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Publication Date

2022-07-01

DOI

10.1016/j.brat.2022.104104

Peer reviewed

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Behaviour Research and Therapy 154 (2022) 104104

Contents lists available at ScienceDirect

Behaviour Research and Therapy

journal homepage: www.elsevier.com/locate/brat

Psychoneuroimmunology in the time of COVID-19: Why neuro-immune interactions matter for mental and physical health

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A B S T R A C T

The brain and immune system are intricately connected, and perturbations in one system have direct effects on the other. This review focuses on these dynamic psychoneuroimmune interactions and their implications for mental and physical health in the context of the COVID-19 pandemic. In particular, we describe how psychological states influence antiviral immunity and the vaccine response, and how immune changes triggered by COVID (either via infection with SARS-CoV-2 or associated stressors) can influence the brain with effects on cognition, emotion, and behavior. We consider negative psychological states, which have been the primary focus of psychological research in the context of COVID-19 (and psychoneuroimmunology more generally). We also consider positive psychological states, including positive affect and eudaimonic well-being, given increasing evidence for their importance as modulators of immunity. We finish with a discussion of interventions that may be effective in improving immune function, the neuro-immune axis, and ultimately, mental and physical health.

1. Introduction to the immune system and brain-immune interactions

The immune system is designed to detect and protect the body from infection, injury, and damage. The immune system has two arms: innate and adaptive. The innate immune system responds quickly to a wide range of pathogens (disease-causing microorganisms such as viruses and bacteria) and danger signals, whereas the adaptive immune system responds more slowly and is targeted to a particular pathogen. Under optimal conditions, these two arms work together to identify and eradicate pathogens. For example, in the context of viral infection, the innate immune system mounts a rapid response that includes production of specific types of cytokines (proteins that facilitate communication between cells), including Type I interferons (IFNs). This response is important for restricting viral replication within infected cells, limiting the spread of infection in the local environment, and mobilizing the adaptive immune response. The adaptive branch of the immune system includes T cells, which kill virally infected cells, as well as B cells, which make antibody to neutralize the virus. This second wave of response ideally manages the systemic infection and also generates memory cells that can respond more rapidly to reinfection with the same virus. This immune response is carefully calibrated to eradicate pathogens while doing minimal damage to the body.

Our understanding of the immune response to SARS-CoV-2 has rapidly developed since the beginning of the pandemic and will undoubtedly continue to evolve. Recent work suggests that some of the pathology of this virus may be due to: 1) efficient evasion of the innate immune system by the virus; and/or 2) ineffective IFN innate immunity (Sette & Crotty, 2021). This leads to a delayed or inadequate initial response by the innate immune system and allows the virus to proliferate before the adaptive immune system can be mobilized. In more serious cases of COVID-19, the adaptive immune response is also impaired; this not only allows the virus to continue replicating, but also leads to continued activation of the innate immune system, which may ultimately cause more harm than good (Sette & Crotty, 2021). In particular, an overactive inflammatory response may underlie the serious respiratory problems seen in more severe cases of COVID, and may also contribute to long COVID.

In addition to biological processes, psychological and behavioral factors might influence these immune dynamics and ultimately, the course of viral infection. Research in psychoneuroimmunology (PNI) has documented close connections between the brain and the immune system, which work together to keep the organism safe from infection and injury. Messages from the central nervous system are communicated to cells and organs of the immune system through the autonomic nervous and neuroendocrine systems; indeed, the discovery that the autonomic

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https://doi.org/10.1016/j.brat.2022.104104
Received 23 December 2021; Accepted 25 April 2022
Available online 6 May 2022

nervous system innervates key immune organs (lymph nodes, spleen) was an important step in establishing neural regulation of immunity (Felten & Felten, 1988). Immune cells also have receptors for hormones of the endocrine system, including glucocorticoids and catecholamines (among others). Further, the immune system relays information to the CNS, allowing the organism to make changes in behavior that support immune function.

2. Effect of negative psychological states on the immune system

Research conducted over the last several decades has documented effects of a variety of psychological states on immunity. In this section, we review PNI research on the top-down effects of negative psychological states on the immune system, with a focus on how these states influence antiviral immunity and the immune response to vaccination. We consider both preclinical and clinical models, including studies using experimental viral inoculation to interrogate links between behavior and immunity in vivo. Studies examining links between psychosocial factors and immunity among individuals infected with SARS-CoV-2 are not yet available. However, there is compelling evidence that individuals with mental disorders are at increased risk for COVID-19-related hospitalization and mortality (Vai et al., 2021; Wang, Xu, & Volkow, 2021), supporting the relevance of negative psychological states for immune defense against SARS-CoV-2.

