



Review article

Mental health during the COVID-19 pandemic and beyond: The importance of the vagus nerve for biopsychosocial resilience

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ARTICLE INFO

Keywords:

COVID-19
Coronavirus disease
Lifestyle interventions
Psychiatric disorders
Social stress
Transcutaneous vagus nerve stimulation

ABSTRACT

The COVID-19 pandemic has led to widespread increases in mental health problems, including anxiety and depression. The development of these and other psychiatric disorders may be related to changes in immune, endocrine, autonomic, cognitive, and affective processes induced by a SARS-CoV-2 infection. Interestingly, many of these same changes can be triggered by psychosocial stressors such as social isolation and rejection, which have become increasingly common due to public policies aimed at reducing the spread of SARS-CoV-2. The present review aims to shed light on these issues by describing how viral infections and stress affect mental health. First, we describe the multi-level mechanisms linking viral infection and life stress exposure with risk for psychopathology. Then, we summarize how resilience can be enhanced by targeting vagus nerve function by, for example, applying transcutaneous vagus nerve stimulation and targeting lifestyle factors, such as exercise. With these biopsychosocial insights in mind, researchers and healthcare professionals will be better equipped to reduce risk for psychopathology and increase resilience during this challenging pandemic period and beyond.

1. Introduction

The effects of the coronavirus disease (COVID-19) pandemic on mental health are becoming increasingly evident. Recent research has suggested that one in five COVID-19 patients present with a (new-onset) mental health issue (Kong et al., 2020; Varatharaj et al., 2020). Moreover, prior studies in SARS-CoV-1 patients showed that psychopathology can develop even when evaluated years after infection (Lam et al., 2009). More broadly, research has indicated that exposure to infection and inflammation significantly increase the risk of developing psychopathology later in life (Benros et al., 2011, 2013; Khandaker et al., 2014; Rosenblat et al., 2014), in part by triggering aberrant mind-body interactions (Rosenblat et al., 2014). At the heart of these mind-body interactions is the autonomic nervous system (ANS) and, more specifically, the vagus nerve, which carries most of the parasympathetic nervous system (PNS) fibers and acts as a major bidirectional

communication pathway between the central nervous system (CNS) and the body.

One factor that strongly affects the activity of the vagus nerve is stress, and during the COVID-19 pandemic, people have been exposed to a variety of different psychosocial stressors that could exert vagus nerve-altering effects. In addition to notable increases in work-, financial-, and housing-related stressors (Nelson et al., 2020; Nicola et al., 2020), individuals have also experienced increases in social isolation (e.g., due to social distancing protocols) and rejection (e.g., due to disagreements involving disease prevention efforts, which have been polarizing and political). Similar to viral infections, social isolation and rejection have been shown to upregulate inflammatory activity, which can in turn lead to aberrant mind-body interactions that negatively impact mental health (Furman et al., 2019; Slavich, 2016, 2020a). Consequently, some researchers have hypothesized that we may witness a ‘wave’ of people developing mental health issues in the near future that is caused by the

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<https://doi.org/10.1016/j.neubiorev.2021.02.010>

Received 5 December 2020; Received in revised form 27 January 2021; Accepted 4 February 2021

Available online 11 February 2021

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heightened risk of viral infection combined with high levels of psychosocial stress (Raony et al., 2020).

The goal of the present review is to describe how viral and social stressors can impact the body to affect mental health. We begin by reviewing the literature describing the impact of a SARS-CoV infection (i.e., SARS-CoV-1 and SARS-CoV-2) on mind-body interactions and the development of mental health issues. Second, we discuss the relation between perceived or actual social exclusion and mental distress, with the aim of providing mechanistic insights into how mind-body interactions may play an important role in influencing mental health. Lastly, based on these mechanistic insights, we highlight several interventions that can target aberrant mind-body interactions by enhancing vagal nerve function, with the hope that such interventions may help enhance resilience, prevent or reduce risk for mental health problems, and lessen the high levels of personal suffering and societal disease burden attributable to mental illness.

2. SARS-CoV-2 infection, maladaptive changes in mind-body interactions, and mental health

Over the past few decades, research has shown that exposure to infection and inflammation can significantly increase the risk of developing psychopathology, even in later life (Benros et al., 2011, 2013; Khandaker et al., 2014; Rosenblat et al., 2014; Slavich and Irwin, 2014). This effect has also been observed during the COVID-19 pandemic. In a recent UK-wide surveillance study, it was shown that one out of five (hospitalized) COVID-19 patients presented with an altered mental status predominantly elicited (in 92 % of cases) by a new-onset neuropsychiatric disorder, such as psychosis, neurocognitive dementia-like syndrome, or an affective disorder (Varatharaj et al., 2020). This effect has been replicated by another study, which indicated that being diagnosed with COVID-19 doubled the risk of being newly diagnosed with a psychiatric disorder (Taquet et al., 2020). Other reports have also revealed an increased prevalence of mood and anxiety disorders, as well as symptoms of posttraumatic stress disorder (PTSD) in acute phase COVID-19 patients, especially for those who are older, female, and have less self-reported social support (Bo et al., 2020; Kong et al., 2020). These findings are consistent with the described acute phase as well as longer phase mental health outcomes of SARS-CoV-1 (for a review, see Raony et al., 2020). Of interest, according to a recent review by Lam (2020), SARS-CoV-1 survivors have been most often diagnosed with PTSD (55 %) or depression (39 %), even when evaluated up to 4 years after the infection.

