right-fronto-insular cortex and the default mode network (DMN) is associated with greater depressive rumination (Hamilton et al., 2011), and increased levels of the cytokine interleukin-6 (IL-6) are associated with decreased insular functional connectivity (Chen et al., 2020). Furthermore, post-stress rumination is associated with prolonged increased levels of cortisol and the hepatic inflammatory marker,

C-reactive protein (CRP) (Zoccola et al., 2014), and one's rumination response can predict inflammatory reaction (Moriarity et al., 2020). It may be that the activity between the insula and other connected structures plays a role in resilience towards stressful experiences (Shao et al., 2018).

The vagus nerve is a primary component of the brain-gut axis and is a bidirectional pathway of signalling between the enteric nervous system (ENS) and the central nervous system (CNS) in which the sympathetic and parasympathetic nervous systems are moderated to maintain homeostasis and immune response (Breit et al., 2018). Treatment of the vagus nerve via stimulation results in inhibition of cytokine production and is an effective method in treatment resistant MDD (Schlaepfer et al., 2008; Breit et al., 2018; O'Keane et al., 2005; Koopman et al., 2016). Given related functions of both the insula and vagus nerve and their communication across the autonomic system and in inflammatory response, it has been suggested that MDD is associated with heightened inflammation likely due to impaired interoception via internal signalling between central and peripheral nervous circuitry important for homeostasis (Avery et al., 2014).

There are several structures and systems within the nervous system that have overlapping functions in both inflammatory processing and affect regulation. Both the default mode network (DMN) and the hypothalamic pituitary adrenal axis (HPA) function as emotional and inflammatory regulators and are disrupted in MDD (Marsland et al., 2017; Menke, 2019; Cowen, 2010; Murrough et al., 2016). One way in which hyperactivity of the HPA affects a significant proportion of depressed individuals is through reduced sensitivity of the glucocorticoid receptors (GR), which fails to provide negative feedback to the HPA and results in sustained corticotropin-releasing factor secretion (Menke, 2019; Holsboer, 2000; Pariante and Miller, 2001). Moreover, dysfunction of the HPA axis results in increased levels of pro-inflammatory cytokines (Tapp et al., 2019). This axis has an important role in integrating emotional responses to stress that are dysfunctional in MDD, leading to increased cortisol and pro-inflammatory cytokines (Iob et al., 2020). Glucocorticoids are believed to be anti-inflammatory under most circumstances and are used as anti-inflammatory treatment (Cruz-Topete and Cidlowski, 2015). Thus, dysfunction of GR, or glucocorticoid receptor resistance (GCR), in MDD likely results in a runaway effect of inflammation. Moreover, GCR is associated with high levels of pro-inflammatory cytokine and can be caused by life stress (Cohen et al., 2012; Perrin et al., 2019). Overall, HPA axis dysfunction is seen in MDD and can be an indication of its prognosis (Varghese and Brown, 2001; Keller et al., 2017). Cytokine presence activates the HPA axis, and if already dysfunctional, results in increased inflammatory response (Dunn, 2006; Tapp et al., 2019).

The DMN is a neural circuitry that is known to be passively active when one is not engaged in externally directed activity (Buckner, 2013). Depressive rumination is correlated with DMN activity, particularly with the dorsal medial prefrontal cortex (dmPFC; Zhou et al., 2020; Hamilton et al., 2015). The medial prefrontal cortex (mPFC) is one of the main structural components of the DMN and is consistently shown to have a decreased volume in MDD, suggested to be caused by HPA axis dysfunction and increased inflammation (Belleau, Treadway, &1 Pizzagalli, 2019). Moreover, psychological stress can induce increased levels of inflammatory cytokines that impact the function and structure of the hippocampus, amygdala, and mPFC (Vecchiarelli et al., 2016; Belleau et al., 2019). Areas of the mPFC have been shown to integrate emotional processes and regulate the HPA axis in response to stress (Diorio et al., 1993; Figueiredo et al., 2003; Spencer et al., 2005; Radley et al., 2006). In MDD, and as a response to life stressors, impairments and global dysfunctions in connectivity occurs in the mPFC, ventral striatum, hippocampus, amygdala, and insular cortex, and is associated with increased C-reactive protein (CRP) levels (Murrough et al., 2016; Zeev-Wolf et al., 2019; Sripada et al., 2014; Yin et al., 2019). Moreover, depressed individuals show increased resting state activity of the DMN and greater activity increase in the DMN in response to negative stimuli

(Grimm et al., 2009; Sheline et al., 2009). Depressed individuals failed to regulate heightened DMN reactivity (Sheline et al., 2009).

System and structure dysfunction may lead to increased inflammatory response and has been measured as per cytokine levels. However, there are other biomarkers now used to indicate inflammatory response in MDD. It may be argued that as the body uses inflammation as an indication of insult or injury, it responds via stress and immune activity that could manifest as MDD (Singhal and Baune, 2017; Bierhaus et al., 2003; Raison et al., 2010). Microglial cells are responsible for a range of complex functions, but primarily respond by modulating the expression of pro- and anti-inflammatory cytokines (Singhal and Baune, 2017). Translocator protein's (TSPO) are proteins that sit on the outer membrane wall of mitochondria of microglia and astrocyte cells (Lee et al., 2016). Microglia and astrocytes respond to damage and inflammation and TSPO activity increases as a response (Lee et al., 2016; Setiawan et al., 2015). Microglia also induce the production of important neurotrophins such as brain-derived neurotrophic factor (BDNF; Singhal and Baune, 2017). The interaction between inflammation and BDNF has been shown to affect different aspects of neuronal integrity such as neurogenesis, long-term potentiation, and dendritic sprouting, and increased inflammatory responses may result in decreased BDNF and increased excitotoxicity (Miller and Raison, 2016). Ligands that bind to TSPO have been shown to supress production of cytokines (Lee et al., 2016). Moreover, serotonergic signaling is an important mechanism for TSPO to produce anxiolytic effects (Yao et al., 2020). A TSPO ligand (i. e., YL-IPA08) was showed to elevate 5-HT levels in the hippocampus of rats (Yao et al., 2020). Furthermore, another TSPO ligand (i.e., ZBD-2) was shown to produce antidepressant effects in mice (Li et al., 2018). Li et al. (2018) assessed TSPO binding via the [18F]FEPPA ligand and found elevated binding in MDD participants in the frontal and temporal cortex that was reduced in response to therapy treatment. Setiawan et al. (2015) used [18F]FEPPA and found a significant increase in TSPO volume of depressed participants in all brain regions examined: PFC, anterior cingulate cortex (ACC), insula, dorsal putamen, ventral striatum, thalamus, and hippocampus. TSPO volume was increased, on average, by 30% in the prefrontal cortex, ACC and insula (Setiawan et al., 2015). Moreover, greater TSPO volume in the ACC correlated with greater MDD severity (Setiawan et al., 2015). A later study found that total duration of untreated MDD was a significant independent predictor of TSPO volume in the prefrontal cortex, anterior cingulate cortex, and insula, while duration of antidepressant exposure was a negative predictor of TSPO volume in these regions (Setiawan et al., 2018). Moreover, years of untreated MDD was a significant predictor of TSPO volume across all sampled grey-matter regions (Setiawan et al., 2018). TSPO volume increased at a rate of 14–18% per decade of untreated illness and could be a biomarker for duration and/or diagnosis of MDD (Setiawan et al., 2018).