Stress: The field of PNI is founded on studies examining links between stress and the immune system. This work is particularly relevant in the context of COVID, which combines all elements of a major stressor: the pandemic is unpredictable, uncontrollable, has generated tremendous fear, loss, and grief, created social and political turmoil, and disrupted almost all aspects of daily life. The effect of stress on antiviral immunity have been elegantly demonstrated in preclinical research, including studies with rodents using restraint stress as a model (Sheridan et al., 1998). This program of work has shown that restraint stress activates the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system, leading to suppression of virus-specific T and B cell responses that ultimately result in more severe viral infection (Sheridan et al., 1998). In nonhuman primates, stress is associated with increased sympathetic innervation of lymph nodes and accelerated progression of simian immunodeficiency virus (SIV), the primate version of HIV (Sloan et al., 2007). In humans, stressors ranging from examination stress to caregiving for a spouse with dementia have been shown to impair aspects of the adaptive immune response relevant for viral infection (Glaser & Kiecolt-Glaser, 2005). Further, studies in which individuals are exposed to a cold or influenza virus have shown that those under chronic stress are more likely to develop upper respiratory infections (Cohen, 2021). These effects extend to vaccine response, such that stressed individuals mount a diminished antibody response to vaccination (Madison, Shrout, Renna, & Kiecolt-Glaser, 2021).

In addition to effects on the adaptive immune system, stress leads to alterations in innate immunity. Short-term stressors stimulate the inflammatory response, leading to increases in proinflammatory cytokines and stimulated cytokine production (Marsland, Walsh, Lockwood, & John-Henderson, 2017). Acute stress also increases expression of proinflammatory cytokine genes and genes supporting innate antiviral responses (e.g., Type 1 interferons) (MacCormack et al., 2021). Chronic stress is also associated with up-regulation of genes involved with inflammation but with *down*-regulation of genes involved in Type I interferon responses. This profile, called the conserved transcriptional response to adversity (CTRA), has been observed across a range of stressors and is driven by activation of the sympathetic nervous system (Cole, 2019). Of note, both impaired IFN innate immunity and increased inflammation would be expected to promote more severe illness in the context of SARS-CoV-2 infection (Sette & Crotty, 2021).

Social isolation and conflict: The COVID pandemic has profoundly disrupted social connections at many levels (personal, professional, and community), leading to a three-fold increase in severe loneliness (O'Sullivan et al., 2021). Loneliness is a potent risk factor for poor health and is associated with pronounced changes in neuroendocrine and immune function (Cacioppo, Cacioppo, Capitanio, & Cole, 2015). In particular, lonely individuals show decreases in antiviral and antibody-related immune responses, increased inflammation, and impaired immune response to vaccination (Cole, Capitanio, et al., 2015; Pressman et al., 2005; Smith, Gavey, Riddell, Kontari, & Victor, 2020). The implications of these effects for viral illness have been clearly demonstrated in studies of HIV and the common cold. For example, in a rhesus macaque model of perceived social isolation (PSI), high-PSI animals showed down-regulation of Type I and Type II interferons and impaired response to infection by the simian immunodeficiency virus (Cole, Capitanio, et al., 2015). Similarly, socially inhibited men with HIV showed faster progression from HIV to AIDS, earlier mortality, and poorer response to antiviral medication (Cole, 2008). Social isolation, as indicated by fewer social contacts, also increases risk for developing a cold after experimental viral exposure (Cohen, 2021).

In addition to the absence of social contacts, social conflict is associated with alterations in immunity. Among married couples, hostile interactions are associated with negative changes in several aspects of adaptive immune function and increased systemic inflammation (Kiecolt-Glaser, 2018). Of note, these dyadic processes may worsen during the pandemic secondary to COVID-related stress (Pietromonaco & Overall, 2021). Conflict and mistrust in social relationships has also been associated with elevated inflammation in adolescents, indicating that immune effects of social stress (and other forms of stress) can be observed across the lifespan (Chiang et al., 2019; Miller, Rohleder, & Cole, 2009). Indeed, adverse childhood experiences are strongly linked to immune alterations which may persist for years and ultimately contribute to elevated morbidity and mortality (Baumeister, Akhtar, Ciufolini, Pariante, & Mondelli, 2016; Kuhlman, Chiang, Horn, & Bower, 2017; Kuhlman, Horn, Chiang, & Bower, 2020).