One mechanism by which exposure to an infection may lead to mental health problems is infection-induced maladaptive changes in mind-body interactions involving immune, endocrine, autonomic, cognitive, and affective functioning (see Fig. 1, path A). First, viral-initiated increases in peripheral inflammation – characterized by enhanced pro-inflammatory cytokine [e.g., Interleukin-6 (IL-6) and Tumor Necrosis Factor- α (TNF- α)] signaling – can trigger activation of the hypothalamic-pituitary-adrenal (HPA) axis. More specifically, via the afferent fibers of the vagus nerve, which is the main nerve of the autonomic PNS, information regarding the presence of peripheral cytokines is conveyed to nuclei in the brainstem such as the nucleus tractus solitarius (NTS) and the hypothalamus, where it can trigger the release of corticotrophin-releasing hormone (CRH) and increase HPA axis activity. HPA axis activation, in turn, is characterized by enhanced cortisol release, which can trigger a generalized physiological and psychological stress response (Raony et al., 2020; Rosenblat et al., 2014). In addition, this signal is propagated to brain regions implicated in physiological, cognitive, and emotional regulation, including the amygdala, insula, anterior cingulate cortex (ACC), and medial prefrontal cortex (mPFC) (Desforges et al., 2020; Pavlov and Tracey, 2012).

To overcome spreading infection, transient cytokine responses and HPA axis activity are beneficial given the immunosuppressive effects of cortisol that trigger reduced cytokine signaling in immune cells (Wohleb

and Godbout, 2013). However, when an infection is more intense or longer lasting and cytokine levels are more chronically elevated, hyperactivation of the HPA axis can result. In this case, glucocorticoid receptors on immune cells become less sensitive to the immunosuppressive effects of cortisol, leading to sustained cytokine signaling and inflammation, and a built-up of cortisol that has been called HPA axis overdrive (Pace and Miller, 2009). With respect to health, it has been hypothesized that sustained cytokine signaling in turn negatively impacts neurotransmitter metabolism (e.g., serotonin) and neuroplasticity, which have been implicated in the pathophysiology of psychopathology (Besedovsky and Del Ray, 2011; Rosenblat et al., 2014; Slavich and Irwin, 2014; Stapelberg et al., 2019; Wohleb and Godbout, 2013). Furthermore, peripheral inflammation may facilitate the development of reward hyposensitivity and anhedonia (Nusslock and Miller, 2016) due to inflammation-induced changes in dopamine signaling in the fronto-striatal reward circuit (for a review, see Miller et al., 2013).

It is through these biological interactions that SARS-CoV-2 infection-induced inflammation may lead to maladaptive mind-body interactions and thereby negatively impact mental health. In this regard, importantly, increasingly high serum levels of IL-6 and TNF- α have indeed been found to be related to SARS-CoV-2 infection severity in COVID-19 patients (see Raony et al., 2020).

3. Psychosocial stress, maladaptive changes in mind-body interactions, and mental health

Interestingly, similarly to an infection, exposure to psychosocial stressors, including interpersonal loss and social rejection, has been shown to trigger changes in mind-body interactions that can have adverse health effects (Slavich et al., 2010a). As shown in Fig. 1, path B, these changes include increased HPA axis activity and reactivity, activation of the innate immune system, and the release of pro-inflammatory cytokines that can lead to the development of systemic chronic inflammation (Haroon et al., 2012; Slavich, 2020b; Steptoe et al., 2007) even when assessed years later (Michopoulos et al., 2017; Tursich et al., 2014). These dynamics are of particular relevance to the COVID-19 pandemic, given that as a result of this situation, many people have been repeatedly exposed to a variety of psychosocial stressors including health, housing, financial, work, and interpersonal stressors (Nelson et al., 2020; Nicola et al., 2020).

Social isolation and rejection are two types of stress that are particularly relevant in this regard, especially given data showing that loneliness and sustained social exclusion have been key consequences of precautions designed to slow the spread of COVID-19 (Miller, 2020). In addition to being strong predictors of poor mental health (Slavich et al., 2009, 2014), these stressors are prevalent among individuals who have been living alone and those who have been prevented from meeting with family members and friends (Mental Health Foundation, 2020; Pancani et al., 2020). Feelings of being socially criticized and rejected have also increased due to societal disagreement and polarization regarding government-installed health precautions (Van Bavel et al., 2020). Finally, many individuals have experienced a heightened sense of threat while outside, which has the benefit of helping people avoid contact with others who could infect the individual with SARS-CoV-2 but has the downside of promoting neurocognitive appraisals of threat that upregulate inflammatory biology (Slavich et al., 2010b; Van Bavel et al., 2020).

This central role for social isolation and rejection in affecting health is consistent with Social Safety Theory (Slavich, 2020a), which posits that social isolation and rejection strongly upregulate inflammatory activity, and with Social Baseline Theory, which argues that the social network is the primary source of safety (Coan, 2010). Indeed, loneliness is one factor that has been associated with generalized unsafety and prolonged physiological activation (Brosschot et al., 2017). All in all, experiencing psychosocial stressors such as social isolation and rejection has been shown to negatively impact mental health (Benros et al., 2013;