Sufferers of MDD are often more vulnerable to adverse effects of stressful life events, and this leads to neurological changes (Yang et al., 2015; Felsten, 2004). Entrapment in a negative mental state, e.g., rumination over negative personal events curtail the capacity to pragmatically address and actively resolve significant sources of life stressors (Morrison and O'Connor, 2010). Studies show a deficit in executive control over rumination in response to stressors, suggesting that those with MDD are less able to control their mental state post-stressor (Quinn and Joormann, 2015). Negative thinking/rumination is an early cognitive symptom of MDD, and is as a strong predictor of relapse rate, chronicity, long-term outcome and severity of MDD (Spinhoven et al., 2018; Michalak et al., 2011; Vanderhasselt et al., 2016). Bierhaus et al. (2003) refers to the consequent somatic activation by stress as psychogenic conversion into cellular activation. Changes in nuclear factor kappa B (NF-κB), an important transcription factor for immune response is instigated by psychosocial stressors, precipitating a cascade of cellular changes in the neuroendocrine axis (Bierhaus et al., 2003). Moreover, increased pro-inflammatory proteins in those with MDD may be linked to suicidal behavior (González-Castro et al., 2021). Psychological stress

has been consistently shown to increase inflammatory response and as a key factor in inflammatory disease (Wirtz and Kanel, 2017; Peters et al., 2012; Mawdsley and Rampton, 2006; Maes et al., 1998; de Pablos et al., 2006). A population-based study by Bremmer et al. (2008) has linked MDD in older adults to significantly higher levels of inflammatory markers. Harrison et al. (2009) induced depressive symptoms in healthy volunteers with a typhoid vaccine and showed a significant increase in IL-6 and a decrease in cognitive performance consistent with cognitive issues seen in patients with MDD.

Pace et al. (2006) found that increased IL-6 and NF-κB binding correlated with MDD severity and may be linked to early life stress. Similar results were shown in a 2012 study that found higher baseline levels of IL-6, TNF-α, and soluble interleukin-2 receptors (sIL-2R) in depressed participants compared to healthy controls (Liu et al., 2012). Chen et al. (2019) found that grey matter volume of the orbitofrontal cortex, lingual gyrus, inferior frontal cortex, middle frontal cortex, and planum temporale were reduced in bipolar disorder as compared to unipolar depression. This reduction was negatively correlated with soluble IL-6 receptor levels (Chen et al., 2019). Rajkowska et al. (1999) discovered a decrease in cortical thickness, neuronal sizes, and neuronal and glial density in a number of areas in the PFC of depressed brains. These structural changes are also seen in inflammation and implicate a neuroplastic responses in MDD (Aktas et al., 2007; Fleischman et al., 2010). CRP has been proposed as a potential biomarker for MDD (Chamberlain et al., 2019). Levels of CRP in patients with MDD have been shown to be elevated as compared to healthy controls (Chamberlain et al., 2019). Moreover, the greatest elevation of CRP is seen in treatment resistant MDD (Chamberlain et al., 2019). Normal activity of cytokines is important for neuroplasticity, and lower levels play a vital role in modulating metabolic and molecular pathways to promote long-term potentiation, neuroplastic changes, neuron health, and learning/memory consolidation (Bourgognon and Cavanagh, 2020). However, excessive presence can cause abnormalities in the structure and behavior of neurons (Barrientos et al., 2003; Ben Menachem-Zidon et al., 2008; Miller et al., 2009; Tilleux and Hermans, 2007; Bourgognon and Cavanagh, 2020). Pro-inflammatory cytokines can reduce the availability of monoamines by increasing the expression and function of presynaptic reuptake pumps leading to decreased synaptic availability of 5-HT and increased depressive-like behaviour (Miller and Raison, 2016). Cytokines can also decrease monoamine precursors by activating the enzyme that breaks them down and have been linked to decreased levels of BDNF (Calabrese et al., 2014). BDNF and 5-HT are crucially involved in neural plasticity and development, and the disruption of these systems especially during critical stages of development can lead to drastic structural/morphological changes (Yu and Chen, 2011; Daubert and Condron, 2010). Therefore, chronic inflammatory-induced monoamine and neurotrophin reduction likely leads to morphological changes seen in MDD. It still remains unclear whether abnormal changes as regards neuroplasticity occur prior to, or after, the onset of MDD symptoms, and if changes are completely reversible (Palazidou, 2012).

The link between inflammation and MDD may also have its evolutionary and adaptive origins. Miller and Raison (2016) gave support to the pathogen-host-defence hypothesis of depression that incorporates the need of inflammatory processes in relation to depressed states that are adaptations for survival. For example, depression-related symptoms and could promote survivability and reproduction in the highly pathogenic environments humans once lived in (Miller and Raison, 2016). This hypothesis is supported by a number of observations and findings. Cross cultural hunter-gatherer history data show many humans died of infectious disease before adulthood, enforcing genetic selectiveness in immune defence (Gurven and Kaplan, 2007). Pathogens increase inflammatory activity associated with depressed states, and this increased depressed behavior promotes survivability (Fumagalli et al., 2011; Kuningas et al., 2009). However, the same increase in inflammation risks increased mortality in non-pathogenic environments (Fumagalli et al., 2011; Kuningas et al., 2009). As such, society is now in a relatively

low risk environment in which pathogenic host defense is less important. Thus, humans are currently genetically and biologically prepared to defend against a number of pathogens, however this increased defense has been used less as our environment is now cleaner. As a result, humans are now dealing with the consequences of being on high alert in a low-risk environment. However, in light of recent pandemic-related issues, this hypothesis may stand to be advantageous. Biological preparedness creates a hypervigilant system that increases inflammatory production that can be dangerous in a non-useful environment (Fumagalli et al., 2011; Kuningas et al., 2009).