Social determinants of health: The pandemic has brought racial and socioeconomic inequities into sharp relief, with higher rates of COVID among communities of color and those of lower SES. These effects can also be observed at the level of the immune system. There is a robust association between SES and inflammation, with those of lower SES showing higher levels of circulating and genomic markers of inflammation (Muscatell, Brosso, & Humphreys, 2020). Low SES has also been associated with decreases in antiviral immunity (Levine, Crimmins, Weir, & Cole, 2017), and increases the likelihood of developing a cold after viral exposure (Cohen, 2021). Experiences of discrimination are also linked to elevated inflammatory activity across the lifespan and may account in part for elevated levels of inflammation observed in Black individuals (Beatty Moody, Brown, Matthews, & Bromberger, 2014; Lewis, Aiello, Leurgans, Kelly, & Barnes, 2010; Thames, Irwin, Breen, & Cole, 2019).

3. Positive psychological states and immunity

Although research in PNI has primarily focused on stress and other negative psychological states, there is growing recognition that positive psychological states may also modulate the immune system and neuroimmune interactions (Bower, Kuhlman, Haydon, Boyle, & Radin, 2019). Here, we consider how positive psychological states, including positive affect, eudaimonic well-being, and social connection/support, are linked with antiviral immunity and inflammation.

Positive affect (PA): Perhaps surprisingly, many individuals are able to maintain relatively high levels of PA during stressful experiences. Indeed, longitudinal studies have shown no change or even increases in PA during the pandemic (Barcellos, Jacobson, & Stone, 2021; Ebert, Bernstein, Carney, & Patrick, 2020). PA has been linked with both mental and physical health, and there is compelling evidence that PA is associated with enhanced antiviral immunity (Pressman, Jenkins, & Moskowitz, 2019). For example, dispositional PA predicted a stronger antibody response to hepatitis B vaccination, lower risk of developing an

upper respiratory infection following infection with a cold or influenza virus, and lower risk of AIDS-related mortality (Cohen, Alper, Doyle, Treanor, & Turner, 2006; Marsland, Cohen, Rabin, & Manuck, 2006; Moskowitz, 2003). PA is also associated with lower levels of circulating inflammatory markers, lower stimulated production of proinflammatory cytokines by immune cells (a measure of inflammatory potential), and reduced inflammatory activity in the laboratory and in daily life (Bower et al., 2019). Importantly, associations between PA and immunity are maintained in analyses controlling for negative affect, demonstrating that PA has a unique link with the immune system.

Unlike stress, there are no validated methods for assessing or eliciting PA in preclinical models. However, investigators have manipulated activity in reward-related neural regions and examined effects on immunity. In one report, activation of dopaminergic neurons in the ventral tegmental area using DREADDs (Designer Receptors Exclusively Activated by Designer Drugs) led to increased innate and adaptive immune responses to bacterial infection (Ben-Shaanan et al., 2016). These findings are consistent with a recent study showing links between activation of reward-related neural regions and changes in inflammatory markers in breast cancer survivors (Dutcher, Boyle, Eisenberger, Cole, & Bower, 2021).

Finding meaning and eudaimonic well-being: Despite (or perhaps because of) the life disruption and distress that accompanies stressful life events, many individuals are able to find positive meaning or benefit from these experiences (Stanton, Bower, & Low, 2006; Tedeschi & Calhoun, 2004). These benefits include enhanced interpersonal relationships, greater appreciation for life, a sense of increased personal strength, greater spirituality, and valued change in life priorities or goals. Initial reports suggest that many individuals are able to find some benefit from the COVID-19 pandemic. For example, in a sample of 1175 individuals in New Zealand, two-thirds reported finding a "silver lining" from the pandemic (Jenkins et al., 2021).

