THE DIFFERENT FACES OF SICKNESS

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THE DIFFERENT FACES OF SICKNESS

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Editorial: The Different Faces of Sickness

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Keywords: sickness behavior, social behavior, psychoneuroimmunology, COVID-19, infection, depression, pain

Editorial on the Research Topic

The Different Faces of Sickness

Sickness not only includes symptoms that classically define an infection (e.g., fever, nausea, headache), but also comes along with profound neurobehavioral consequences for the infected individual. These include anhedonia, anorexia, pain, lethargy, fatigue, sleepiness, and social withdrawal, and are collectively called "sickness behavior" (1). Sickness behavior in the infected individual is triggered by mediators of the activated immune system that signal to the brain, thus linking the immunological (inflammatory) response with the psychological (behavioral) response to a pathogen. These inflammatory mediators include cytokines (e.g., interleukins, IL; tumor necrosis factor, TNF) that can be assessed in the circulation in addition to clinical markers of inflammation (e.g., C-reactive protein, CRP). Inflammation and sickness behavior are paralleled by neuroendocrine changes including activation of the autonomic nervous system and the hypothalamus-pituitary-adrenal (HPA) axis (1), which are both critical for the feedback regulation of the immune response.

Sickness also has consequences for the social environment. Unaffected partners, peers, and relatives of a sick person will adapt behaviorally by expressing e.g., fear of infection, and avoiding or helping behaviors - disease-control strategies that can be observed in animals as well (2, 3). However, the consequences can also extend beyond the immediate social environment, as the COVID-19 pandemic has shown: worldwide efforts to prevent disease by monitoring and restricting social interactions ultimately led to governmental actions that markedly affected the freedom and social life of individuals. The aim of this Research Topic was to bring together original research articles, reviews, and opinion articles that shed light on the interplay between the immune system, sickness (behavior) and social as well as psychological consequences. We here summarize ten accepted manuscripts that cover a wide range of these topics (see **Figure 1**).

Parts of the Research Topic address the concept of sickness behavior and provide insights into its historical development and the underlying neuro-immune mediators. Konsman discusses the concepts of sickness, disease, and illness, and what is considered to be "sickness behavior" and "illness behavior" across the fields of Biology, Psychology, and Sociology. Although these concepts have evolved differently between the fields, due to different traditions of research, many aspects are similar and compatible. This calls for an interdisciplinary approach to deepen

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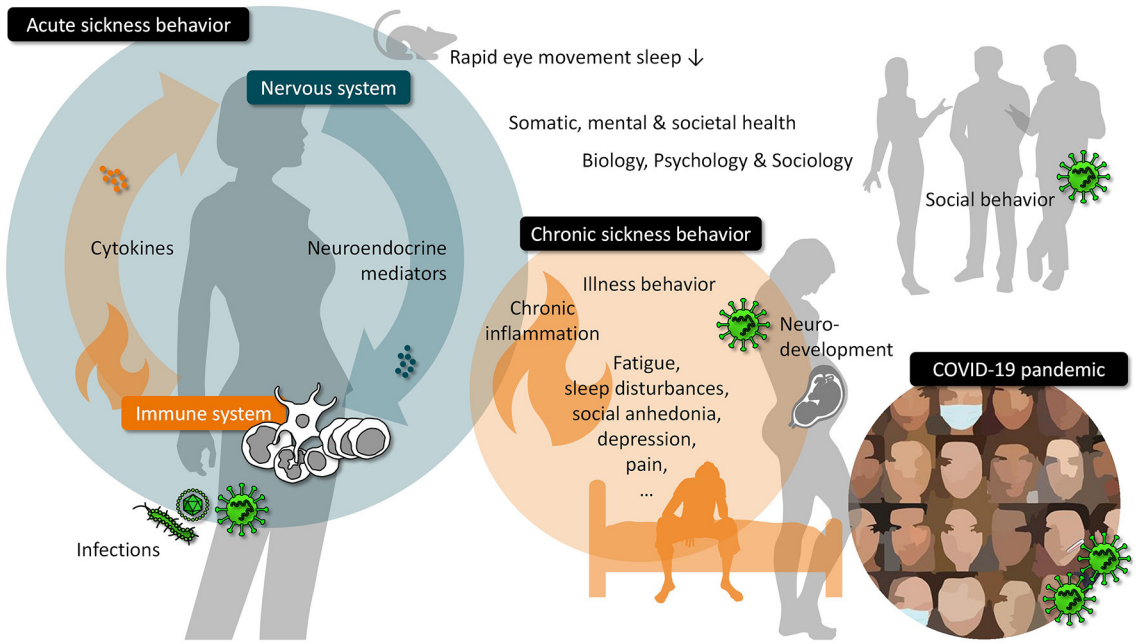

FIGURE 1 | Overview on topics related to the interplay between the immune system, sickness (behavior) and social as well as psychological consequences.

our understanding of sickness behavior. Taking a historical perspective on fever and sickness behavior research, Kelley and Kent highlight the importance of concepts that link immunology and systemic physiology. They discuss immune to brain signaling pathways such as cytokines and central nervous responses to immune signals such as activation of the HPA-axis. One important neuronal target region of immune signals is the hypothalamus, which regulates fever, stress systems, sleep-wake behavior, food intake, and social behavior. Using fiber photometry in mice, Borniger and de Lecea demonstrate that activity of GABAergic neurons in the lateral hypothalamus is highest during rapid eye movement (REM) sleep. Immune activation by injection of lipopolysaccharide acutely suppressed the activity of these neurons and eliminated REM sleep behavior.