Within the last decade or so, Serhan (2011) has coined the term "resolution" in the context of a complete return to homeostasis after the inflammatory response (Panigrahy et al., 2020; Serhan, 2017; Serhan and Savill, 2005; Serhan et al., 2008). This may be the missing link that completes the termination of prolonged inflammation. It is likely that resolution confirms the end of the inflammatory process, and while anti-inflammation gives us a glimpse into symptom relief, it does not provide proper resolution. Moreover, it is likely that the complexity of the issue is beyond our current understanding and that treatments that provide long-term relief after a small or single dose may hold some of the answers to acquiring treatment induced resolution. One possibility maybe that there is a systematic dysfunction between the DMN, the hypothalamic-pituitary-adrenal axis (HPA) axis, and negative cognition (i.e., rumination) that interferes with resolution. Psychogenic stress induces activation of numerous pathways, and chronic activation results in maladaptive functional and structural changes. Notably, the mPFC sees both a decrease in volume and an increase in activity in MDD. Furthermore, the HPA axis becomes dysfunctional in response to increased inflammation from chronic stress (Tapp et al., 2019; Silverman and Sternberg, 2012; Guilliams and Edwards 2010). Thus, the mPFC fails to provide appropriate modulation and signaling to the HPA axis, as a result of dysfunction due to chronic stress, which in turn increases inflammation, leading to the dysfunction of the HPA axis. This is a vicious cycle that causes perpetual effects, likely resulting in neurodegeneration.

3. Environmental and genetic risks of inflammation and MDD

Biological contribution to MDD manifestation is only one of many factors involved. It is understood that there is a complex interaction of factors that include environmental and genetic risks and can cause neurological changes to occur in individuals (van den Bosch and Meyer-Lindenberg, 2019; World Health Organization, 2020). Moreover, there is a link between these risks of MDD and increased inflammatory activity (van den Bosch and Meyer-Lindenberg, 2019).

Known environmental risk factors of MDD include substance abuse, lack of peer support, marital problems, low socioeconomic status, low education, obesity/diet, exercise, and stressful life events and all of which have been linked to increased inflammatory activity, further linking the relationship between inflammation and MDD (Dobson and Dozois, 2008; Muscatell et al., 2020; Martinez et al., 2018; Lacey et al., 2014; Fagundes et al., 2011; Friedman and Herd, 2010; Ljungberg et al., 2020). It is likely that these less-than-ideal circumstances exert stressful events and biological changes that are converted into increased inflammatory response. Altering some aspects of one's environment, such as lifestyle choices, can cause neurological changes corresponding with symptom relief (Lopresti et al., 2013). It is likely that similar types of neuroplastic changes are seen in cognitive behavioral therapy and may explain why it has increasingly become popular and effective for the treatment of MDD (Driessen and Hollon, 2011).

Poor diet is one factor of which poses increased risk of MDD and inflammation (Ljungberg et al., 2020). The prevalence of MDD has been increasing along side rates of obesity and sugar consumption, which are also linked to inflammation (Ellulu et al., 2017; Greenberg et al., 2021; Stierman et al., 2021; Bentley et al., 2020). The link between gut biome and neuroscience has been a common topic relevant to behavioural

consequences and psychological disorders for roughly the past decade (Cryan and O'Mahony, 2011; Lyte, 2013; Moulton et al., 2019). Hsu et al. (2015) used a rat model to find that overconsumption of sugars, specifically high fructose corn syrup (HFCS-55), induced hippocampal and metabolic dysfunction, as well as significant increases in IL-6 and interleukin-1β (IL-1β); especially when consumed during the adolescent period. Other studies show increased neuroinflammatory markers TNF-α and IL-6, and anxiety and depression behaviors as a result of high carbohydrate induced obesity in mice (Gomes et al., 2020). Daneshzad et al. (2020) studied women with type 2 diabetes and compared their carbohydrate dietary intake and found a negative relationship between incidences of depressive symptoms, anxiety, and sleep quality with level of carbohydrate diet (Daneshzad et al., 2020). This evidence base can give us important cues about why we have widespread simultaneous increases in mental disorder instances and obesity rates, with MDD and dysthymia being the most prevalent disorders globally (Avila et al., 2015; Baxter et al., 2013).

Inverse-diet studies provide evidence of how dietary adjustment can influence psychological health. Xu et al. (2021) published findings on the ketogenic diet in a mouse model of Alzheimer's disease and found that it ameliorated cognitive impairment and significantly reduced neuroinflammation. Koh et al. (2020) describe the improved immunomodulatory effects of the ketogenic diet. Results indicated powerful anti-inflammatory and neuroprotective effects on the nervous system shown in the improved outcomes after application of the diet on neurological disorder models and patients. Improvements resulting from the immunomodulation and improved polyunsaturated fatty acid intake may be supported by, or result from, favourable gut microbiota modifications due to this dietary change.

Certain types of sedentary lifestyles are linked with MDD and risk the development of increased inflammation, diabetes, and obesity (Hallgren et al., 2020; Lira et al., 2010). Physical exercise has been shown to induce the production of testosterone and attenuate cortisol production, mitigating the effects of perpetual inflammation (Brownlee et al., 2005). Testosterone has neuroprotective properties and is associated with neuroplasticity and synaptogenesis (Camacho-Arroyo et al., 2020). Excess cortisol is a major factor in the onset and maintenance of MDD and is a major contributing factor of inflammation (Jia et al., 2019; Furtado and Katzman, 2015). Further, Gold et al. (2008) demonstrated the neuroprotective effects of testosterone in male multiple sclerosis patients. They found significant increases in BDNF and platelet-derived growth factor (PDGF) via improved immunomodulation (Gold et al., 2008). Testosterone supplementation in diagnosed hypogonadal men has been shown to result in extreme and rapid recovery from treatment-resistant MDD with even low supplementation dosage which resulted in low-normal serum testosterone (Seidman and Rabkin, 1998).