Finding meaning or benefit following stress is thought to promote psychological adjustment (Taylor, 1983; Tedeschi & Calhoun, 2004), and has also been linked with antiviral immunity. In an early study of men with HIV who had lost a close friend or partner to AIDS, those who reported finding meaning from the loss showed higher T cell levels and lower AIDS-related mortality (Bower, Kemeny, Taylor, & Fahey, 1998). A recent report also found that meaning in life predicted greater survival in a diverse sample of individuals with HIV (Ironson, Verhagen, da Rosa, & Hylton, 2021). Further, among women who had lost their mothers to breast cancer, those who rated meaning-related goals as more important had higher levels of natural killer (NK) cell activity; these cells are an important component of the immune system's defense against viruses (Bower, Kemeny, Taylor, & Fahey, 2003).

A sense of meaning and purpose in life is one component of eudaimonic well-being, a broader construct that also includes self-acceptance, mastery, autonomy, positive relationships, and the potential for personal growth as well as social coherence, acceptance, and contribution (Keyes, 2002; Ryff, 2014). Eudaimonic well-being is associated with lower CTRA gene expression in middle-aged and older adults in the US and other countries, even after controlling for positive affect and measures of distress (Cole, Levine, et al., 2015; Fredrickson et al., 2013, 2015; Kitayama, Akutsu, Uchida, & Cole, 2016).

Social connection and support: There is a large literature demonstrating beneficial effects of social relationships on mental and physical health, including measures of immunity. Of potential relevance for COVID, early studies found that social support was associated with enhanced NK cell activity and measures of adaptive immune function (Baron, Cutrona, Hicklin, Russell, & Lubaroff, 1990; Esterling, Kiecolt-Glaser, & Glaser, 1996; Uchino, Cacioppo, & Kiecolt-Glaser, 1996). A larger body of research has documented links between social support, social integration, and lower levels of inflammation (Kiecolt--Glaser, Gouin, & Hantsoo, 2010; Uchino et al., 2018). Social support is also associated with stronger immune response to hepatitis B vaccination in medical students, although the broader literature on social support and response to vaccination is more mixed (Glaser et al., 1992; Uchino, Landvatter, Zee, & Bolger, 2020).

In addition to these direct links with immunity, social support may *buffer* the negative effects of stress on the immune system. For example, in a study of adolescents, social support buffered the detrimental effect of examination stress on NK cell activity (Kang, Coe, Karaszewski, & McCarthy, 1998). Further, social support buffered the negative effect of caregiver stress on measures of adaptive immunity in older adults (Kiecolt-Glaser, Dura, Speicher, Trask, & Glaser, 1991). Social relationships may also buffer effects of lower socioeconomic status; indeed, maternal warmth buffered the association between childhood SES and adult inflammation, and positive relationships with parents buffered the association between childhood SES and development of a cold after viral infection in adulthood (Chen, Miller, Kobor, & Cole, 2010; Cohen, Chiang, Janicki-Deverts, & Miller, 2020).

One recent study used a nonhuman primate model to examine the immune effects of "shelter in place" (SIP) policies, which have been widespread during the pandemic, and how social interaction may ameliorate these effects (Cole et al., 2021). Adult male rhesus macaques were moved from communal field cage communities to individual indoor shelters for two weeks, which led to pronounced decreases in Type I interferon gene expression. After a recovery period, the same animals were subject to a second period of SIP; however, this time each animal was co-housed with a novel juvenile macaque. Co-habituation reversed the detrimental effects of SIP on gene expression, demonstrating the promise of prosocial approaches for enhancing antiviral immunity. Of note, the adult macaques spent only 23% of their time directly interacting with juveniles (in grooming or play); the other 51% was spent in the same cage, and 26% was spent apart from the juvenile (in their adjacent shelters). This situation is quite different from the demands of parenting young children experienced by many during pandemic lockdowns and periods of virtual schooling.

4. Effects of the immune system on the brain and behavior

Communication between the brain and the immune system is a two-way street; just as psychological states can influence the immune response, so too can activation of the immune system influence the brain and behavior. These bi-directional interactions are highly relevant in the context of COVID, as both infection with SARS-CoV-2 and pandemic-related stress may stimulate the immune system, leading to alterations in mood, cognition, and behavior. These effects may be subtle or more pronounced, depending on the nature of the immune stimulation and characteristics of the host that modulate the neuro-immune network. In this section, we review evidence for immune effects on psychological states and behavior, focusing on emerging research on long COVID.

