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REVIEW ARTICLE

Depression, dementia and immune dysregulation

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Major depression is a prevalent illness that increases the risk of several neurological conditions. These include stroke, cardiovascular disease, and dementia including Alzheimer's disease. In this review we ask whether certain types of depression and associated loneliness may be a harbinger of cognitive decline and possibly even dementia. We propose that chronic stress and inflammation combine to compromise vascular and brain function. The resulting increases in proinflammatory cytokines and microglial activation drive brain pathology leading to depression and mild cognitive impairment, which may progress to dementia. We present evidence that by treating the inflammatory changes, depression can be reversed in many cases. Importantly, there is evidence that anti-inflammatory and antidepressant treatments may reduce or prevent dementia in people with depression. Thus, we propose a model in which chronic stress and inflammation combine to increase brain permeability and cytokine production. This leads to microglial activation, white matter damage, neuronal and glial cell loss. This is first manifest as depression and mild cognitive impairment, but can eventually evolve into dementia. Further research may identify clinical subgroups with inflammatory depression at risk for dementia. It would then be possible to address in clinical trials whether effective treatment of the depression can delay the onset of dementia.

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Abbreviations: LPS = lipopolysaccharide; MDD = major depressive disorder; NSAID = non-steroidal anti-inflammatory drug; SSRI = selective serotonin reuptake inhibitor

Introduction

Major depressive disorder (MDD) is one of the most common psychiatric disorders worldwide (Kessler and Bromet, 2013). In the USA, the lifetime prevalence of an MDD exceeds 20% (Hasin *et al.*, 2018), and the WHO ranks MDD as the leading cause of the global burden of disease (WHO, 2017). It is also notable that there is a significant sex difference in the incidence of major depression, with females affected twice as often as males (WHO, 2017; Hasin *et al.*, 2018). Moreover, with an ageing population, factors such as social isolation and loneliness, combined with the increasing number of other illnesses a person faces over time, is only expected to further increase the overall impact of MDD upon the population. The state of social isolation constitutes a major stressor leading to increased cytokine levels, anxiety- and depression-like behaviour in social species including rodents (Krügel *et al.*, 2014; Arakawa, 2018) and primates (Hennessy *et al.*, 2014).

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Loneliness is the distressing perception that quantitatively, and especially qualitatively, one's social relationships are diminishing below one's expectations. Loneliness and the sense of isolation it imparts is highly correlated with depression (Cacioppo and Patrick, 2008), and if you feel alone, you are in good company! It is estimated that 40% of Americans feel lonely (Hawkley and Cacioppo, 2010). A survey by Statistics Canada in 2012 reported that 20% of older people in Canada declare feeling lonely (Gilmour, 2012). Surprisingly, loneliness is also a serious concern for our youth. In Vancouver, Canada, a charity carried out a survey and found that one-third of all 25–34-year-olds were more alone than they liked (Vancouver-Foundation, 2012). These statistics—being alone and feeling lonely—are essentially double what they were 30 years ago, and they are expected to rise further with the worldwide shift in demographic profile towards an elderly population. Importantly, loneliness is not only associated with depression, but also with earlier onset of dementia (Holwerda *et al.*, 2014). On the other hand, elders with an active social life appear to be protected from loneliness and dementia as they age (Fratiglioni *et al.*, 2004). Here, we will review the link between depression and dementia. It is our contention that dysregulation of aspects of the immune system may underlie the co-development of these two illnesses of the CNS. We posit that at least in certain cases, depressive illness, possibly through inflammatory mechanisms, might lead to the evolution of dementia.

Impact of depression on our cognitive health

Depression and dementia

Depression and dementia are now entities that can be measured and quantitatively ascertained by a variety of methods. For example, the severity of cognitive deficits can be assessed using the Montreal Cognitive Assessment Test (MoCA) (Nasreddine *et al.*, 2005) and depression assessed using the validated Patient Health Questionnaire (PHQ-9) (Kroenke *et al.*, 2001). These and other methods have been used to confirm a link between depression and dementia. In a systematic review of the factors associated with cognitive decline in later life, Plassman *et al.* (2010) reviewed all large observational studies and randomized controlled trials published over 25 years. They concluded that there was an association between depression and the development of dementia. In a nationwide Swedish cohort followed for over 10 years, those who had been identified in the Swedish National Patient Register as being depressed had a 2.5-fold greater likelihood of dementia compared to those who had not. Within 6 months of a depression diagnosis, the likelihood of a dementia diagnosis increased 15-fold (Holmquist *et al.*, 2020). Indeed, Köhler and colleagues, using a symptom checklist to diagnose depression and applying multiple tests including the Mini-Mental State Examination of neurocognitive functions, reported that half of patients with major depressive disorders exhibited generalized thinking and memory impairment, early signs of dementia (Kohler *et al.*, 2010). Similarly, in aged veterans with moderate to severe depression, dementia was twice as prevalent as in those without depression (Byers *et al.*, 2012). In another study, the oldest old females who had depression displayed a nearly 4-fold increase in the prevalence of mild cognitive impairment (Spira *et al.*, 2012). These findings point to some degree of convergence of depressive and cognitive symptoms.

The path from depression to dementia likely involves several intermediary steps, since the state of depression impacts several physical and neurological functions and is bidirectionally associated with a variety of medical and neurological conditions (Evans *et al.*, 2005). First, depression seems to accelerate the process of ageing. When scientists in the Netherlands measured telomere length, they reported that individuals who were or had been depressed had shorter telomeres, meaning their bodies had aged more rapidly, even when all other factors were considered (Verhoeven *et al.*, 2016). In the state of depression the likelihood of diabetes and obesity are also increased (Windle and Windle, 2013). Depression in many cases undermines the ability to regulate appetite and can result in obesity. Echoing this, in his book *Loneliness*, Cacioppo says, 'We want to soothe the pain we feel by maintaining high levels of sugar and fat delivered to the pleasure centers of the brain' (Cacioppo and Patrick, 2008). This can result in a 'vicious cycle', wherein the obesity associated with depression serves to accelerate a decline in vascular networks in the body, ultimately impacting cognitive health and leading to vascular depression and dementia.