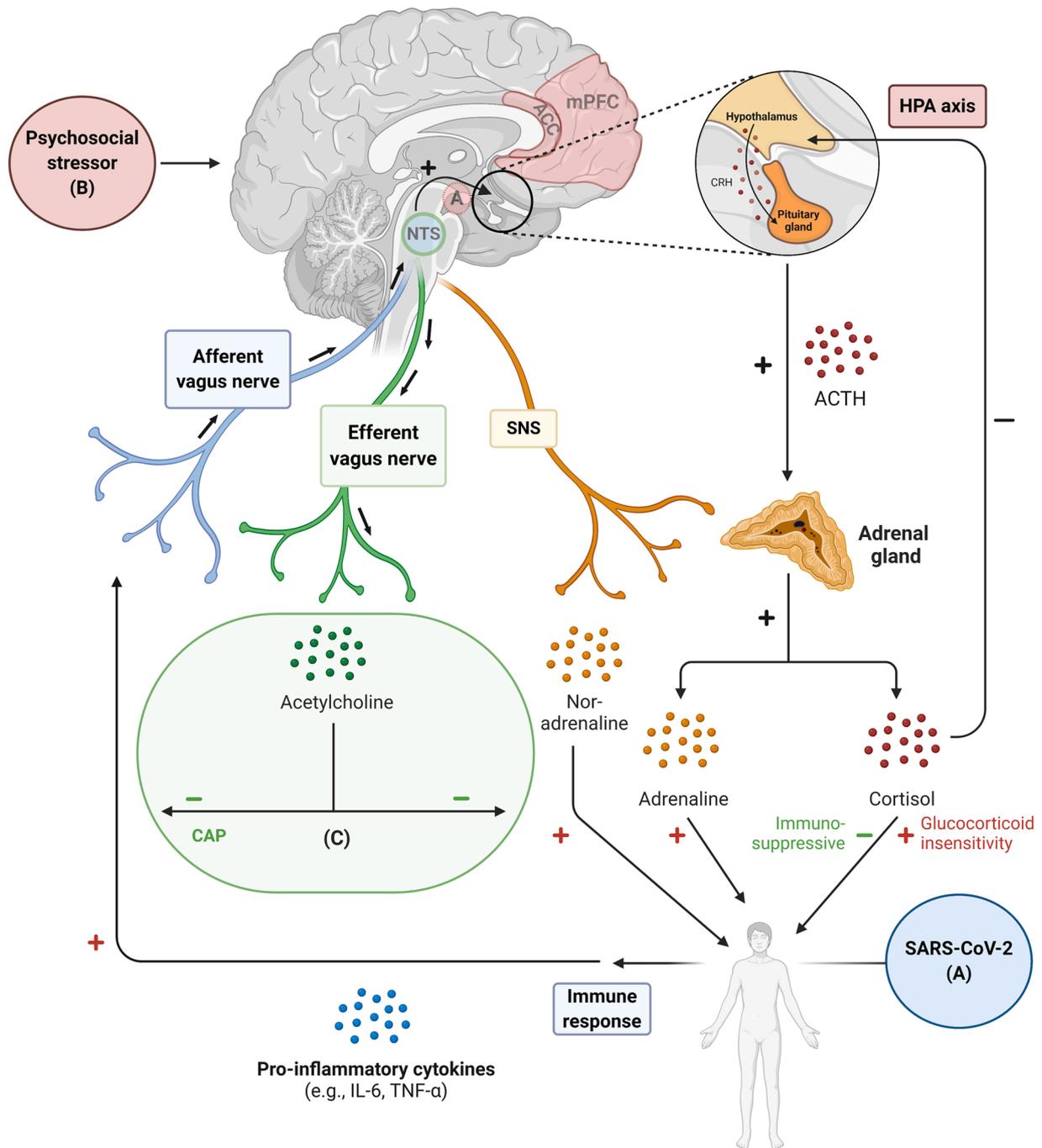


Fig. 1. Pathways by which exposure to SARS-CoV-2 and psychosocial stressors can negatively impact mental health. (A) Exposure to SARS-CoV-2 can upregulate inflammatory activity, characterized by increased pro-inflammatory cytokine (e.g., IL-6, TNF- α) production. Via the afferent vagus nerve fibers, information regarding the presence of cytokines is conveyed to the NTS and subsequently to the hypothalamus where it can activate the HPA axis. When this occurs, CRH released from the hypothalamus triggers ACTH release from the pituitary, and increased cortisol secretion from the adrenal cortex, leading to a generalized stress response. When transient, this response is beneficial, as cortisol generally reduces pro-inflammatory cytokine signaling in immune cells. However, when cytokine levels are frequently or persistently elevated, the HPA axis can become hyperactivated and glucocorticoid receptors on immune cells can become insensitive to the immunosuppressive effects of cortisol, leading to cortisol build-up and sustained inflammation. This chronic inflammatory state can affect neurotransmitter (e.g., serotonin) metabolism and negatively impact mental health. Afferent vagal projections are also propagated to other brain regions involved in the pathophysiology of mental health problems, including the amygdala, ACC, and mPFC. (B) Psychosocial stressors, such as social isolation and rejection, can also upregulate inflammatory activity and affect mental health. These stressors are processed by the brain and can activate the HPA axis, leading to increased cortisol release. Psychosocial stressors can also trigger strong cardiovascular reactivity and increased noradrenaline signaling, indicative of a shift toward SNS dominance over PNS activation. Third, these stressors have been associated with glucocorticoid insensitivity, meaning they can trigger immune cells to become resistant to the immunosuppressive effects of cortisol, which can in turn lead to a chronic inflammatory state. (C) Finally, it is important to note that the vagal PNS and the SNS are strongly interactive. Efferent vagal neurons project back from the NTS to cells in bodily tissues (e.g., heart, lungs, gastrointestinal system) where they release acetylcholine. Efferent vagal fibers can counteract a sustained activation of the SNS (e.g., by slowing heart rate and blood pressure). They can also reduce pro-inflammatory cytokine production through the CAP. Abbreviations: ACC, anterior cingulate cortex; ACTH, adrenocorticotropic hormone; A, amygdala; CAP, cholinergic anti-inflammatory pathway; CRH, corticotropin-releasing hormone; HPA axis, hypothalamic-pituitary-adrenal axis; IL-6, interleukin 6; mPFC, medial prefrontal cortex; NTS, nucleus solitary tract; PNS, parasympathetic nervous system; SNS, sympathetic nervous system; TNF- α , tumor necrosis factor- α .

Rosenblat et al., 2014; Slavich, 2016), and this has been particularly relevant over the past year given that the COVID-19 pandemic has led to notable increases in the base rates of these stressors.

What is also interesting is that these social stressors have been shown to be particularly strongly related to changes in mind-body interactions that can affect health. As alluded to above, for example, social exclusion has been related to increased inflammatory activity, as indexed by IL-6, TNF- α , and C-reactive protein (CRP) (Slavich et al., 2010b; Smith, 2020). In fact, interpersonal loss and social exclusion stressors appear to be the strongest psychosocial triggers of inflammation (Slavich et al., 2010a). Social exclusion also has been related to (hyper) HPA axis activation and has been associated with a slower cortisol recovery following stressful experiences (Dickerson and Kemeny, 2004).