Inflammation and "sickness behavior": When exposed to pathogens or other immune triggers, cells of the innate immune system release proinflammatory and antiviral cytokines. In addition to effects on the local environment, inflammatory cytokines signal the central nervous system where they lead to a variety of behavioral changes called "sickness behavior." These changes have been well-characterized in animal models and include decreased motor activity, social withdrawal, reduced food and water intake, and increased slow wave sleep (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008). Sick animals also exhibit depressive-like behaviors, including increased immobility in the forced swim and tail suspension tests, reduced preference for saccharin solutions (indicating anhedonia), and reduced incentive motivation (Lasselin, Lekander, Benson, Schedlowski, & Engler, 2021). In humans, studies using endotoxin and other immune stimulants to trigger an inflammatory response have documented similar effects. Experimental immune activation leads to acute increases in depressed and anxious mood, social disconnection, fatigue, cognitive disturbance, and psychomotor slowing, as well as attenuated reward processing, increased reactivity to negative-valenced experiences (i.e., stress, threat, conflict) and corresponding changes in neural regions involved in emotion regulation,

processing, and interoception (Dooley et al., 2018; Lasselin et al., 2021). Importantly, although these changes are most notable following administration of endotoxin (which elicits a large inflammatory response), smaller changes in peripheral inflammation induced by vaccination also lead to changes in symptoms and underlying neural activity. For example, vaccine-induced increases in the proinflammatory cytokine IL-6 are associated with mood deterioration and alterations in subgenual cingulate activity and mesolimbic connectivity following typhoid vaccination, as well as increases in depressed mood and confusion following influenza vaccination (Harrison et al., 2009; Kuhlman et al., 2018).

In the short term, these effects are thought to be adaptive, promoting conservation of energy (to support the immune response), social isolation (to minimize spread of infection), and hypervigilance (to minimize threat of future attack) (Miller & Raison, 2016). However, chronic inflammation may lead to more persistent and severe symptoms, including episdodes of major depressive disorder. Indeed, low grade inflammation predicts the development of depression, elevations in proinflammatory cytokines are observed in a subgroup of individuals with depression, and anti-inflammatory therapies are effective in treating depression in those with elevated inflammation (Miller & Raison, 2016). Interestingly, a recent study found that higher levels of pre-pandemic inflammation (as indexed by C reactive protein, a marker of systemic inflammation) was associated with a 40% greater chance of developing depressive symptoms during the pandemic (Hamilton, Cadar, & Steptoe, 2021). Elevated inflammation has also been observed among individuals with other psychiatric disorders (e.g., anxiety, schizophrenia) as well as those with other disease-related symptoms (e.g., cancer-related fatigue), demonstrating the transdiagnostic relevance of inflammatory activity (Bower, 2019; Miller & Raison, 2016).

5. Long COVID: infection and stress-induced immune effects on the brain

Infection with SARS-CoV-2 directly activates the innate immune system, leading to release of proinflammatory cytokines that may propagate to the brain to induce "sickness behavior", including profound fatigue. For many individuals, these effects are limited to the acute stage of infection and immune response and subside within 4 weeks after symptom onset. However, some individuals experience more persistent symptoms, referred to as "post acute COVID syndrome", "long haul COVID", or simply "long COVID", the term we use here. Symptoms of long COVID are observed across physiological systems and include disturbances in respiratory, cardiovascular, and psychiatric/behavioral function (Nalbandian et al., 2021). The prevalence of long COVID varies across reports depending on the nature of the sample, assessment approach, and symptom of interest. Studies conducted with individuals who were hospitalized for COVID and those recruited from long COVID clinics have generally yielded higher prevalence estimates than studies conducted with community-based samples of individuals with confirmed SARS-CoV-2 infection. For example, 87% of patients attending a post-acute COVID clinic in Italy reported at least one symptom two months after hospital discharge (Carfì, Bernabei, & Landi, 2020), whereas 3–11% of previously-infected individuals involved in a population-based registry in the United Kingdom reported at least one symptom three months after diagnosis (Office for National Statistics, United Kingdom, 2021). Notably, although illness severity is associated with long COVID, individuals with milder cases of COVID may also experience persistent symptoms (Yong, 2021). There is growing evidence that host factors, including demographic factors (age, sex) but also psychiatric history, may influence the emergence and duration of these symptoms (Nalbandian et al., 2021).

Long COVID symptoms are hypothesized to stem in part from unresolved peripheral inflammation following infection (Yong, 2021). Here, we focus on three key symptoms that have been shown to be affected by inflammation – depressed mood, fatigue, and cognitive dysfunction – and review emerging studies that have examined links with inflammation in the context of COVID-19. We also consider stress as a risk factor, both as an elicitor of the inflammatory response (introducing a "double hit" of psychological and viral challenge) and as a moderator of the association between inflammation and behavior.