Depression and brain structure

Several studies show that MDD not only impacts neurotransmitter and hormonal systems, but can also affect the physical structure of multiple brain networks (Scheinost *et al.*, 2018). A reduction in both the volume of the anterior cingulate cortex and the functional connectivity in the medial prefrontal cortex in major depression have been reported (Murrough *et al.*, 2016; Wise *et al.*, 2017). Others have shown that depression is specifically associated with reductions in the grey matter volume of the hippocampus and medial prefrontal cortex (Belleau *et al.*, 2019), lesions that affect brain connectivity. This has allowed the subdivision of patients with depression into four neurophysiological subtypes, defined by distinct patterns of dysfunctional connectivity in limbic and frontostriatal networks (Drysdale *et al.*, 2017). Thus, depression may now be subcategorized based on resting state connectivity.

A recent study suggests that alterations in prefrontal cortical connectivity correlate most consistently with depressive behaviour (Scheinost *et al.*, 2018). A series of intriguing studies also found that reductions in hippocampal volume observed in MDD patients were correlated with how long

depression went untreated, but could be reversed by successful antidepressant treatment (MacQueen *et al.*, 2003; Maller *et al.*, 2018; Roddy *et al.*, 2019). These reductions in grey matter may involve structural lesions, such as reductions of dendritic arborization or neurogenesis, which can be amended by a variety of antidepressant strategies (Czéh *et al.*, 2001; Wu *et al.*, 2014; Powell *et al.*, 2017). Hence, depressive illness alone may not lead to neuronal death but it may augment the neurodegenerative or debilitating effects of other illnesses or insults, such as cerebral stroke (Frank *et al.*, 2012; Espinosa-Garcia *et al.*, 2017).

MDD can also affect brain structure and function by increasing the incidence of cardiovascular disease (Hakim, 2011). Multiple reports confirm that MDD increases the likelihood of heart attack and stroke through several mechanisms, and this in turn can adversely impact affective and neurocognitive circuitry. Indeed, MDD negatively impacts the haemodynamic, structural and inflammatory pathways that can lead to stroke. When the impact of emotions on the function of heart and blood vessels was studied, sadness resulted in a distinct pattern, with moderate increases in blood pressure and vascular resistance, and a decrease in the heart's pumping capacity (Schwartz *et al.*, 1981; van Middendorp *et al.*, 2013), all factors that increase the risk for strokes. Similarly, Sinha and colleagues examined the cardiovascular mechanisms governing blood pressure changes during the emotions of joy, sadness, fear, and anger; sadness resulted in moderate increases in blood pressure and vascular resistance and a decrease in cardiac output (Sinha *et al.*, 1992). Since the brain is exceedingly sensitive to increases in blood pressure (Sörös *et al.*, 2013), such sustained cardiovascular changes can contribute to the development of ischaemic brain damage by occluding and damaging blood vessels. Correspondingly, in stroke due to large vessel occlusion, one-third of patients exhibit immediate cognitive difficulties, and over time the incidence of dementia increases after an evident stroke (Gorelick *et al.*, 2011; Kalaria *et al.*, 2016).

Depression has been associated with a higher incidence of small vessel disease leading to white matter lesions (Brookes *et al.*, 2014; Wang *et al.*, 2014; Hakim, 2019). Depressed individuals show abnormalities in the same brain regions known to be vulnerable to the development of arteriolar occlusions causing white matter strokes (Aizenstein *et al.*, 2011). The structures most impacted include the hippocampus, amygdala, thalamus and frontal as well as prefrontal cortices. Deep cortical white matter is also reported to suffer microstructural abnormalities in normal ageing (Caunca *et al.*, 2019), perhaps indicating why older individuals may be more vulnerable to the development of white matter damage in the setting of depression (van Velzen *et al.*, 2020). In an attempt at elucidating the sequence of events between white matter disease, depression, and dementia, analysis of data from the Northern Manhattan Study showed that depressive symptoms were associated with worse episodic memory and silent brain infarcts, but were not significantly associated with white matter hyperintensity volume (Al Hazzouri *et al.*, 2018). Respino and colleagues (2019) further defined the link by showing that white matter hyperintensities evident in late-life depression were associated with region-specific disruptions in cortical and subcortical grey matter areas involved in attentional aspects of cognitive control as well as sensorimotor processing, resulting in both slower processing speed and reduced attentional set-shifting (Respino *et al.*, 2019). This may suggest that small vessel disease and its consequent white matter hyperintensities may lead to depression and cognitive deficits, but the reverse is less likely.

Immune dysregulation: a link between depression and cognitive decline?

Potentially one of the most prominent mechanisms linking depression to strokes and cognitive decline is dysregulation of the immune system (Box 1). The roots of the immune hypothesis of depression can be traced back to the early 1990s, first appearing as the 'macrophage theory of depression' otherwise known as the 'cytokine hypothesis of depression' (Smith, 1991; Maes *et al.*, 1995). This hypothesis holds that immune-inflammatory processes contribute to depression pathogenesis and are not mere epiphenomena of the disease. It links release of pro-inflammatory cytokines from macrophages or related cells, particularly interleukin (IL)-1β, IL-6 and tumour necrosis factor (TNF)-α, to emergence of neurovegetative symptoms of depression. Growing evidence indicates a strong link between depression and abnormalities in immune mechanisms beyond acute innate mechanisms, involving chronic adaptive immunity (Box 1). In parallel, this immune dysregulation may simultaneously drive other co-morbid medical conditions, such as stroke or cardiac conditions, which can increase risk of dementia. More recently, several variants of the immune hypothesis for depression have emerged, including 'parainflammation' involving hyper-activation of neuroinflammatory microglia (Wohleb, 2016) and inflammation stemming from dysregulated gut-brain axis (Pereira *et al.*, 2019).