5-HT related gene polymorphisms have also been shown to disrupt 5-HT signalling as well as increase inflammatory cytokine levels. Polymorphism specifically in the SERT gene (*SLC6A4*), particularly the 5-HT-transporter-linked promoter region (*5-HTTLPR*) of depressed individuals increases activity of the amygdala, while reducing the connectivity between the amygdala and the subgenual region of the anterior cingulate cortex, the dorsal region of the anterior cingulate cortex, and the dorsolateral prefrontal cortex (Pezawas et al., 2005; Costafreda et al., 2013). Moreover, *5-HTTLPR* is responsible for regulating IL-6ß during acute stress, and polymorphisms result in increased cytokine levels (Yamakawa et al., 2015). Carriers of the *RS6295* gene has been shown to reduce 5-HT transmission in way of altered 5-HT1A autoreceptor activity and induce anxiety and depressive like behaviors (Albert, 2012). Even after recovery from MDD, cortical 5-HT1A binding potential is lowered, likely causing a trait abnormality that puts people at risk of subsequent major depressive episodes (Bhagwagar et al., 2004). Carriers of a specific gene variant that reduces the expression of SERT are more sensitive to stress-induced activation of the amygdala (Hariri et al., 2002). Epigenetic changes, e.g., significantly lower methylation of *SLC6A4*, has been found in depressed patients, which

correlate with decreased amygdala reactivity (Schneider et al., 2018).

MDD is deeply associated with environmental and genetic risk factors that are now known to influence inflammatory proteins, furthering the link between inflammation and MDD. See Fig. 1 for a concept map synthesis of the hypothesized relationship of the risk factors of MDD and inflammation. Greater exposure to environmental risks should increase the prevalence of both MDD and inflammation. Finding new ways to prevent exposure to these factors could provide better outcomes for individuals, as well as a path for researchers to further investigate the relationship between inflammation and MDD.

4. Antidepressant's effect on inflammation

The most common treatment administered is the prescription of selective 5-HT reuptake inhibitor (SSRI) antidepressants. SSRI's target 5-HT transporter (SERT) protein as its mechanism of prolonged 5-HT neurotransmitter exposure in the synaptic cleft. While SSRI's do provide relief for some, research shows that activity involving SERT degrades over the course of prolonged treatment and may become less effective (Descarries and Riad, 2012). Meta-analyses typically report antidepressants as being 20%–30% more effective than placebo but

indicate that effectiveness varies as a function of symptom severity, with greatest efficacy in severe MDD (Penn and Tracey, 2012). Historically it has been believed that SSRI's efficacy relied on restoring the balance of 5-HT in the brain. However, new evidence suggests that SSRIs have modest anti-inflammatory effects that may explain their limited effectiveness.

It is now apparent that there is a tight relation between inflammation, 5-HT, and MDD (Catena-Dell'Osso et al., 2013). One study compared the mechanisms of action of anti-inflammatories and antidepressants on enzymes responsible for the metabolism of tryptophan, the precursor to 5-HT (Regan et al., 2018). This study found that increased inflammation due to exposure to lipopolysaccharide (LPS), an endotoxin frequently used to induce inflammatory animal models, and the cytokine interferon alpha (IFN-α) upregulated the expression of genes responsible for the production of tryptophan enzymes (Regan et al., 2018). Moreover, anti-inflammatories, but not antidepressants, mitigated the effects of gene expression (Regan et al., 2018). Concluding that inflammation can cause a depletion of tryptophan that can be protected against through the use of some anti-inflammatory compounds (Regan et al., 2018). The fact that there was no effect from anti-depressants suggests either a more potent anti-inflammatory is required, or there
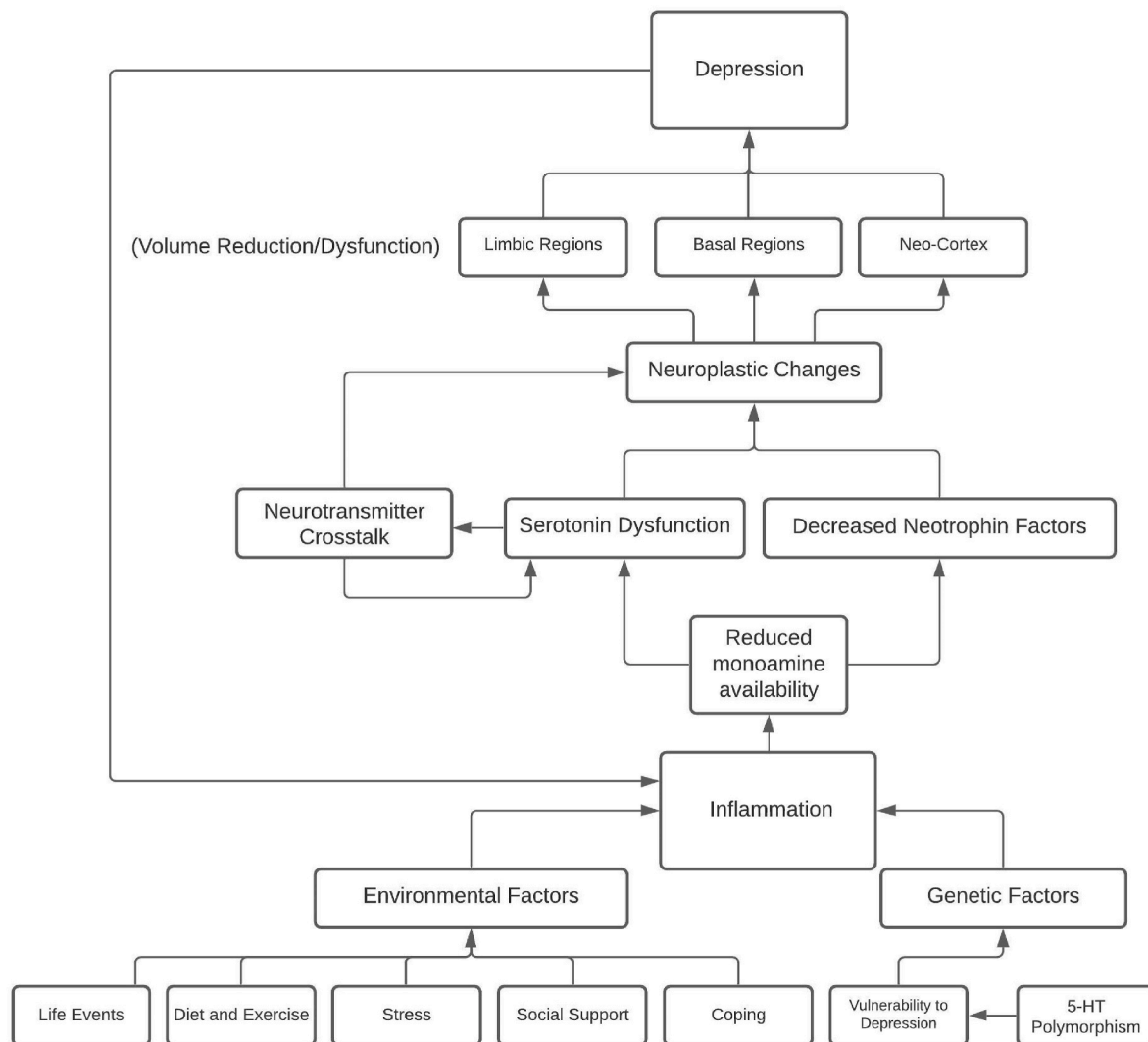