Theoretically, prolonged exposure to cortisol and pro-inflammatory cytokines as a result of chronic social exclusion may influence glucocorticoid receptor functioning on immune cells, which can cause glucocorticoid insensitivity and a reduced sensitivity of immune cells to the immunosuppressive influence of cortisol, leading to sustained inflammation (see above). Consistent with this possibility, social exclusion has been associated with abnormal glucocorticoid levels (Serra et al., 2005; Wohleb et al., 2015). In addition, exposure to social exclusion has been related to increased noradrenaline signaling and strong cardiovascular reactivity, which is indicative of autonomic sympathetic nervous system (SNS) activation rather than PNS activation (Slavich et al., 2010a), and to an increased risk for developing psychopathology (Masten et al., 2011; Monroe et al., 2014; Slavich, 2016). This may be particularly true when experiences of social isolation or exclusion are prolonged, as has been the case during the COVID-19 pandemic.

The mind-body interactions reviewed above that are triggered by psychosocial stress (i.e., in the absence of an infection) have also been directly implicated in the development of mental health problems such as mood and anxiety disorders, which may occur in part through the aforementioned impact of cytokine signaling on neurotransmitter activity or metabolism (Felger and Lotrich, 2013; Schiepers et al., 2005; Stapelberg et al., 2019). Consistent with this possibility, meta-analyses have shown that levels of IL-6 and TNF- α are associated with the severity of several disorders including depression, PTSD, psychosis, and sleep disorders (Passos et al., 2015; Raony et al., 2020). This may help explain why recent lockdowns aimed at slowing the transmission of SARS-CoV-2 have been related to an increased prevalence of depression, anxiety, PTSD, and other psychiatric disorders (Brooks et al., 2020). Given the largescale and fast spread of SARS-CoV-2 and the major life stressors caused by the resulting public health precautions, the mental healthcare system is likely to be burdened even if only a fraction of COVID-19 survivors develop psychopathology. It is therefore crucial to understand the mechanisms underlying these increases in mental health problems during and in the aftermath of the COVID-19 pandemic, with this work ideally helping to inform the development of interventions that could reduce the likelihood of, or help prevent the development of, mental health problems.

4. The vagus nerve – at the crossroad of mind-body interactions

One key pathway linking exposure to both viruses (e.g., SARS-CoV-2 infection) and psychosocial stressors (e.g., social isolation and rejection) with mental health is the ANS. This system is centrally involved in the exchange of health-relevant information from the periphery to the brain and vice versa; additionally, it coordinates the body's reactivity to and recovery from stressors. As illustrated in Fig. 1, the vagus nerve is particularly important in this regard, as it contains most of the PNS fibers.

The vagus nerve is the longest nerve of the body and is composed of approximately 80 % afferent fibers that convey peripheral bodily information (e.g., cytokine levels) to the brain. The afferent vagal fibers enter the brain bilaterally and primarily target the NTS in the brainstem, the hypothalamus, and brain areas that have been implicated in the

regulation of physiology, cognition, and affect (e.g., amygdala, ACC, mPFC; Pavlov and Tracey, 2012; Thayer and Sternberg, 2010). When pro-inflammatory cytokines are present due to an infection, for example, they can activate afferent vagal neurons and cause increased HPA axis activity and cortisol release (i.e., by triggering the release of CRH in the hypothalamus), leading to a systemic stress response (see above). Importantly, from the NTS, efferent vagal neurons also project back to cells in different organ systems throughout the body, including the heart, lungs, and gastrointestinal system. These efferent vagal neurons release acetylcholine, which counteracts pro-inflammatory cytokine (e.g., TNF- α) signaling and is called the cholinergic anti-inflammatory pathway (CAP) (Burger et al., 2020; Kaniusas et al., 2019; Thayer, 2009). Increased afferent vagal activity can thus (indirectly via activating NTS neurons) impact the immune response by increasing efferent PNS influence (Tracey, 2009; Wohleb and Godbout, 2013).

The PNS also strongly interacts with the other component of the ANS: the SNS. During acute infection or psychosocial stress, SNS dominance is adaptive because it triggers a noradrenaline release at target tissues, which helps to mobilize energy resources by increasing heart rate and systolic and diastolic blood pressure (i.e., the fight-or-flight response; Epel et al., 2018). However, more chronic SNS activation, which has been found in COVID-19 patients (Porzionato et al., 2020), has also been related to increased cytokine production and the HPA axis overdrive described above (Tracey, 2009). In this regard, increased efferent vagal activity puts a 'break' on the continued activation of the SNS. The vagus nerve is, therefore, apart from immunomodulation, also implicated in autonomic control over cardiac activity (Kaniusas et al., 2019).

This is of particular importance given that by measuring the variability in the time interval between successive heartbeats—called, *heart rate variability* (HRV)—it is possible to infer the degree of vagal activity. Increased efferent vagal activity triggers neurons projecting to the sinoatrial node of the heart to release acetylcholine, thereby decreasing heart rate and increasing HRV (Burger et al., 2020). Particularly, the root mean square of successive differences (RMSSD) and high-frequency (HF) components can be used as indirect measures of (efferent) vagal function.