Stress, cytokines and 'inflammatory' depression

Many of the effects of stressors on brain function and behaviour may be mediated by actions of cytokines in the brain (Box 2). Over the past 20+ years, numerous studies have shown that pro-inflammatory cytokines are increased in depressed humans and animal stress models of the illness (Dantzer *et al.*, 2008; Wohleb *et al.*, 2016). In addition, a plethora of rodent studies have shown that pro-inflammatory cytokines IL-1β, TNF-α and the interferons (IFNs) provoke an anhedonia-like phenotype and signs of sickness. Sickness phenotypes are coupled with marked elevations in

Box 1 The immune systems

The two fundamental branches of immunity, innate and adaptive, are both interconnected and interact with the brain in a bidirectional manner. These systems use as messengers soluble cytokines and chemokines, which are released from a variety of immune cells and microglia and influence immune cell trafficking, as well peripheral neural fibre projections to the brain. Cytokines signalling has been strongly implicated in psychiatric, particularly depression, and neurological conditions including Alzheimer's and Parkinson's disease. Innate immunity can give rise to inflammation in response to immediate immunological threats. This is characterized by several clinical features, including fever, pain, oedema, and redness and is mediated by a variety of immune cells, including circulating neutrophils, macrophages, dendritic cells, and natural killer cells (i.e. leucocytes). Innate immune cells detect pathogens through their pathogen-associated molecular pattern receptors (PAMPs). PAMPs detect a variety of ligands including lipopolysaccharides and phosphatidylserine to promote phagocytosis and lysosomal degradation of the threat and induce inflammatory signals through NF-κB and the production of inflammatory cytokines. PAMPs can also elicit oxidative stress and apoptotic responses to eliminate pathogens. Cytokines in turn, act to limit the spread of infection by further mobilizing immune cells and facilitating neuro-immune communication in the brain (Shtrichman and Samuel, 2001; Hayley and Litteljohn, 2013). They do so through either NF-κB or mitogen-activated protein (MAP) kinases, and Janus tyrosine kinases (Jaks) and signal transducers and activators of transcription (STATs) (Lin and Leonard, 2000; Lin *et al.*, 2008).

Within the CNS, innate neuroinflammation is mainly mediated by the activation state of immunocompetent microglia. Indeed, these highly plastic immune cells constantly perform surveillance of their microenvironment and are the first responders to immune challenges. They are highly sensitive to any pathogenic stimuli, cellular debris or damage and can rapidly phagocytose or otherwise engage with such stimuli. Microglia utilize an acute respiratory burst of superoxide against viable pathogens encountered. In the case of chronic threats or damage related to disease, these immune cells may act to target and destroy otherwise healthy neurons. This is a prime example of the beneficial and deleterious consequences of immunity, the so-called 'doubled-edged' sword concept of inflammation, which can actually be applied to all cells with immunological capacity.

Following innate immune processes, the more specific and longer-lasting adaptive branch of immunity can be engaged. This typically involves the induction of T and B lymphocytes with highly specialized antigen receptors and produces a long-lasting immunological memory. Although less attention has been devoted to the role of adaptive immunity in depression, many reports show that such long-term immune processes are dysregulated in depression. Furthermore, innate cells (macrophages and dendritic cells) bridge the innate and adaptive branches of immunity by presenting antigen to the adaptive immune cell, thereby engaging a long-term immune memory. While innate immunity is generally considered non-specific, acute response to pathogen, some degree of innate immunological 'memory' is engendered (Salani *et al.*, 2019). Indeed, key innate cells, including macrophages and microglia can be pre-programmed by pathogenic or other stressors, such that their response is augmented with later re-exposure to such stimuli. Unlike adaptive immune memory that requires genetic rearrangement, such innate memory might be mediated by epigenetic marks together with metabolic changes (Seeley and Ghosh, 2017). Together, these two interconnected immune responses are necessary for long-term immunological memory and survival.

In the periphery, activation of leucocytes following immune challenge or injury occurs rapidly, leading to the mobilization and trafficking of these cells throughout the body, including into the brain meninges (Alves de Lima *et al.*, 2020). Inflammation of the CNS (i.e. neuroinflammation) occurs once immune cells enter the brain and communicate with local glial cells (Jessen *et al.*, 2015). Thus, reprogramming of microglia and astrocytes is observed during virtually any CNS insult, including infection, traumatic injury, or exposure to metabolic toxins. Acute neuroinflammation is an essential response to clear the tissue from pathogens or debris and to promote tissue repair. However, if unresolved, it can lead to chronic CNS inflammation and neurodegeneration. However, 'over-activation' or inappropriate long-term neuroinflammation can lead to many problems, including autoimmune disease, tissue damage, cancer and psychiatric disorders, especially depression.

One remarkable finding of recent years is the fact that 'sterile inflammation' can occur in the absence of any particular antigen (Gong *et al.*, 2020). Much attention has focused on the possibility that various stressors that are linked to depressive illness elicit sterile inflammation. In this regard, it is believed that the stressor induces the production of damage associated molecular patterns (DAMPs), such as high-mobility group box 1 (HMGB1), S100 proteins, and heat shock proteins (HSPs) and even extracellular ATP from damaged cells. These DAMPs directly bind to PAMPs that are normally reserved for detection of viral, bacterial or other pathogens. Hence, this is an intriguing evolutionarily conserved mechanism through which different types of stressors might be recognized and dealt with. Intriguingly as well, long standing low-grade sterile inflammation resulting in chronic DAMP activity, which has been called 'inflammaging', might result in pathological ageing that can give rise to a number of diseases of the elderly, including dementia (Royce *et al.*, 2019). It could be that inflammaging in depressed individuals, could over time predispose towards dementia or other co-morbid disease clusters.