Fig. 1. This concept map visualizes the hypothesized complexity of the relationship between multiple factors of depression and inflammation. Summarized; Environmental and genetic factors predispose individuals to a level of vulnerability to inflammatory response of which reduces monoamine availability and leads to cascading effects of neurotransmitter dysfunction and decreased neurotrophin factors. This perpetual process provides chronic neuroplastic changes in the affected regions and systems that result in depressive symptoms. Finally, depression results in a cyclic circumstance in which inflammation is increased and resumes the aforementioned effects. Effective treatment would be one that breaks this cycle, providing anti-inflammatory and anti-depressant effects.

was no direct mechanistic effect on the specific gene expression investigated. Limited efficacy of antidepressants alludes to the likely maximum effect antidepressants have on inflammation. Conversely, some common anti-inflammatory drugs have positive antidepressant effects (Schmidt et al., 2016). Indeed, common antidepressants of different classes have been found to have acute anti-inflammatory effects (Tomaz et al., 2020). This contributes to the explanation of how antidepressants work for some individuals. However, there is a concerning issue with efficacy of antidepressants that is likely attributed to the diffuse nature of antidepressants and the complex physiological behaviors of individuals. For instance, SSRI's can worsen rumination which then leads to worsened inflammatory and neurological processes and rumination is a predictor of relapse in MDD (Andrews et al., 2015; Michalak et al., 2011).

It has been shown that antidepressants may induce neurogenesis and neuroplasticity (Duman et al., 2016; Serafini, 2012). Further, SSRIs have been shown to increase BDNF related processes (Martinowich and Lu, 2008). BDNF plays a role in neurogenesis, neuroplasticity, as well as promotes the survival of serotonergic neurons (Martinowich and Lu, 2008). The association is then that neuroprogression of MDD is accompanied and worsened by inflammation, and antidepressants work to mitigate the negative affects of inflammation such as decreased spine density, less dendrites, loss of synapses, and loss of glia cells (Serafini, 2012). Given that many antidepressants affect both the serotonergic and glutamatergic system, there are implications that antidepressants may in fact promote neuroplasticity (Azmitia, 1999). Manipulating certain aspects of 5-HT neurons', such as the activity pattern and microstructure, can prevent the loss of synapses (Azmitia, 1999). Neural adaptation to environmental changes relies on the involvement of serotonergic plasticity (see more in Figure, 7 of Azmitia, 1999). There is a consensus on the role of 5-HT as it is related to plasticity and its implications in MDD (Liu et al., 2017).

5-HT dysfunction has been historically linked to MDD, and treatment commonly focuses on manipulating 5-HT. New evidence sheds light on the relationship between 5-HT-function and inflammatory regulation and may explain common antidepressant efficacy. The 5-HT system as plays an important role in inflammation regulation. Thus, dysfunction would cause increased inflammatory activity and 5-HT related medications would likely provide some assistance in re-establishing regulation. However, low-rate efficacy suggests that SSRI's may not sufficiently suppress inflammatory-induced dysfunction and that additional mechanisms are involved. Thus, it is imperative that researchers turn their focus to investigating mechanisms of compounds or interventions that show high-rate long-term efficacy.

5. Alternative treatments

Alternative treatments may provide greater efficacy in treating MDD symptoms and may commonly exhibit potent anti-inflammatory properties. See Table 1 for a summary of pharmacological effects of alternative treatments on inflammation and MDD.

5.1. Ketamine

Serotonergic manipulation plays one role in antidepressant and anti-inflammatory action, however, mechanisms involved in MDD continue to be investigated revealing new and complex processes. Huang et al. (2017) proposed that new treatment options based on the glutamatergic system may yield better outcomes related to MDD relief and neuroplasticity. Ketamine treatment has been accredited for having promising fast-acting results in relieving depressive symptoms and inducing plastic changes and mood improvement (Huang et al., 2017). Ketamine, as a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, blocks transmission of glutamate at the NMDA receptor (Molero et al., 2018). Ketamine has anti-inflammatory properties (Loix et al., 2011; Cathomas et al., 2022; Chen et al., 2021; Kopra et al., 2021). Moreover,

Table 1
Anti-inflammatory properties of alternative antidepressant treatments.

Drug Classification	Mood/Affect	Inflammation	Sources
Ketamine/ NMDA receptor antagonists	- rapid onset (30 min) of antidepressant effects, especially in treatment resistant depression - decreased rumination, depressive behaviors, and depression scores - Antidepressant effects persist for up to 7 days	- Decreased pro-inflammatory cytokines (i.e., TNF-α) that are correlated with decreased depression	Human ● Cathomas et al. (2022) ● Chen et al. (2018) ● Chen et al. (2021) ● Lehmann et al. (2016) ● Liebrenz et al. (2009) ● Su et al. (2017) ● Zarate et al. (2006) ● Zhan et al. (2020) Animal ● Chang et al. (2018) ● Wang et al. (2015) ● Zhao et al. (2020)
Cannabis/ Cannabinoid	- THC, CBD, and HU-580 show antidepressant-like effects in rodent behavioral tests - UCS decreases eCB signalling - FAAH enzyme inhibition leads to anti-depressant effects	- Decreased inflammatory cytokines (e.g., IL-6, TNF-α, IFN-ß) - Decreased PGE2, COX activity, oxygen-derived free radicals, and nitric oxide - Chronic stress induces inflammation which is rescued by cannabinoid treatment	Human ● Karoly et al. (2018) ● Motwani et al. (2018) ● Morissette et al., 2021 Animal ● Hill et al. (2005) ● Haj-Dahmane and Shen (2014) ● Bambico et al. (2016) ● Bambico et al., 2010a,b ● Elbatsh et al. (2012) ● Costa et al. (2004) ● Abohalaka et al. (2020) ● Hen-Shoval et al. (2018) ● Verrico et al. (2020) ● Yekhtin et al. (2022)
Psychedelics	- Decreased stress and anxiety-related behaviors - Rapid and long-term antidepressant effects in MDD lasting up to 6 months	- Decreased CRP that correlates with decreased depression - 5-MeO-DsMT increased cortisol and decreased IL-6	Human ● Galvão-Coelho et al. (2020) ● Uthaug et al. (2020) ● Griffiths et al. (2016) ● Davis et al. (2021) ● Barrett et al. (2020) Animal ● Yu et al. (2008) ● Flanagan et al. (2021)