The ability to maintain high HRV during the presence of stressors has been suggested to be a flexible, adaptive physiological response to stress (i.e., high vagal control). Furthermore, individuals with high resting-state HRV (i.e., high vagal tone) have been shown to recover faster in their acute immune, endocrine, and cardiovascular responses to stress (Kaniusas et al., 2019; Weber et al., 2010). In contrast, low HRV has been related to elevated inflammatory markers (Sloan et al., 2007), which can indicate a deficiency in the CAP. Moreover, individuals presenting with low (as compared to high) resting-state HRV have been found to experience more psychosocial stress, which might be exacerbated by different levels of social support (Lischke et al., 2018). Lastly, low HRV has been related to aberrant activity in a neural network that includes prefrontal and (para-)limbic brain regions that are involved in emotional and cognitive functioning, and that have been implicated in subjective, behavioral, and endocrine reactions to psychosocial stressors (Thayer et al., 2009, 2012). These bidirectional pathways between the brain and visceral organs via the ANS may also explain why sustained experiences of social isolation and exclusion negatively affect mental and physical health.

In sum, autonomic vagus nerve function plays a central role in governing mind-body interactions that have immune, endocrine, neurocognitive, and affective effects. Adaptive vagus nerve functioning is therefore considered crucial for the ability to inhibit ongoing physiological and psychosocial stress reactivity, and is thus essential for enhancing physical and mental resilience.

5. Mental health interventions for promoting resilience

The above-described influence of both viral infections and psychosocial stressors on mind-body interactions provides one framework for

understanding how notable increases in anxiety, mood, and other disorders are likely to occur during and in the aftermath of the COVID-19 pandemic. Although effective mental health interventions are available and have been shown to reduce health-damaging inflammation (e.g., Shields et al., 2020), cost-effectiveness models (based on epidemiological and socio-economic data) suggest that even in the unlikely event of optimal treatment being delivered, only 35 %–50 % of the overall burden of psychiatric disorders, such as anxiety disorders and depression, would be alleviated (Andrews et al., 2004). Therefore, there is an urgent need to develop prevention and treatment options that are safe, tolerable, affordable, and rapidly deployable on a large scale. Based on the above-described mechanistic picture, we propose that such interventions could benefit from targeting the vagus nerve in order to reduce the risk for mental and physical disorders, and enhance resilience to physiological and psychological stress. Consistent with this possibility, it was recently proposed that the balance between the PNS and the SNS might be crucial for understanding how individuals respond to threats associated with the COVID-19 pandemic (Porges, 2020).

5.1. Transcutaneous vagus nerve stimulation (tVNS)

As illustrated in Fig. 2A, one promising, cost-effective approach to increase vagal activity is to apply non-invasive transcutaneous vagus nerve stimulation (tVNS), which has the potential to reduce SNS dominance, decrease pro-inflammatory markers, increase resiliency to and recovery from physiological and psychosocial stress, and reduce the risk of mental health complaints. There are two main ways to administer tVNS. The first is to superficially apply stimulation to the neck with a specialized device (e.g., GammaCore) to target the cervical branch of the vagus nerve. The second way is to apply stimulation at the cymba concha of the ear. This tissue is innervated by the exclusively afferent auricular branch of the vagus nerve (ABVN), which fibers terminate in the NTS and subsequently project to the hypothalamus and forebrain regions (Pavlov and Tracey, 2012). fMRI studies have suggested that tVNS can indeed activate these ‘classic’ vagal pathways, as tVNS administration has been associated with altered activity in the NTS, hypothalamus, amygdala, hippocampus, ACC, insula, and nucleus