plasma stress hormones (adrenocorticotrophic hormone, corticosterone) and widespread alterations in brain monoamines (Brebner *et al.*, 2000; O'Brien *et al.*, 2004; Hayley *et al.*, 2008; Litteljohn *et al.*, 2014; Clark *et al.*, 2015; Hennessy *et al.*, 2017). This sickness syndrome is thought to mimic neurovegetative symptoms of human depression, such as fatigue and changes in feeding and sleep. Furthermore, pro-inflammatory cytokines sensitize stress responses to neural and hormonal factors such as corticotrophin-releasing hormone (CRH) and vasopressin. This results in long-term increases in the response to subsequent stressor exposure (Hayley *et al.*, 2001; Schmidt *et al.*, 2003; Frank *et al.*,

Box 2 Cytokine and immune cell entry in the brain

Cytokines are relatively large, soluble polypeptides that do not readily cross the blood–brain barrier. However, limited amounts can enter the brain through saturable transporters for specific cytokines, including IL-1β, TNF-α and others (Banks, 2005) or via the circumventricular organs (e.g. the median eminence and area postrema), which lack a fully functional blood–brain barrier (Blatteis, 2000). A majority of immune cells enter the brain through the meninges, via meningeal blood vessels or through the choroid plexus (Alves de Lima *et al.*, 2020). Vessel pulsing could move cytokines, other solutes or immune cells along the periarterial space into the parenchyma. The choroid plexus, which produces CSF, is fenestrated, thus allowing accumulation and easy access to the brain of cells or cytokines from circulation (Kipnis, 2016). For example, meningeal blood vessels recruit T lymphocytes and facilitate their migration across the pia mater to reach parenchyma (Radjavi *et al.*, 2014). This entry is augmented during neuroinflammatory states in response to local production of chemokines, which attract immune cells and increase endothelial cell adhesion molecules to aid immune cell infiltration. In addition to circulatory routes, cytokines can also influence central processes through afferent projection fibres, such as the visceral branches of the vagus nerve (Anisman *et al.*, 2008; Miller *et al.*, 2009). Once inside the CNS, cytokines signal through receptors on cells comprising or proximal to the brain microvasculature (e.g. endothelial cells and glia) and can penetrate deep into the brain parenchyma through volume transmission.

Immune cells may interact with local glia or may exit the CNS via specialized lymphatic drainage (Engelhardt *et al.*, 2017). Indeed, Louveau *et al.* (2015) demonstrated the existence of functional lymphatic vessels lining the dural sinuses and connected to the deep cervical lymph nodes. Immune factors might exit via the cribriform plate along the olfactory nerves and eventually reach deep cervical lymph nodes. At the lymph node these cells may engage in antigen presentation to facilitate adaptive immunity that could target brain antigens. This could be protective, but also damaging. In the case of the unmasking of brain antigens resulting from ageing and stress-induced depressive pathology, this maladaptive immunity induce neuronal damage resulting in cognitive impairment and ultimately dementia.

2012; Tuchscherer *et al.*, 2018). Sensitization in cytokine or stress response may increase vulnerability for depressive illness in response to subsequent stressors. For instance, chronic increases in pro-inflammatory cytokines, such as IL-1β or TNF-α, induce protracted neurochemical and hormonal changes, increasing behavioural vulnerability to subsequent challenges (Hayley *et al.*, 2003; Kim *et al.*, 2016). Ultimately, the timing and chronicity of immune and non-immune insults could shape the evolution of depressive pathology.

Chronic repeated immune dysregulation models aspects of lifetime exposure to various immune challenges that when paired with psychosocial or other stressors, could lay the groundwork for depression. For instance, serum levels of IL-6 and TNF-α are significantly elevated in individuals with major depression and have been associated with suicidality (Black and Miller, 2015; Marini *et al.*, 2016). Post-mortem studies have shown increased cytokine levels in the brains of depressed individuals. In particular, those who died by suicide have elevated TNF-α and IL-6 expression in the prefrontal and orbitofrontal cortices (Tonelli *et al.*, 2008; Pandey *et al.*, 2012, 2018). One recent meta-analysis found elevated CSF levels of IL-6 and TNF-α, along with increased translocator protein (TSPO, a marker of inflammation) in the anterior cingulate cortex and temporal cortex of depressed patients (Enache *et al.*, 2019). Proinflammatory cytokines can also reduce brain serotonin by stimulating indoleamine-pyrrole 2,3-dioxygenase (IDO), which metabolizes tryptophan. This results in the accumulation of toxic by-products of oxidative stress, such as quinolinic acid (Wichers and Maes, 2004; Myint and Kim, 2014), which may be a common factor linking depression and dementia (Kim and Na, 2016; Garcia-Garcia *et al.*, 2017). Serotonin itself activates immune cells (Abdouh *et al.*, 2001, 2004), increasing cytokine release from macrophages and T lymphocytes, and activating macrophage phagocytosis, while suppressing natural killer cell levels (Herr *et al.*, 2017). Thus, critical mood regulatory neurotransmitters like serotonin directly modulate specific immune cells, allowing for the co-regulation of neuro-immune processes. Antidepressants that target serotonin also impact inflammatory processes and reduce inflammatory cytokines in the serum of anxiety and depression patients (Kohler *et al.*, 2018; Hou *et al.*, 2019). Recently, by acting in the gut where 95% of body serotonin is synthesized, antidepressants have been shown in mice to increase luminal serotonin levels, altering bacterial composition to reduce bacterial infection and mediate in part antidepressant actions (Fung *et al.*, 2019; Lukić *et al.*, 2019; Kumar *et al.*, 2020), indicating that antidepressants may act not only in the brain but also in the periphery to improve depression. Taken together, these findings highlight the cross-talk between inflammatory and monoamine systems implicated in depression (Steiner *et al.*, 2013) and raise the possibility that the presence of altered microglia, immune cells and cytokines in depression may signal a specific type of 'inflammatory' depression that could accelerate the onset of dementia as discussed below.