Note: Acronyms: UCS – unpredictable chronic stress, eCB – endocannabinoids, FAAH - Fatty acid amide hydrolase, TNF-α - Tumor necrosis factor alpha, IFN-ß – Tumor necrosis factor beta, PGE2 - Prostaglandin E2, COX – cyclooxygenase, CRP – C-reactive protein, 5-MeO-DMT - 5-methoxy-N,N-dimethyltryptamine, IL-6 – Interleukin-6, HU-580 – cannabidiolic acid methyl ester, MDD – major depressive disorder.

ketamine modulates the DMN and reduces self-directed negative cognition (e.g., rumination; Lehmann et al., 2016). Its primary use has been as a dissociative anesthesia, but studies found that it reduced inflammatory response to surgery (Dale et al., 2012). Ketamine has been shown to reduce TNF-a and IL-6 expression in immune cells such as macrophages and glial cells (Chang et al., 2009, 2010; Yuhas et al., 2015). Single-dose monotherapy has shown great efficacy in treating MDD and can rapidly reduce suicidal thoughts (Molero et al., 2018). Indeed, ketamine has been shown to produce antidepressant effects as quickly as 30-min after administration (Liebrenz et al., 2009). In animal models, this rapid antidepressant effect has been linked with down-regulating pro-inflammatory cytokines in the hippocampus (Wang et al., 2015), without any sex differences in its neurobiological/physiological effects despite apparent sex differences in antidepressant behavioural phenotype (Chang et al., 2018). Since the efficacy of ketamine is tied with mammalian target of rapamycin (mTOR) activation and the production of BDNF, Su et al. (2017) assessed the efficacy of ketamine in treatment-resistant MDD participants who carried a low functioning BDNF gene. This study found that ketamine was not effective in low severity MDD but was increasingly effective as depression severity increased (Su et al., 2017). Chen et al. (2018) specifically looked at providing low-dose ketamine infusions in treatment-resistant MDD patients as well. They found rapid reduction in the proinflammatory cytokine TNF-α that correlated with decreased scores on a depression scale (Chen et al., 2018). Moreover, a dose-dependent effect was seen, and as dose increased from control to 0.2 mg/kg to 0.5 mg/kg, depression scores decreased accordingly (Chen et al., 2018). Low-dose efficacy of ketamine has been recently shown in animal models of depression as well, and researchers link its effects to anti-inflammatory pathways (Zhao et al., 2020). Zhan et al. (2020) investigated a large number of cytokines in MDD patients and found that there were 14 different inflammatory factors downregulated after 12 days of treatment with ketamine. Moreover, interleukin-17A (IL-17A) and IL-6 were both positively correlated with improved symptoms.

One promise of ketamine's potential is that it requires infrequent administration and is likely easier to maintain long-term. For example, Zarate et al. (2006) showed that the antidepressant effects of a single administration persisted for up to 7 days. Drug adherence is an issue in effective long-term treatment in MDD (Dell'Osso et al., 2020). Thus, ketamine may provide a treatment plan that is more forgiving. Ketamine also has a good safety profile with minimal adverse effects and has been frequently used in children (Green et al., 1996; Dolansky et al., 2008).

5.2. Cannabinoids

Research and proper regulation of cannabis products for medicinal purposes as a treatment option for MDD is scarce. The use of cannabis has been historically associated with worsening or initiating the onset of MDD; however, recent investigations have begun to explore the potential of an inverse relationship (Feingold and Weinstein, 2021). The relationship between cannabis and MDD has not been well elucidated, and there are now indications that it may be an effective alternative treatment for MDD (Martin et al., 2021). For example, while it has been found that those who used cannabis had worsened MDD, this was only the case for heavy users and was a modest effect (Degenhardt et al., 2003). Reviews have been able to show a high comorbidity between cannabis use disorder and MDD (Onaemo et al., 2021), however the perspective of this relationship may be biased by the historical prohibition of cannabis products. For instance, cannabis may fare better as an effective treatment in which those who have MDD use it to self-medicate, explaining a high rate of cannabis consumption among those with MDD (Wieckiewicz et al., 2022). Delta (9)-tetrahydrocannabinol (THC) and cannabidiol (CBD) are two well-known constituents of cannabis that continue to show anti-depressant and anti-inflammatory effects (Henshaw et al., 2021; Sales et al., 2018; El-Alfy et al., 2010). While there are many other

constituents of cannabis, research on these is still fairly new. Recently, Faouzi et al. (2022) showed anti-inflammatory effects of cannabigerolic acid by blocking nuclear factor of activated T-cells and interleukin-2 (IL-2) production. In 2005, Hill et al. (2005) revealed that unpredictable stress induced dysfunction of the cannabinoid system of which was rescued via exogenous cannabinoid treatment. It was later showed that chronic stress reduced the production of endocannabinoids and led to depressive-like behavior (Haj-Dahmane and Shen, 2014).

The endocannabinoid system modulates serotonergic neurotransmission via the CB1 receptor to produce antidepressant effects (Gobbi et al., 2016; Bambico et al., 2016). Fatty acid amide hydrolase (FAAH) is an enzyme responsible for degradation of endocannabinoids, and when genetic expression is removed effects appear to be anxiogenic and anti-depressant in mice (Bambico et al., 2010a,b; Gobbi et al., 2016). Moreover, by providing more availability of endogenous cannabinoids, serotonergic transmission is altered (Bambico et al., 2010, 2016; Gobbi et al., 2016). Bambico et al. (2016) was able show a connection between the endocannabinoid system, BDNF, and antidepressant and anxiolytic effects. Using single and repeated dose of the endocannabinoid enhancer drug URB597, animal models showed reduced depressed- and anxious-like behaviors in the forced swim test, elevated plus maze, and novelty-supressed feeding test (Bambico et al., 2016). URB597 is an inhibitor of the enzyme fatty acid amide hydrolase (FAAH) that degrades the endocannabinoid anandamide (AEA; Bambico et al., 2016). Repeated URB597 treatment was associated with increased BDNF and showed profound antidepressant-like and anxiolytic-like effects compared to a single dose (Bambico et al., 2016). In addition, non-steroidal anti-inflammatory drugs (NSAIDs, e.g., oleamide, arachidonamide and stearoylamide) are linked to FAAH inhibition (Dongdem et al., 2022). URB597 has also been linked to anti-inflammatory effects across animal models of inflammation (Jayamanne et al., 2009; Murphy et al., 2012). A recent lipopolysaccharide (LPS)-induced inflammation mouse model study showed that inhibiting enzymes responsible for the degradation of endocannabinoids using URB597 and JZL184 can decrease inflammatory response and pro-inflammatory cytokines (Abohalaka et al., 2020). Moreover, these inhibitors decreased 5-HT hyperactivity and it was suggested that inhibition of endocannabinoid enzymes prevented inflammation-induced 5-HT hyperactivity.