Depression: Depression is common among COVID survivors. For example, in a large survey study of US adults, 52% of those with previous COVID infection met criteria for moderate depression on the PHQ-9 (Perlis et al., 2021). Early studies with hospitalized COVID patients in Italy suggest that inflammation may contribute to post-COVID depressive symptoms; inflammation during hospitalization for COVID predicted depressive symptoms one month (Mazza et al., 2020) and three months after discharge (Benedetti, Mazza, et al., 2021; Mazza et al., 2021) with corresponding alterations in brain structure and connectivity (Benedetti, Palladini, et al., 2021). Further, patients who received medications that block the effect of proinflammatory cytokines IL-6 and IL-1β (tocilizumab and anakinra, respectively) exhibited fewer depressive symptoms following hospitalization (Benedetti, Mazza, et al., 2021).

Fatigue: One of the most common and persistent long COVID symptoms is fatigue. A recent meta-analysis of 68 studies found that 27–37% of patients previously infected with SARS-CoV-2 report fatigue at least three months after diagnosis (Ceban et al., 2021). Prevalence estimates are even higher among previously hospitalized patients; for example, 63% of previously hospitalized COVID patients in China reported fatigue 6 months after discharge (Huang et al., 2021). Another meta-analysis examining duration of long COVID symptoms found that fatigue may continue to be a problem for more than 12 months post-infection (Alkodaymi et al., 2022). In terms of associations with inflammation, an initial study of 128 patients seen at an outpatient post-COVID clinic found no association between fatigue and inflammatory markers, including CRP and IL-6 (Townsend et al., 2020). However, fatigue is associated with elevated inflammatory markers in the context of other disorders (Bower, 2019), and additional work is needed to further interrogate this association in the context of COVID-19.

Cognitive dysfunction: Described as "COVID brain fog" by patients, cognitive dysfunction is another common symptom of long COVID. A recent meta-analysis of 43 studies found that 17–28% of patients either report or exhibit cognitive impairment at least three months following COVID diagnosis (Ceban et al., 2021). Studies using objective neuropsychological assessment show deficits in processing speed and executive functioning, verbal fluency, and memory encoding and recall (Becker et al., 2021), with some evidence of corresponding neural alterations (Hellgren et al., 2021). Initial studies have found that performance on neuropsychological tests is linked with inflammation among individuals with long COVID, such that those who perform more poorly have elevated inflammatory markers (Mazza et al., 2021; Zhou et al., 2020). To our knowledge, there has yet to be a study examining associations between inflammatory markers and subjective cognitive problems in long COVID.

Stress as a risk factor: Given that stress activates the inflammatory response, long COVID might be conceptualized as the result of a "double hit" (psychological plus viral inflammatory stimuli). Indeed, there is evidence demonstrating the synergistic effects of psychological stress and infection on inflammation in the context of vaccination (Brydon et al., 2009). In addition to direct effects on inflammation, stress may heighten the association between inflammation and behavioral symptoms. For example, among women recovering from breast cancer, those who reported higher levels of stress showed increased sensitivity to inflammation-related depressive symptoms in two independent cohorts (Manigault, Ganz, et al., 2021; Manigault, Kuhlman, et al., 2021). Similar effects have been observed in the context of endotoxin administration and vaccination (Kuhlman et al., 2019; Lasselin et al., 2021). These effects may be due to stress-related alterations in the blood-brain interface or increased activation of microglia, both of which can increase

sensitivity to peripheral inflammation (Bower et al., 2019). Of note, psychosocial resilience factors (e.g., positive affect, social connection, mindfulness) may buffer these effects (Manigault, Kuhlman, et al., in press) and can be cultivated by psychological interventions, considered in the next section. Even in the absence of viral infection, low-grade inflammation stemming from pandemic stress may increase depressed and anxious mood, and may also heighten affective reactivity to daily stressors (Sin, Graham-Engeland, Ong, & Almeida, 2015) and interfere with pursuit of rewarding activities (including social interactions) and positive health behaviors (exercise, sleep), creating a downward spiral that leads to further mood disturbance.