Inflammatory insults induce a spectrum of pro-inflammatory cytokine changes that often act in an additive or synergistic manner to exacerbate stress or disease responses. For example, patients with metabolic conditions or heart disease with greatly elevated pro-inflammatory cytokines have a much greater risk of depression (Chan *et al.*, 2019). In laboratory rodent studies, the inflammatory response to injection of the bacterial mimic lipopolysaccharide (LPS) into the prefrontal cortex was further increased in rats that had also been stressed, and a modest neurodegenerative response was also evident (de Pablos *et al.*, 2006). Likewise, a

pronounced loss of hippocampal neurons was induced by the combination of a chronic stressor plus LPS treatment (Espinosa-Oliva *et al.*, 2011). Most interestingly, the combination of these insults also provoked depression-like behaviours that were dependent upon IL-1 receptor signalling (Goshen *et al.*, 2008). Similarly, LPS and other immune challenges synergistically increased the impact of stress on plasma corticosterone levels and sickness symptoms (Gandhi *et al.*, 2007; Gibb *et al.*, 2008; Litteljohn *et al.*, 2017). They also additively or synergistically enhanced mRNA expression of proinflammatory cytokines IL6, IL10 and TNF-α in the prefrontal cortex and hippocampus. Chronic stressors such as social defeat also increase brain cytokines and induce microglial activation, which exacerbates the impact of immunological challenges on depressive behaviours (Stein *et al.*, 2017; Weber *et al.*, 2019). Depletion of brain microglia protected mice from chronic stress-induced recruitment of monocytes, release of reactive oxygen species and stress-sensitive anxiety and depressive behaviours (Lehmann *et al.*, 2019; Weber *et al.*, 2019). In addition, microglial activation by complement factors (Alawieh *et al.*, 2018) or stress-induced neuronal colony-stimulating factor (Wohleb *et al.*, 2018) can directly affect neuronal integrity associated with depression and dementia. Stress induces microglial release of cytokines, activation of CX3CR1 chemokine receptors and generation of reactive oxygen species that can trigger microglia to phagocytose neuronal spines (trogocytosis) (Weinhard *et al.*, 2018), vulnerable neurons (phagoptosis) (Brown and Neher, 2014), and to trigger reactive astrogliosis for ongoing neuronal death (Liddelow *et al.*, 2017). These examples collectively show the synergistic effects of inflammatory and stress systems on brain function that can lead to depressive behaviour.

Cytokines and the blood–brain barrier

While inflammatory processes are often initiated outside the brain, it is now well established that the brain, although immune-privileged because of the blood–brain barrier, engages fundamentally with the immune system. Circulating leucocytes routinely enter the brain (albeit in limited concentrations), whereupon they perform various 'housekeeping' tasks critical for immuno-surveillance (Litteljohn *et al.*, 2014; Ellwardt *et al.*, 2016). In fact, there is a clear bi-directional relationship between the brain and immune system. Inflammatory immune changes influence neurotransmission and correspondingly, depression-induced neurochemical changes modulate immunological responses. As a result of this dynamic crosstalk, psychological stressors linked to depressive illness can also affect the immune system. When such disturbances are severe or prolonged, secondary damage may arise resulting in co-morbid illnesses with cognitive consequences.

Psychological, immunological and chemical stressors can all induce blood–brain barrier leakiness (Abdel-Rahman *et al.*, 2002; Northrop and Yamamoto, 2012) to facilitate cytokine access to the brain and contribute to depression. For example, stress-induced corticotrophin-releasing hormone release may also promote the activation of brain mast cells and resident microglia. This leads to enhanced local secretion of pro-inflammatory cytokines, chemokines (chemoattractant cytokines) and growth factors, including IL-6, IL-8/C-X-C motif chemokine ligand 8, monocyte chemoattractant protein-1 (MCP1/CCL2) and vascular endothelial growth factor (VEGF) (Esposito *et al.*, 2002; Theoharides and Konstantinidou, 2007). Exposure to stress induces bacterial translocation from the gastrointestinal tract and the activation of cytokine-producing inflammasomes in circulating myeloid cells and brain-resident glia (Zareie *et al.*, 2006; Gustin *et al.*, 2015). These microbiota induced immune changes were seen in depressed compared to normal subjects (Maes *et al.*, 2013). Pro-inflammatory cytokines can directly increase blood–brain barrier permeability, in part by upregulating endothelial cell adhesion molecules to promote lymphocyte invasion (Wong *et al.*, 1999; Varatharaj and Galea, 2017; Cheng *et al.*, 2018; Liebner *et al.*, 2018). For example, TNF-α reduces blood–brain barrier integrity and has been implicated in stressor (learned helplessness) induced blood–brain barrier permeability (Cheng *et al.*, 2018). Similarly, IL-17A increases blood–brain barrier leakiness that was related to diminished cognitive capacity in aged rodents (Ni *et al.*, 2018). Increased blood–brain barrier permeability has the dual effect of enhancing cytokine production at vascular sites in a positive feedback loop, and augmenting T-cell trafficking across the blood–brain barrier (Cayrol *et al.*, 2008; Lopes Pinheiro *et al.*, 2016). It should be noted that blood–brain barrier vulnerability can vary as a function of brain region. One study found that LPS increased permeability in the frontal cortex and brainstem compared to the hypothalamus (Banks *et al.*, 2015). Chronic social stress in mice increases blood–brain barrier permeability selectively in vulnerable brain regions, such as the nucleus accumbens (Menard *et al.*, 2017). This involves the downregulation of the important endothelial tight junction protein claudin-5, and results in IL-6 permeation into the brain. Thus, stress-induced cytokines are implicated in brain region-selective blood–brain barrier permeability that contributes to risk of depression. In addition, recent evidence shows more convincingly that the blood–brain barrier is also disrupted in mild cognitive impairment, particularly in the hippocampus and medial temporal lobe (Montagne *et al.*, 2015, 2020; Nation *et al.*, 2019). Thus, region-specific blood–brain barrier permeability may be a harbinger of both depression and dementia.