CBD is increasingly used for medical purposes, and is known to be neuroprotective, cardioprotective, and anti-inflammatory (Britch et al., 2021). CBD's neuroprotective potential has strong implications in helping reduce symptoms of neurodegenerative diseases such as ALS, Parkinson's disease, Huntington's disease, Alzheimer's disease, and multiple sclerosis (Iuvone et al., 2009). CBD has a low affinity for cannabinoid receptor 2 (CB2), and it activates 5-HT1A and transient receptor potential vanilloid (TRPV) receptor subtypes, which may implicate its medicinal use in neuroplasticity and inflammation (Britch et al., 2021; Bujak et al., 2019). Rodent models and human clinical trials reveal antidepressant and anxiolytic effects of CBD (García-Gutiérrez et al., 2020). A synthetic analogue precursor of CBD, cannabidiolic acid methyl ester (HU-580), has also been shown to rescue animals from depressive-like behaviors (Hen-Shoval et al., 2018). CBD and THC have been shown to be anti-inflammatory and can be effective in symptom relief in conditions such as gastrointestinal inflammation, ulcerative colitis, ocular hypertension and glaucoma, graft-versus-host disease, and diabetes (Britch et al., 2021; Nagarkatti et al., 2009). While CBD has been shown to affect many mechanisms with indirect action on inflammation, there are few studies directly testing its effect on pro-inflammatory cytokines (Atalay et al., 2019). Costa et al. (2007) found that CBD was effective in reducing hyperalgesia in an inflammatory model of rats and showed that a single-dose CBD injection decreased edema in carrageenan-induced inflammation (Costa et al., 2004). After three doses of CBD, rodents showed decreased prostaglandin E2 (PGE2) plasma levels, tissue COX activity, production of oxygen-derived free radicals, and nitric oxide; all of which play a role in maintenance of inflammatory processing (Costa et al., 2004). Petrosino

et al. (2018) tested CBD's effect on pro-inflammatory cytokines and AEA levels in vitro. They found that CBD increase AEA and decreased IL-6, interleukin-8 (IL-8), and TNF-α. This was also blocked by CB2 and TRPV1 antagonism revealing the mechanisms involved for pro-inflammatory reduction. Jean-Gilles et al. (2015) were able to show an association between peripheral immune cell CB1/CB2 upregulation and pro-inflammatory cytokines IL-1ß, IL-6, and TNF-α in patients with multiple sclerosis, primarily an inflammatory disease. Two randomized controlled trials were able to show CBD decreased inflammatory cytokines (Morissette et al., 2021; Verrico et al., 2020), however, to our knowledge there is no findings of this nature in the context of MDD. Thus, it is imperative to further investigate the possible link between the anti-inflammation and anti-depressant effects of CBD.

In 2012, a study was conducted using rats to assess behavioral outcomes of chronic THC administration. The results indicated that THC increased BDNF and had antidepressant-like behavioral changes (Elbatsh et al., 2012). Motwani et al. (2018) discovered powerful anti-inflammatory properties of delta(8)-tetrahydocannabinol (THC)-11-oic acid (anabasum), a synthetic analog of THC, in humans. Yekhtin et al. (2022) tested both THC and CBD in an inflammatory model using mice and found a reduction in the pro-inflammatory cytokines IL-6, TNF-α, and interferon-beta (IFN-ß). Notably, they tested the effects of both forms of pure cannabinoids and cannabis extract and found stronger effects from cannabis extract.

Karoly et al. (2018) conducted a preliminary study to assess the anti-inflammatory potential of cannabis in people who use alcohol and cannabis. Alcohol is a frequently used substance that also tends to cause increased inflammation making it a prime target for this study. Although this study was based on self-report data, the results showed an interaction effect in that IL-6 levels were strongly associated with non-cannabis users who drank alcohol (Karoly et al., 2018). Moreover, there was a negative correlation between cannabis and IL-1ß. It was concluded that cannabis may mitigate the inflammatory effects of alcohol (Karoly et al., 2018).

5.3. Psychedelics

Psychedelics as a classification have been identified to mediate inflammation via the 5-HT2A receptor, but there have been very little specific investigations on psychedelic compounds (Flanagan and Nichols, 2018). In 2008, Yu et al. showed that psychedelics could inhibit TNF-α inflammatory processes via the 5-HT2A receptor subtype, and this was considered groundbreaking and sparked future research. Flanagan and Nichols hypothesized that psychedelics halted perpetual neural processes by resetting resting state functional connectivity (RFSC; Flanagan and Nichols, 2018). Thus, psychedelics likely reduce neuroinflammation and stop cascading processes in the brain from reoccurring, causing lasting therapeutic effects (Flanagan and Nichols, 2018). Indeed, psychedelics have recently taken new light as a therapeutic treatment option for MDD and inflammation, and there is a great push for more clinical research to further link this relationship (Szabo, 2019). Flanagan et al. (2021) confirmed the hypothesis that anti-inflammatory action of a number of psychedelics occurred via 5-HT2A receptor activity and found the compound 2C-H produced the strongest anti-inflammatory action. Galvão-Coelho et al. (2020) conducted a double-blind placebo-controlled trial with treatment-resistant MDD patients to assess the efficacy and anti-inflammatory effects of ayahuasca; treatment resistant patients were compared to healthy controls. Results showed that treatment resistant patients had higher levels of baseline C-reactive protein (Galvão-Coelho et al., 2020). Both healthy and treatmen-resistant patients seen a reduction in CRP in response to ayahuasca treatment, and greater reduction of CRP in treatment-resistant patients was correlated with lower depression scores (Galvão-Coelho et al., 2020).

Another recent study assessed the effects of 5-MeO-DMT on inflammatory biomarkers and behavioral measures (Uthaug et al., 2020).