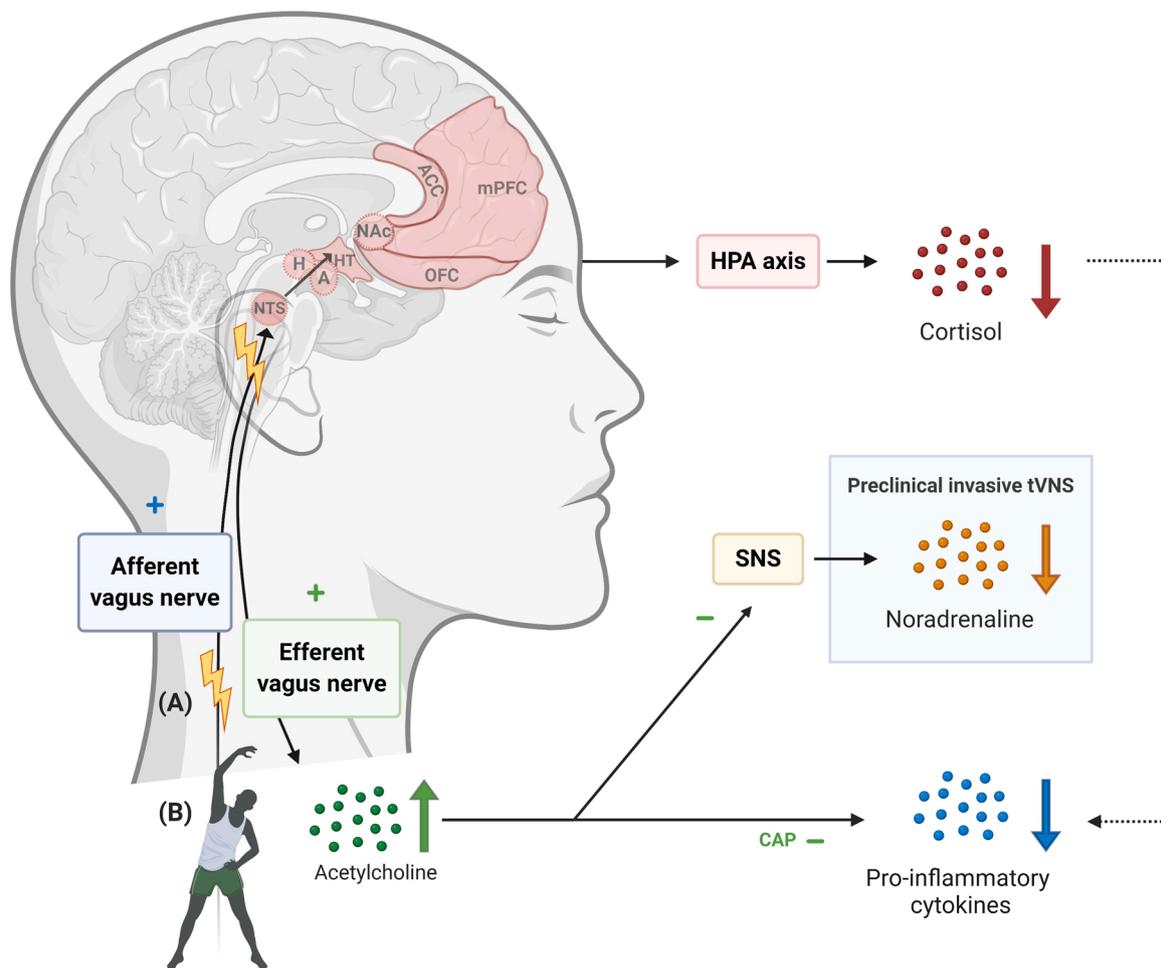


Fig. 2. Pathways by which vagal function-enhancing interventions can normalize biological functioning and improve mental health. (A) tVNS applied to the afferent cervical (neck) or auricular branch of the vagus nerve (cymba concha of the ear) modulates activity in the NTS, hypothalamus, hippocampus, amygdala, ACC, and other mental health-relevant brain regions. tVNS may have anti-inflammatory effects by targeting the HPA axis (i.e., dashed arrow) and by activating the CAP via enhanced efferent vagal activity. Preclinical invasive VNS studies suggest that tVNS may also improve the PNS/SNS balance, thereby reducing SNS dominance and modulating noradrenaline release. In depressed patients, tVNS has been shown to improve symptomatology and functioning in neural networks and brain regions involved in cognitive and affective regulation, including the ACC, insula, NAC, mPFC, and DLPFC. **(B)** Regular physical exercise can also enhance vagal function and may improve the PNS/SNS balance. Habitual exercise can reduce pro-inflammatory activity (e.g., by activating the CAP) and improve HPA axis-related endocrine function (e.g., reduced cortisol reactivity to psychosocial stressors). Lastly, exercise improves cognitive and affective regulation, as reflected in part by improved neural functioning in health-relevant brain regions and networks, including the ACC and PFC. Abbreviations: ACC, anterior cingulate cortex; A, amygdala; CAP, cholinergic anti-inflammatory pathway; DLPFC, dorsolateral prefrontal cortex; H, hippocampus; HPA axis, hypothalamic-pituitary-adrenal axis; HT, hypothalamus; mPFC, medial prefrontal cortex; NAC, nucleus accumbens; NTS, nucleus solitary tract; PFC, prefrontal cortex; PNS, parasympathetic nervous system; SNS, sympathetic nervous system; tVNS, transcutaneous vagus nerve stimulation.

accumbens (Frangos et al., 2015; Kong et al., 2018; Kraus et al., 2007; Yakunina et al., 2017; see also Burger and Verkuil, 2018).

It has been suggested that tVNS induces anti-inflammatory effects directly by targeting the HPA axis (Bonaz et al., 2017), and indirectly by increasing activity in NTS neurons and activating the CAP (Bonaz et al., 2017; Thayer and Sternberg, 2010). In this regard, studies have shown evidence of decreases in both salivary cortisol levels (Warren et al., 2019) and pro-inflammatory cytokine levels (e.g., TNF- α , IL-8, and possibly IL-6) after applying tVNS (Bremner et al., 2020; Brock et al., 2017), with long-lasting effects (Lerman et al., 2016). There is also some evidence showing that tVNS applied either after exposure to a stressor or without such exposure may improve the balance between the PNS and SNS (Brock et al., 2017; Gurel et al., 2020), and thereby increase HRV (Clancy et al., 2014; however, see also Borges et al., 2019).

Furthermore, based on preclinical invasive VNS studies, tVNS could potentially modulate serotonin and noradrenaline release in the hippocampus, amygdala, and mPFC, and increase neurogenesis and neuroplasticity in the hippocampus (Grimonprez et al., 2015). Lastly, recent studies have shown that multiple sessions of tVNS can be successfully applied as an intervention for disorders such as major depression, with improvements being seen in depression and anxiety symptoms, sleep, hopelessness, and cognitive function (Fang et al., 2016; Liu et al., 2016; Rong et al., 2016). In these studies, reductions in depression severity were associated with changes in resting-state functional connectivity (rsFC) in brain networks implicated in physiological, cognitive, and emotional regulation. After four weeks of tVNS, depressed patients who reported more substantial symptom improvements also exhibited greater decreases in rsFC between the default mode network (DMN), including the mPFC and ACC) and the anterior insula and parahippocampal gyrus (Fang et al., 2016); they also exhibited greater increases in rsFC between (a) the orbitofrontal cortex and the precuneus (Fang et al., 2016), (b) the nucleus accumbens (NAcc) and the rostral ACC/mPFC (Wang et al., 2018), and (c) the amygdala and the left dorsolateral prefrontal cortex (DLPFC; Liu et al., 2016).

In the context of the COVID-19 pandemic, lower cytokine (e.g., IL-6) levels have been associated with better treatment efficacy and remission of SARS-CoV-2 (Liu et al., 2020). The few ongoing, pre-registered clinical trials that have investigated the efficacy of tVNS have focused on the physical health effects (e.g., respiratory function, cytokine storm) of cervically applied stimulation in inpatients during the acute infection phase (see Tornero et al., 2020). As of now, however, there are no pre-registered studies that have investigated the potential of tVNS to improve mental health in COVID-19 survivors. Given the mechanistic overview provided above, however, tVNS may be a potentially useful therapeutic intervention for COVID-19 survivors who have developed comorbid psychopathology, especially given that it is tolerable and can be applied safely with limited side-effects, even if used repeatedly (Redgrave et al., 2018). In addition, tVNS devices are relatively inexpensive, small and mobile, and easy to apply. In fact, under medical supervision, patients can be taught to self-administer the treatment at home (Fang et al., 2016; Rong et al., 2016).