Cytokines, depression and cognitive function

In addition to their actions on blood–brain barrier permeability, chronic stress induced elevation of cytokines can

remodel or damage blood vessels. For example, activation of IL-1β and the NLRP3 inflammasome has been linked to atherosclerosis and directly damages blood vessels (Baldrighi *et al.*, 2017). In mice, chronic restraint stress induced pro-inflammatory cytokines and reduced claudin-5 levels in the cortex, leading to increased cortical blood–brain barrier permeability and reduced blood vessel diameter (Lee *et al.*, 2018). Similarly, in the ventral but not dorsal hippocampus of mice sensitive to chronic social defeat, vascular remodelling, microglial activation and proinflammatory genes were induced compared to control or resilient mice. Intraventricular administration of VEGF increased stress sensitivity, while anti-inflammatory treatment promoted stress resilience (Pearson-Leary *et al.*, 2017).

Depression may cause the same kind of inflammatory damage to blood vessels as we see with smoking, obesity, and the ageing process, all of which are associated with a chronic low-grade increase in inflammatory cytokines (Gorelick *et al.*, 2011, 2016). Some have gone so far as to suggest that depression might even reflect aspects of a prodromal state for dementias such as Alzheimer's disease (Herbert and Lucassen, 2016). It was also posited that the state of depression could sensitize the brain to further hits that could shape the evolution of dementia. Alternatively, living with chronic depression may accelerate brain ageing by causing epigenetic alterations that lead to more rapid decline in brain functions (Herbert and Lucassen, 2016).

Cytokines also have a direct impact on cognitive processes. Several studies have found that increases in pro-inflammatory cytokines IL-1β and TNF-α impair long-term potentiation, spatial learning and memory (Yirmiya and Goshen, 2011; Eyre and Baune, 2012; Lynch, 2015; Prieto *et al.*, 2019). The effects of these cytokines on hippocampal long-term potentiation were reversed by the anti-inflammatory cytokines IL-10 and transforming growth factor (TGF)-β (Lynch *et al.*, 2004; Nenov *et al.*, 2019). Pro-inflammatory cytokines also reduce hippocampal neurotrophin levels and their signalling, resulting in diminished dendritic arborization (Tong *et al.*, 2012; Golia *et al.*, 2019), as is seen in chronic stress models (Serafini *et al.*, 2014). The inflammatory microenvironment induced by such cytokines in the brain may gradually damage hippocampal and other neural circuits that underlie cognitive functions. Along these lines, increased hippocampal levels of IL-1β and TNF-α, memory impairments and depressive-like behaviours were evident in amyloid-$\beta_{1\text{-}42}$-treated rats in an Alzheimer's model, and the anti-inflammatory drug minocycline reversed these effects (Garcez *et al.*, 2017; Amani *et al.*, 2019). These findings are supported by a recent meta-analysis that found increased peripheral IL-1β levels in depressed subjects and Alzheimer's patients compared to their age-matched counterparts (Ng *et al.*, 2018). Accordingly, antidepressant treatments can reduce the incidence of Alzheimer's disease, an effect correlated with increased levels of the anti-inflammatory cytokine, TGF-β1 (Caraci *et al.*, 2018). In effect, in depressed patients the use of anti-inflammatory agents could reduce damage to systems implicated in the development of dementia.

Cytokines may also contribute to the development of depression and dementia through altering the tryptophan-kynurenine pathway (Dantzer *et al.*, 2011; Leonard, 2017). This IDO-driven pathway is strongly implicated in inflammation (e.g. LPS) provoked depressive-like sickness behaviours observed in rodents (Dantzer *et al.*, 2008; O'Connor *et al.*, 2009). Endogenous pro-inflammatory cytokines appear to underlie this process. In particular, IFN-α and TNF-α promote the production of quinolinic acid, a neurotoxic by-product of this pathway. Quinolinic acid induces oxidative stress leading to neural and glial damage (Ting *et al.*, 2009) and eventually resulting in dementia or other pathologies (Lovelace *et al.*, 2017).

In addition to peripheral cytokine and immune changes (Dowlati *et al.*, 2010; Kohler *et al.*, 2017), post-mortem studies in human brain have detected inflammatory cytokines and microglial activation markers in depression and suicide (Enache *et al.*, 2019). In addition, several post-mortem studies have shown reduced density, activity and altered morphology of astrocytes in the frontal cortex, amygdala, and hippocampus of depressed individuals (Rajkowska and Stockmeier, 2013; Mechawar and Savitz, 2016; Torres-Platas *et al.*, 2016). Along these lines, targeted pharmacological ablation of astroglia has been shown to induce depressive-like behaviour in rodents (Banasr and Duman, 2008).

Cytokines as markers of inflammatory depression

To identify inflammatory depression in patients diagnosed with depression, serum cytokine levels should be elevated. However, caution should be exercised when considering the possibility of using cytokines as biomarkers for depression. Indeed, cytokines are altered in other psychiatric disorders and affected by many environmental factors, and are thus unlikely to be specific markers. Although cytokines correlate with some subtypes of depression, they may not associate with the behavioural criteria used in current diagnostic manuals (Himmerich *et al.*, 2019). Improved diagnostic approaches might strengthen the use of cytokines as biomarkers for a new 'cytokine-associated' subtype of depression. This subtype of depression would likely have prominent neurovegetative features. These could include feeding and sleeping disturbances, as well as general malaise (Maes *et al.*, 2012). For example, the depressive features elicited in cancer patients receiving IFN-α immunotherapy were associated with such somatic symptoms (Su *et al.*, 2019). Cytokines may also be involved in subtypes of depression that have associated cognitive features, such as impaired concentration and trouble learning new routines. Indeed, maladaptive neuroinflammatory processes may underlie the cognitive deficits observed in

depression and other psychiatric disorders (Fourrier *et al.*, 2019). These associations suggest a new 'inflammatory-cognitive' subtype of depression that could inform patient-specific treatment options. These could include use of adjunctive anti-inflammatory medications (see below) together with traditional neurotransmitter-targeting antidepressant drugs. Since chronic inflammatory activation compromises vascular function, such individuals might also be at greater risk to progress to 'vascular' depression and dementia.