6. Interventions to reduce stress and promote well-being: relevance for immunity

Demand for mental health services has soared during the pandemic as people struggle to cope with the fear, loss, uncertainty, loneliness, and life disruption caused by COVID. Importantly, psychosocial interventions designed to improve mental health may also enhance immune status. A recent meta-analysis of 56 randomized controlled trials showed a beneficial effect of psychosocial interventions on immune outcomes, including increased activity of NK cells, increased ability of B and T cells to proliferate after stimulation, and decreases in markers of inflammation, all of which are relevant for antiviral defense (Shields, Spahr, & Slavich, 2020). Below we highlight work on specific interventions that have demonstrated links with immunity. We focus here on psychosocial interventions but note that interventions targeting physical activity and sleep disturbance can also influence the immune system and neuro-immune network (Bower et al., 2019).

Cognitive behavioral therapy (CBT): The relevance of CBT for antiviral immunity has been elegantly demonstrated in research conducted in individuals with HIV/AIDS. Antoni and colleagues have developed an intervention that combines CBT and stress management (Cognitive Behavioral Stress Management, or CBSM) for individuals facing chronic illness. In studies of men with HIV, CBSM leads to decreases in depression, anxiety, and stress, as well as increases in T cells and decreases in HIV viral load (Antoni, 2003). Similar benefits of CBSM have been demonstrated among women with HIV (Lopez et al., 2013). These investigators have also examined CBSM effects among women with breast cancer and found increases in Type I interferon gene expression and decreases in inflammation-related genes, as well as decreases in depression and anxiety (Antoni et al., 2012). Of note, these effects have persisted for up to a year post-intervention, suggesting enduring effects on mood and immunity (Carrico et al., 2005).

Mind-body interventions: With their focus on mind *and* body, interventions such as Tai Chi, Qi Gong, meditation, and yoga have considerable promise for improving mental and physical health, including immunity. Indeed, a meta-analysis of 34 trials of mind-body interventions showed beneficial effects on immune response to vaccination and markers of inflammation (Morgan, Irwin, Chung, & Wang, 2014). Other reviews focusing specifically on inflammation have also documented beneficial effects of mind-body approaches, particularly on measures of inflammatory gene expression (Bower & Irwin, 2016). The relevance of these findings for antiviral immunity was clearly demonstrated in a study of older adults, in which Tai Chi led to increases in immunity specifically to the varicella zoster virus (VZV) *and* augmented the antiviral response to VZV vaccination (Irwin, Olmstead, & Oxman, 2007). Tai Chi has also been shown to reduce production of proinflammatory cytokines and proinflammatory gene expression in trials with older adults and breast cancer survivors with insomnia (Irwin et al., 2014, 2015).

Mindfulness meditation has emerged as an effective intervention for reducing depression, anxiety, and loneliness, and also increases positive affect and meaning/purpose in life (Bower et al., 2015; Garland, Farb, Goldin, & Fredrickson, 2015; Goldberg et al., 2018; Goyal et al., 2014; Wielgosz, Goldberg, Kral, Dunne, & Davidson, 2019). A growing number of studies have examined effects of mindfulness interventions on immunity. An early study found that an 8-week mindfulness-based stress reduction (MBSR) program led to reductions in anxiety and increases in antibody response to influenza vaccination among healthy employees (Davidson et al., 2003). Of note, the intervention also led to significant increases in left-sided anterior activation as measured by EEG, a neural pattern associated with positive affect, which predicted the magnitude of change in antibody response. MBSR showed beneficial effects on antiviral immunity in a trial conducted with HIV + men, buffering the decline in CD4 T cells (which are infected by the HIV virus) observed in the control group (Creswell, Myers, Cole, & Irwin, 2009).

With respect to inflammation, there is evidence that mindfulness interventions lead to decreases in inflammatory gene expression and in some studies, circulating inflammatory markers (Bower & Irwin, 2016). In research with breast cancer survivors, we have shown that a 6-week mindfulness program (Mindful Awareness Practices) leads to decreases in stress and depression, increases in well-being, and changes in immune-related gene expression (including decreases in proinflammatory gene expression and increases in Type I interferon responses) (Bower et al., 2015; Boyle, Cole, Dutcher, Eisenberger, & Bower, 2019). Of note, changes in expression of immune-related genes were correlated with increases in well-being, but not with decreases in distress, following the MAPs intervention (Boyle et al., 2019). We also examined intervention-related changes in neural activity and links with immunity, focusing on activity in threat and reward-related neural regions given their relevance for downstream immune processes (Eisenberger & Cole, 2012). Results showed increases in ventral striatum (VS) activity in response to viewing positive images and decreases in amygdala activity to viewing threatening faces from pre-to post-intervention (Dutcher et al., 2021). However, only increases in VS activity were correlated with changes in immune markers; women who showed a greater increase in VS activity to the positive images showed a significantly greater reduction in circulating levels of IL-6. These effects highlight the role of positive psychological processes, and underlying neural activity, in structuring the immune response to mindfulness meditation.