5.2. Lifestyle interventions to increase vagal function

Apart from applying tVNS, activity in afferent vagal fibers can be increased using behavioral lifestyle interventions (see Fig. 2B). Substantial research has shown that lifestyle interventions such as physical exercise, and mind-body interventions such as slow breathing (i.e., low respiration rate, long exhalations) and meditation, can improve vagal nerve functioning (Gerritsen and Band, 2018). During moderate-to-vigorous physical exercise (e.g., running, cycling, rowing, swimming), for example, SNS activity and (nor)adrenaline production increases, elevating heart rate, blood pressure, and breathing rate above basal levels. Concurrently, vagal control drops. However, based on the continuous interaction between the PNS and the SNS branches of the ANS, vagal control (as measured using HRV) will rise again following

the exercise (Stanley et al., 2013; Michael et al., 2017). In line with these effects, regular physical exercise of moderate intensity has been shown to increase vagal tone (i.e., during rest) and vagal control (i.e., in response to a stressor; for a review, see Lujan and DiCarlo, 2013). In contrast, a sedentary lifestyle has been associated with PNS/SNS imbalance, as characterized by reduced vagal nerve function (e.g., reduced HRV) (Thayer and Lane, 2009). In sum, therefore, physical exercise has been found to enhance vagal nerve functioning.

Consistent with the notion that vagal nerve functioning is a critical, health-relevant process, interventions based on physical exercise have also been shown to influence immune, endocrine, and CNS function (for a review, see Hendrikse et al., 2017). Systematic reviews and meta-analyses in healthy individuals have shown that even though physical exercise triggers an acute inflammatory response (e.g., due to muscle contractions and damage), it induces both short- and long-term anti-inflammatory effects. More specifically, exercise has been shown to reduce pro-inflammatory cytokine (e.g., IL-6, TNF- α) and CRP levels (Metsios et al., 2020), which may depend on the intensity of the training and individuals' age (Cronin et al., 2017; Souza et al., 2020). Interestingly, it has been suggested that daily exercise triggers an activation of the CAP, thereby protecting against inflammation (Lujan and DiCarlo, 2013). Research has also shown that healthy individuals who are under sustained stress exhibit improved mental health (i.e., fewer depressive symptoms) when they exercise at a moderate intensity for six weeks, as compared to individuals who do not exercise or who exercise at high intensity. Importantly, the beneficial effects of moderate exercise on mental health appear to be accompanied by decreases in levels of the pro-inflammatory cytokine TNF- α (Paolucci et al., 2018).

In addition to having anti-inflammatory effects, research has indicated that prolonged physical exercise can improve HPA axis-related endocrine function. Acute exercise triggers HPA axis activation and cortisol secretion (among other factors), depending on the intensity and duration of the exercise. This hypercortisolism lasts for up to 2 h following the exercise and is needed for energy mobilization but it also has beneficial, anti-inflammatory effects that help inhibit the exercise-induced inflammatory responses in muscles. Interestingly, however, individuals who are physically active, and thus repeatedly exposed to the associated physiological stress response, appear to be better protected against the damaging effects of chronically elevated cortisol levels (Duclos and Tabarin, 2011). Relatedly, physically fit individuals have been found to exhibit a blunted cortisol response to laboratory-induced psychosocial stress as compared to moderately fit and untrained individuals (Rimmele et al., 2009).

Finally, the effects of physical exercise on CNS functioning, including neuroplasticity, cognitive, and affective functioning, are well known. Physical exercise has been shown to positively influence the connectivity of neural networks implicated in vagal and cognitive function (Mandolesi et al., 2018). Relatedly, exercise has been associated with improved prefrontal cortical and ACC functioning, which has been implicated in cognitive as well as emotional functioning (Kandola et al., 2019). Interestingly, a recent pilot study in which depressed patients completed a 12-week exercise program demonstrated improvements in cardiorespiratory fitness that were associated with increased ACC volume (Gujral et al., 2019). Lastly, physical exercise has also been associated with improved cognitive (Fernandes et al., 2017) and affective function (e.g., less persistent states of stress, anxiety, and depression; Harvey et al., 2018; von Haaren et al., 2015). In sum, physical exercise appears to strengthen resilience at least in part by facilitating recovery from stress on a physiological, immunological, endocrine, and psychological level, with improved vagal nerve function being a potential key mechanism of action. Hence, the importance of physical exercise during the COVID-19 pandemic and beyond should not be underestimated.

Other lifestyle interventions such as yoga-based mind-body interventions that include posture, slow breathing, and meditation have also been shown to improve vagal nerve function (e.g., increase HRV) and thereby restore potential imbalances between the PNS and SNS

(Streeter et al., 2012; Sullivan et al., 2018; Wells et al., 2016). These mind-body interventions have been associated with improved endocrine responses (i.e., decreases in cortisol levels; Streeter et al., 2012; Wells et al., 2016), improved immune function (i.e., decreases in pro-inflammatory markers; Black & Slavich, 2016; Gautam et al., 2020; Sullivan et al., 2018), increased telomerase activity (Black and Slavich, 2016), and adaptive changes in brain regions that are involved in cognitive and affective regulation (e.g., amygdala, prefrontal cortex, hippocampus; Kinser et al., 2012; Streeter et al., 2012). This may help explain why such interventions have a positive effect on emotional well-being and stress resiliency. Indeed, yoga-based mind-body interventions have been shown to reduce self-reported stress, anxiety, and depression levels in both clinical and non-clinical populations (Gautam et al., 2020; Gerbarg et al., 2015; Streeter et al., 2012; Wells et al., 2016).