Anti-inflammatory and antidepressant agents for depression and dementia

Targeting cytokines to treat inflammatory depression

Clinical administration of IFN-α can elicit depressive-like behaviour (anhedonia) in patients undergoing immunotherapy for hepatitis C or melanoma (Raison *et al.*, 2010; Felger *et al.*, 2016). Importantly, antidepressant treatment attenuated IFN-α-induced depression (Raison *et al.*, 2007), and is used prophylactically at the start of IFN-α immunotherapy (Udina *et al.*, 2014). These observations indicate that pro-inflammatory cytokines can induce depression-like behaviour in human subjects that involves brain systems like the serotonin system that are targeted by antidepressants. But is the converse true; can anti-cytokine treatments be used to treat depression?

Standard antidepressants are only effective in a proportion of patients (~50–66%), and this could be related to inflammatory processes that are not directly targeted by such treatments. Accordingly, recent studies have focused on the possibility that anti-inflammatory agents might have clinical utility as adjuvants in the treatment of depression. There is already evidence that IFN-treated autoimmune patients who received TNF-α inhibitors (antagonist etanercept or neutralizing antibody infliximab) had reduced depressive symptoms (Kekow *et al.*, 2011; Raison *et al.*, 2013). One meta-analysis found that TNF-α inhibition modestly reduced depressive ratings (Kappelmann *et al.*, 2018). Another found that patients with major depression responsive to antidepressant treatment had diminished TNF-α and IL-8 levels, relative to non-responders (Liu *et al.*, 2020). A third meta-analysis found that various antidepressant treatments reduced IL-4, IL-6, and IL-10 and selective serotonin reuptake inhibitors (SSRIs) specifically reduce IL-1β circulating levels while IL-2, TNF-α, IFN-γ and CRP were not significantly altered (Więdłocha *et al.*, 2018). An assessment of 36 randomized clinical trials revealed that anti-inflammatory agents [including non-steroidal anti-inflammatory drugs (NSAIDs), minocycline, cytokine inhibitors, statins and glucocorticoids] are effective in augmentation studies with traditional antidepressants, and even as monotherapy in milder cases of depression (Köhler-Forsberg *et al.*, 2019). Similarly, NSAIDs diminish depressive-like effects in rodents (Asnis and De La Garza, 2006) and augment antidepressant efficacy (Köhler-Forsberg *et al.*, 2019). Conversely, an earlier meta-analysis found that NSAIDs had 'negligible' effects on depression (Eyre *et al.*, 2015), while a more recent one has found beneficial effects (Bai *et al.*, 2020). Some have argued that the effectiveness of SSRIs could be diminished by anti-inflammatory agents (Warner-Schmidt *et al.*, 2011). It is likely that the lack of specificity of NSAIDs makes them generally unsuitable as adjuvants for treatment of depression. Indeed, a cytokine-targeted approach would likely be far more suitable.

In this regard, many have turned to specific cytokine ligands or other immunomodulatory factors. In particular, genetic or pharmacologic inhibition of pro-inflammatory cytokines can mitigate the pro-depressive effects of LPS and various stress paradigms in rodents (e.g. chronic variable or restraint stress, social defeat). For instance, Koo and Duman (2008) reported that IL-1β signalling blockade via treatment with an IL-1β receptor inhibitor or the use of IL-1 receptor knockout (KO) mice mitigated the deleterious effects of stress on hippocampal neurogenesis and hedonic responding. Similarly, administration of the TNF-α antagonist infliximab attenuated depression- and anxiety-like symptoms in rats exposed to chronic mild stress (Karson *et al.*, 2013). Voorhees *et al.* (2013) showed that chronic restraint-induced behavioural despair was ameliorated by exogenous application of IL-10. Consistent with this finding, IL-10 null mice exhibited depressive-like behaviour that was responsive to IL-10 treatment, whereas transgenic mice overexpressing this cytokine displayed an antidepressant-like phenotype (Mesquita *et al.*, 2008).

Increasing evidence suggests that immunomodulation may contribute mechanistically to the therapeutic action of antidepressant drugs. Indeed, several commonly used antidepressants, including SSRIs, reduce pro-inflammatory cytokines (e.g. IL-1β, IL-6, TNF-α) and/or increase anti-inflammatory ones (e.g. IL-4, IL-10) (Himmerich *et al.*, 2010). New and emerging antidepressants, including the *N*-methyl-D-aspartate receptor antagonist ketamine, also possess rapid and potent immunomodulatory properties (Chang *et al.*, 2009; Nowak *et al.*, 2019; Verdonk *et al.*, 2019). Ketamine-induced reductions in proinflammatory serum cytokines were correlated with improvement in depression symptoms in one trial (Chen *et al.*, 2018), but not in another (Park *et al.*, 2017). Indeed, ketamine attenuated the LPS-induced increase in hippocampal IL-1β and TNF-α levels, while concomitantly increasing adult hippocampal neurogenesis (Clarke *et al.*, 2017).

Given the role of immune dysregulation in depression, several studies have assessed whether anti-inflammatory treatment can improve depression. A recent meta-analysis of anti-inflammatory trials confirmed their antidepressant activity, particularly in augmenting monoamine-targeted antidepressants (Bai *et al.*, 2020). Anti-inflammatory agents tested

included NSAIDs, omega-3 fatty acids, statins and minocycline. Similarly, another meta-analysis showed that a high quality diet (e.g. Mediterranean) reduces the risk of depression (Molendijk *et al.*, 2018). Healthy diets are also known to improve inflammatory immune functioning and diminish cardiovascular risk factors, leading to improved cognitive outcomes (Widmer *et al.*, 2015). Even a short (3-week) diet intervention in adolescence may blunt some, albeit modest, depressive symptoms (Francis *et al.*, 2019). Prescreening for inflammatory markers or indoleamine-2,3-dioxygenase in blood may indicate those patients most responsive to anti-inflammatory treatment (Kopschina Feltes *et al.*, 2017), although this remains to be tested. If validated, inflammatory screening could provide a quantitative method to identify inflammation-related psychiatric disorders. This could lead to the transformative development of personalized medicine approaches targeting specific inflammatory processes.