Prosocial interventions: Given links between social integration, well-being, and immune function, interventions that specifically target prosocial states may also influence immune outcomes. Investigators have been particularly interested in interventions designed to increase a sense of social connection and contribution. In one trial, healthy adults randomized to perform prosocial activities ("acts of kindness") showed decreases in CTRA gene expression, including decreases in inflammation-related genes and increases in antiviral genes (Nelson-Coffey, Fritz, Lyubomirsky, & Cole, 2017). Among older adults, participation in an intergenerational mentoring program was also associated with decreases in CTRA gene expression; these effects were mediated by increases in eudaimonic well-being (Seeman, Merkin, Goldwater, & Cole, 2020). Further, adolescents who participated in a volunteering intervention showed decreases in IL-6 (Schreier, Schonert-Reichl, & Chen, 2013).

7. Summary and conclusions

The COVID-19 pandemic poses tremendous challenges to mental and physical health, which have typically been considered separately in prevention and treatment efforts. However, decades of research in psychoneuroimmunology has revealed intimate connections between the mind and the immune system that support the use of an integrated approach to prevention, intervention, and policy. Many of the psychological states exacerbated by the pandemic (stress, social isolation, social conflict) can undermine aspects of the immune system that protect against viral infection. In particular, stress can suppress the innate antiviral response (important for early control of the virus), decrease the function of T and B cells (critical for neutralizing the virus and killing virally infected cells), and increase inflammation (leading to greater

tissue pathology and long-term behavioral symptoms). In contrast, social support and connection are associated with enhanced T and B cell activity and lower inflammation and may buffer the negative impact of stress on the immune response. Further, growing evidence suggests that positive affect and eudaimonic well-being also have beneficial immune effects relevant for viral illness.

Infection with SARS-CoV-2 and pandemic-related stressors can also influence mental health through activation of the proinflammatory cytokine network. Proinflammatory cytokines released in response to infection or injury signal the brain and lead to changes in mood and behavior, many of which are seen in the context of long COVID. Indeed, preliminary studies suggests a role for inflammation in COVID-related depression and cognitive disturbance. Intriguing evidence from experimental and observational studies suggests that stress (and other psychological factors) may increase sensitivity to inflammation-related behavioral symptoms outside of the context of COVID; this work should inform the investigation of risk factors for persistent post-COVID neuropsychiatric symptoms.

There is compelling evidence that behavioral interventions can increase adaptive immunity and decrease inflammation, and may thus enhance the immune response to SARS-CoV-2. In particular, cognitive behavioral therapy, mind-body approaches (mindfulness, Tai Chi, yoga), and prosocial interventions have all shown promise as modulators of virus-related immunity, although effects specifically against SARS-CoV-2 have not been assessed. Psychosocial interventions could potentially be utilized preventatively to bolster antiviral immunity, including the immune response to vaccination. For example, a study with older adults found that a 16-week Tai Chi intervention administered prior to VZV vaccination produced a substantially higher level of anti-VZV immunity than vaccine alone (Irwin et al., 2007). These approaches might also be effective for reducing post-COVID symptoms and underlying immune dysregulation, as we have shown among cancer survivors with persistent fatigue, sleep disturbance, and depression (Bower et al., 2014, 2015; Irwin et al., 2014). A key advantage of psychosocial and behavioral interventions in the context of COVID is their ability to improve mental, physical, and (in the case of prosocial interventions) social and community well-being. Leveraging these behavioral and psychosocial factors through public health policy and interventions will be essential for promoting resilience as the repercussions of the COVID-19 pandemic are realized in the months and year ahead.

Financial support

Dr. Bower was supported in part by the National Institutes of Health/National Cancer Institute (R01CA200977, R01CA23753) and by the Breast Cancer Research Foundation.

Declaration of competing interest

The authors report no conflicts of interest.

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