Participants were measured at baseline, about 1 h directly after their inhalation, and during a seven-day follow up. This study found that inhaling a synthetic 5-MeO-DMT resulted in increased cortisol and decreased IL-6 (Uthaug et al., 2020). Stress and anxiety as per survey measures were significantly lower 7 days later and correlations were found between participants' ratings of the psychedelic experiences and improved affect (Uthaug et al., 2020). The quality of a psychedelic experience is important in one's perception of the experience and thus affects the efficacy of treatment (Yaden and Griffiths, 2021). Indeed, subjective experience and psychological state do affect one's physiology (Bierhaus et al., 2003). Thus, while negative psychological experiences influence inflammation and respective cascading biological events, it is likely that positive psychological experiences provide an opposing effect. It turns out that positive affective traits do in fact predict later lower levels of IL-6 (Stellar et al., 2015). This is likely a contributing factor in the efficacy of treatments that also induce positive experiences (e.g., psychedelics).

In a 2016 breakthrough randomized double-blind trial, Griffiths et al. (2016) provided psilocybin to patients with terminal cancer. Intuitively, dealing with a life-threatening illness would induce depressed mood and anxiety. This study concluded that psilocybin produced large decreases in depression and anxiety, as well as specifically death anxiety (Griffiths et al., 2016). Further, patients seen an increase in quality of life, particularly optimism (Griffiths et al., 2016). Six months later, it has been found that 80% of patients sustained these effects. One important follow up study by Davis et al. (2021) showed outstanding results in the antidepressant effect of psilocybin. This randomized clinical trial study provided two psychotherapy-assisted psilocybin treatment sessions for participants who were diagnosed with MDD. Results of this study showed a rapid onset of antidepressant effects that persisted for up to four weeks (Davis et al., 2021). Moreover, 71% of the participants at weeks one and four had a clinically significant reduction in depressive symptoms, and 58% were in full remission (Davis et al., 2021).

Barrett et al. (2020) ran a pilot study to investigate the effect of psilocybin on brain structure activity in response to depression and anxiety provoking stimuli. Results showed that negative affect and amygdala activity in response to facial stimuli were reduced, suggesting that reactivity to emotionally charged stimuli is decreased (Barrett et al., 2020). Further, when participants responded to emotionally conflicting stimuli, positive affect and dorsal lateral prefrontal and medial orbitofrontal cortex activity were increased (Barrett et al., 2020). This suggests that participants are more able to employ executive functions (e.g., rational and logical thinking) when processing emotionally relevant stimuli due to their psilocybin experience. This study also found lasting effects up to one month after consuming psilocybin. Trait anxiety was reduced, and functional connectivity was better increased after one month of treatment than after one week of treatment (Barrett et al., 2020). Researchers concluded that psilocybin likely increases functional brain plasticity in response to emotional stimuli (Barrett et al., 2020).

Contrary to most literature, Porr et al. (2020) found that SSRIs in conjunction with environmental changes had better outcomes for decreasing depressed behaviors as compared to psychedelics. While the results for psychedelics were mixed in this study, it should be noted that this study used animal subjects and the subjective experience may be a key factor in treatment efficacy (Yaden and Griffiths, 2021). Biologically, psychedelics modulate the DMN and decrease its resting activity, and this alteration has been linked to their efficacy (Palhano-Fontes et al., 2015; Smigielski et al., 2019; Ruban and Kołodziej, 2018). Psychologically, psychedelics provide alternative perspectives and understandings of the connections between the self and the outside world. Several hypothesizes are being developed on the way in which psychedelics tend to disrupt one's way of thinking and provide new positive beliefs (Carhart-Harris, 2019). This highlights a likely important cognitive factor of one's own beliefs and the risk of relapse of depressive rumination (Michalak et al., 2011). However, current research outcomes

are lacking explanatory power on the mechanisms involved in the treatment efficacy of psychedelics. Therefore, it is paramount that future research investigates the precise mechanisms of psychedelics in the context of MDD and inflammation to further elucidate this relationship and provide insights into long term relief.

6. Conclusions

This review was set out to describe the importance of the impact of inflammation on MDD by elucidating the relationship. Inflammation impacts monoamine systems, neural structures, and system functions related to MDD. The presented literature depicts a very complex and dynamic picture of the important functions of many biological processes in relation to MDD that are also influenced by inflammatory activity. Moreover, given the complex biopsychosocial nature of MDD, it is even more challenging to find consistent data on these processes. Through the presence of and changes in cytokine levels, we can now see that inflammation is greater in those with MDD than those without. Moreover, individuals with MDD also show higher immune-related activities that are known to respond to inflammation. There are a number of environmental risks of MDD that can alter neurological and inflammatory activity, and changes in these can decrease inflammation and depressive symptoms.

Common treatment for MDD can be effective for some, while not being effective for others. This discrepancy in effectiveness has provided the motivation to find new alternative drug treatments that can be more effective than common treatment and provide long-term relief. The proposed alternatives provide a promising future for the treatment of MDD by potentially influencing a inflammatory resolution mechanism. We propose that through the effects of its own presence at a threshold, inflammatory cytokines influence a perpetual process that is increasingly difficult to bring to resolution, and the aforementioned alternatives provide insights of a potential resolution not yet understood. Specifically, psychedelics have breakthrough treatment efficacy in MDD long term. Thus, it is imperative that researchers investigate the anti-inflammatory natures of these compounds to further elucidate the mechanisms involved in their resolution potential. This would provide individuals with a potential treatment more efficacious than current options and would greatly alleviate the pressure on health care professionals. Moreover, having several alternatives available provides the client with more options to fit their comfort level.

There are limitations to some of the presented findings, however. Most importantly, many results are based on correlations. For this reason, causality and generalizability can still be improved by future investigations, especially with the use of preclinical experimental models. Given the nature of the topic, sample sizes are often small, and controllability and validity of measures are sometimes limited. Despite this, there seems to be some degree of replicability. This research is still in its infancy, and because of this, much of the proposed relationships are theoretical. At this time, animal models continue to offer invaluable information despite issues with translatability. Future clinical instigations on early diagnoses of MDD and prodromal markers that align with preclinical models would enrich and improve longitudinal and experimental designs. This would allow researchers to track inflammatory processes, neurological changes, and MDD phenotype over time. Alternatively, more research is required on each of the mentioned drug treatment alternatives, especially in the context of DMN and HPA axis functioning. To further substantiate the inflammation hypothesis of MDD, clinical investigations should be conducted on related and/or comorbid disorders (e.g., anxiety, TBI) that may be linked to inflammation. A major factor in causality and/or exacerbation of MDD is increased inflammatory processes that can be mediated and treated by multiple treatment options that have both antidepressant and anti-inflammation properties.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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