But do anti-inflammatory drugs improve dementia? This question remains highly controversial. Accumulating evidence suggests that dementia is associated with a chronic inflammatory state. For instance, as an example, one recent study found that increased levels of LPS-like peptides were associated with increased incidence of Alzheimer's disease (Andre *et al.*, 2019). Although early clinical trials of NSAIDs showed some reduction in Alzheimer's disease incidence in pre-symptomatic subjects (Breitner *et al.*, 2011), more recent studies found no benefit of NSAIDs for Alzheimer's disease progression (Meyer *et al.*, 2019). A more targeted approach that involves only specific immune factors may be advantageous. This could involve more specific immunomodulatory treatments or possibly those that target certain cytokines. For instance, patients receiving etanercept or other drugs targeting TNF-α for treatment of rheumatoid arthritis show reduced rates of depression, suggesting a potential benefit (Chou *et al.*, 2016). However, no clinical trial has addressed whether TNF-α antagonists can delay or prevent dementia. Because etanercept does not normally cross the blood–brain barrier, its effect may be limited. In support of this, an anti-TNF-α antibody engineered to enter the brain was more effective than etanercept in improving cognitive performance in several mouse models of Alzheimer's disease (Chang *et al.*, 2017). It may be that early intervention before blood–brain barrier permeability is affected with anti-inflammatory compounds that can enter the brain will be more effective for dementia. Clinical subgroups with inflammatory depression may provide a target population to test whether effective anti-inflammatory treatment of the depression also delays the onset of dementia.

Can antidepressant strategies alleviate dementia?

As discussed above, lifetime depression is a risk factor (1.5-fold) for dementia (Chan *et al.*, 2019). Furthermore, persistent affective disorders have been associated with mid- and late-life cognitive impairments (James *et al.*, 2018; John *et al.*, 2019). This raises the question of whether antidepressant treatments may reduce or delay dementia, or at least diminish cognitive impairment. Studies in rodents subjected to chronic stress or following a focal stroke support this contention. Chronic treatment of these rodent models with antidepressants like fluoxetine not only reverses anxiety and depressive phenotypes, but also improves cognitive impairment (Gottschalk *et al.*, 2018; Vahid-Ansari and Albert, 2018). More recent evidence indicates that SSRIs might also reverse depressive-like and cognitive impairments in animal models of Alzheimer's disease, such as amyloid-β treated mice (Torrisi *et al.*, 2019). In other mouse models of Alzheimer's disease (including 3xTgAD, APPswe/PSEN1dE9) and Down syndrome (Bianchi *et al.*, 2010), chronic SSRI treatment, especially during adolescence, similarly improved cognitive outcomes in adulthood (Jin *et al.*, 2017; Ma *et al.*, 2017; Sun *et al.*, 2017). The mechanisms responsible for the cognitive improvement elicited by antidepressants may involve reduced activation of glial cells (Qiao *et al.*, 2016) or enhanced neurotrophin activity (Ma *et al.*, 2017; Sun *et al.*, 2017).

In human studies, monoamine-targeted antidepressants appear to reduce the death rate in older Alzheimer's patients, although the mechanisms are unclear (Kollhorst *et al.*, 2019). A few studies have found that antidepressants can exacerbate dementia (Moraros *et al.*, 2017; Chan *et al.*, 2019). However, a recent meta-analysis found that while short-term fluoxetine treatment (<4 weeks) may have detrimental effects, longer-term treatment (8–12 weeks) reduced cognitive deficits in Alzheimer's and vascular dementias (Xie *et al.*, 2019). Similarly, fluoxetine-induced cognitive improvement was seen in vascular dementia patients and was correlated with an increase in brain-derived neurotrophin levels (Liu *et al.*, 2014). Like their short-term anxiety provoking effects in some patients, the deleterious effects of antidepressants in dementia might be relatively transient. Thus, chronic antidepressant treatment may be necessary before the beneficial effects on cognition are seen, as is the case for improvement in depression. Taken together, these studies support the early and sustained use of monoamine-directed antidepressants to manage depression as a way to reduce the risk of progressive cognitive impairment and dementia.

Conclusion

Clinical and epidemiological data indicate that depression and dementia often occur together. Indeed, loneliness and other elements of depression may precede and worsen the progression of dementia. This comorbidity may involve in part the combined effects of chronic stress and inflammation that lead to inflammatory depression. The examples given illustrate the concept that chronic inflammation can hasten and exacerbate the effects of other risk factors for depression and/or dementia, such as stress, vascular or brain injury. A variety of mechanisms can contribute to stress- and

inflammation-related vulnerability. These include increases in blood–brain barrier permeability, microglial activation, and of pro-inflammatory cytokine levels in vulnerable regions of the brain. These changes increase free radicals and reduce neurotrophin function, contributing to a loss of neurons and glia. Over time, the brain damage wrought by these mechanisms may lead to cognitive decline and dementia. This raises the possibility that treating the root causes of inflammatory depression may protect against dementia. Use of serum cytokine biomarkers may help to identify patients with inflammatory depression. It is likely that persistent elevation of combinations of pro-inflammatory cytokines will be implicated in inflammatory depression. These patients could be treated with clinically approved anti-inflammatory agents or cytokine inhibitors. Standard antidepressants that target monoamines may also protect the brain from the effects of chronic inflammation. In combination, antidepressants that target both inflammation and depression may delay or prevent dementia in selected patient populations.

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Competing interests

The authors report no competing interests.

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