Importantly, several of these lifestyle interventions are low cost, low risk, easily taught, rapidly effective, and sustainable first-line interventions that can have both preventive and therapeutic effects. Although lifestyle interventions have been studied in the context of resilience, the impact of vagal functioning has not been considered a central psychophysiological mechanism of change. Therefore, we believe that a more thorough understanding of how these and other lifestyle interventions promote emotional well-being acutely and over time – and how they influence mind-body interactions – will help advance the search for effective strategies for improving mental and physical health and motivating healthy behaviors to reduce disease risk and enhance immunity.

6. Open questions and future directions

Looking forward, there are several avenues of investigation that could help advance our understanding of vagal function, health, and resilience. First, our review highlights a need for more information regarding the extent to which psychopathological complaints in COVID-19 survivors are related to aberrant inflammatory (e.g., IL-6, TNF- α), endocrine (e.g., cortisol), CNS (e.g., cortical thickness, functional connectivity), and ANS (e.g., vagal) function. Research is also needed to examine if these associations differ by infection severity (e.g., asymptomatic, mild, moderate, severe), or actual or perceived psychosocial stress levels. Along these lines, we also need to better understand the extent to which psychosocial stress plays a role in initial psychopathological symptoms in the general (non-infected) population, given that COVID-19-related restrictions increase the social isolation that all individuals experience. To accomplish this goal, researchers could conduct prospective, longitudinal studies in healthy individuals to evaluate if experiencing social isolation during the pandemic is related to harmful immune-neuroendocrine dynamics and, in addition, whether these changes are related to the development of cognitive or affective complaints over time.

Second, the potential of tVNS and lifestyle interventions to improve mind-body interactions (i.e., immune-neuroendocrine function, autonomic function, cognitive and affective processing) and mental health should be further evaluated. Particularly important in this context is the goal to identify whether such interventions reduce individuals' stress levels and, if so, what neural and biological mechanisms underlie these intervention-related changes in stress (Slavich, 2015). Given that the brain is the central organ responsible for perceiving stress and regulating peripheral biological responses to stressors, integrating neuroimaging into this research would be especially fruitful as it would help elucidate neural mechanisms that may underlie the efficacy of these interventions. For example, some prior research has identified links between the brain and peripheral inflammation (e.g., Muscatell et al., 2015, 2016; Slavich et al., 2010b), but overall, this literature is small.

Furthermore, it will be important to evaluate whether individuals who present with distinct vagal function profiles at baseline (i.e., vagal endophenotypes) respond differently to interventions that aim to

specifically target the vagus nerve. Consistent with the National Institute of Mental Health Research Domain Criteria (RDoC) approach (Cuthbert and Insel, 2013), we suggest that investigating vagal function as a dimensional human trait to predict response to a lifestyle intervention or tVNS would be desirable. Possibly, individuals who present with efficient vagal function might show ceiling effects in response to these interventions, as there might be less room for improvement. In contrast, those with more aberrant vagal function may benefit most from these interventions (see Brock et al., 2017), because they are experiencing a pre-interventional ANS imbalance characterized by higher SNS dominance and reduced PNS engagement. Altogether, future research is needed to understand how these interventions work and when they should be recommended for increasing resilience toward viral and psychosocial stressors, and, in addition, whether this is particularly true for individuals presenting with certain vagal endophenotypes.

Lastly, consistent with diathesis-stress models of psychopathology (e.g., Monroe and Simons, 1991), some people may be more prone to develop mental health problems following stressor exposure than others owing to neural, genetic, or other vulnerabilities (e.g., Quinn et al., 2020; Seiler et al., 2020; Slavich et al., 2014). For instance, individuals may exhibit prefrontal-mediated cognitive biases in response to psychosocial stressors, including the tendency to direct attention toward negative information, difficulty disengaging from it, or negative biases in interpreting social cues. Such cognitive biases may increase the risk of developing psychopathology such as mood and anxiety disorders (De Raedt and Koster, 2010). Of relevance here is whether biased neural processing of social exclusion is related to heightened stress reactivity. Experiencing social exclusion has been associated with increased activity in the insula, rostral ACC, and mPFC – particularly in individuals who are more vulnerable to develop psychopathology – thus reflecting increased reactivity toward social exclusion (for a review, see Dedoncker, 2020). Increased insula and ACC activity during social exclusion has also been related to TNF- α responses to social stress (Slavich et al., 2010a). Furthermore, the failure to engage the prefrontal cortex to (cognitively) control the stress response has also been associated with decreased HRV – and, relatedly, SNS/PNS imbalance (Thayer et al., 2009; Smith et al., 2017). Individuals with the lowest vagal tone may therefore also benefit from prefrontally-targeted neuromodulatory interventions with techniques other than tVNS, such as transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS; Remue et al., 2016), which particularly target these cognitive control processes to improve emotion regulation (for a review, see Dedoncker et al., 2020).

7. Conclusion

In conclusion, aberrant mind-body interactions can emerge from both being exposed to viral challenges, such as an infection, as well as in response to experiencing social stressors, such as social isolation or rejection. Risk for both exposure types has been greatly elevated during the COVID-19 pandemic, thus having profound implications for mental health and well-being on a worldwide level. On a positive note, several safe and tolerable mental health interventions already exist that can be implemented to reduce psychiatric risk and improve well-being. However, more research is needed to identify the specific types of interventions that are most affordable and effective for improving human health during these challenging times.

Funding sources

This work was supported by a Society in Science—Branco Weiss Fellowship, Brain & Behavior Research Foundation NARSAD Young Investigator Grant [grant number 23958], and National Institutes of Health grant [grant number K08 MH103443] to GMS; the Fonds Wetenschappelijk Onderzoek, Flanders research projects 'Rode Neuzen' [grant number G0F4617N]; the Bijzonder Onderzoeksfonds [grant

numbers BOF16/GOA/017, BOFSTA2017002501]; and the Sapienza University of Rome [grant number RM11715C7F74C683]. These funders had no role in planning or writing this article, or the decision to submit the article for publication.

Declaration of Competing Interest

The authors report no declarations of interest.

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