All aspects of sickness behavior in response to acute infection, including changes in sleep, are seen as adaptive, as they presumably serve immune defense and recovery, e.g., by saving energy that can be re-allocated to the fighting immune system (4). In chronic conditions, however, long-lasting sickness behavior can become maladaptive and contribute to disease symptoms. In recent years, many studies have suggested a causal link between ongoing inflammation and impaired mental health (1). Apart from depressive symptoms, this may also hold true for other aspects of sickness behavior such as pain and fatigue. However, in populations with low-grade to normal cytokine levels, or subclinical distress, the relationship between cytokine levels and clinical features may be complex. Straka et al. use a community sample of 2,077 individuals to investigate the effect of age on the, at this point, fairly established relationship between inflammatory markers and depressive states. They show that while a positive relationship was seen between the inflammatory markers IL-6 and CRP and somatic complaints, a negative relationship between these markers and anhedonia appeared. Most importantly, these effects were stronger with increasing age. Karshikoff et al. investigate the relationship of inflammatory markers and clinical features in 261 patients with pelvic pain. This population has similar inflammatory levels as the healthy controls, and a negative correlation was seen between the pro-inflammatory cytokine IL-8 and the widespreadness of pain, while a positive relationship was seen for the regulatory cytokine granulocyte-macrophage colony-stimulating factor. This study also suggests that fatigue is more strongly related to cytokine levels in the chronic pain group, than pain intensity or depressive symptoms. These findings suggest that inflammatory mechanisms related to pain and depression are complex and multifactorial. Munk et al. build on this notion and propose to apply the Cognitive Activation Theory of Stress (CATS) to chronic post-surgical pain after breast cancer surgery. CATS is a psychobiological theoretical framework bringing expectancies at the center of the stress response and health outcomes. Munk et al. argue that coping ("the acquired expectancy that most or all responses to a situation will lead to a positive outcome"), helplessness ("the acquired expectancy of one's actions having no impact on the outcome of an aversive event"), and hopelessness ("the expectancy of most or all responses leading to negative outcomes") can modulate the physiological stress response to the post-surgical pain in women with breast cancer. A sustained stress response can in turn lead to chronic pain, through mechanisms such as chronic inflammation, central sensitization, and cortisol dysfunction, and could be treated by

targeting outcome expectancies, for instance using Acceptance and Commitment Therapy or hypnosis. These examples of clinical conditions emphasize the importance of understanding acute, physiological, adaptive brain-immune interactions, and their chronic, pathological, maladaptive dysregulation in patients.

In addition to ongoing inflammation, maternal infection during pregnancy has also been identified as a risk factor for mental disorders with neurodevelopmental etiology. When occurring during vulnerable phases of fetal brain development, infection of the mother can change the offspring's neurodevelopmental trajectories and can increase its risk to develop a severe mental illness such as schizophrenia, autism spectrum disorder, and bipolar disorder later in life (5). Against this background, Reyes-Lagos et al. discuss in their perspective article the potential implications and long-term consequences of the COVID-19 pandemic on mental health, and illustrate why there is an urgent need for longitudinal studies in affected pregnant women and their offspring. Given the important role of the cholinergic anti-inflammatory pathway for immune homeostasis they propose to analyze this pathway during gestational infection with SARS-CoV-2, and to explore vagus nerve stimulation or the use of cholinergic agonists as therapeutic options for dampening virus-induced maternal and fetal inflammation.

One objective of this Research Topic was to consider the interplay between immune activation and social behavior. In their review, Smith and Bilbo summarize literature on the bi-directional relationship between immune functions and social life. They describe how infection and inflammation alter social behavior and how, on the other hand, social experiences can influence the immune system. Smith and Bilbo additionally give an outlook on how these findings might be relevant in the context of the COVID-19 pandemic. Two other manuscripts focus specifically on the social and psychological consequences of the COVID-19 pandemic. In their review, Saladino et al. describe the impact of the pandemic on the well-being and mental health of children, young adults, as well as health care workers. Furthermore, the authors discuss the consequences for interpersonal relationships and interactions and consider the potential role of online psychological support and psychotherapy. Stierand et al. investigate how the appraisal of situations involving close or distant contact with other people changed from before to during the first wave of the COVID-19 pandemic in Germany. They report that both the risk associated with a particular situation and the individual's general perception of current infection risk are related to changes in comfort in social situations. These articles show the far-reaching consequences of a virus pandemic and the associated measures for the psyche and for social interactions.

In conclusion, our Research Topic brought together scientists from different disciplines, reporting basic and clinical research in animals and humans to delineate brain-immune interactions in systemic physiology and in clinical conditions, and to understand the immunological mechanisms of mental illness, pain, fatigue, and social anhedonia across the lifespan. The COVID-19 pandemic has featured the relevance of brain-immune interactions for somatic, mental, and societal health, and the need for comprehensive, longitudinal studies that monitor immunological, neurobehavioral, and psychological parameters in parallel. Only with such an interdisciplinary approach we might one day understand the transition from acute, adaptive to chronic, maladaptive conditions and thus the complexity of sickness behavior.

AUTHOR CONTRIBUTIONS

All authors have contributed to writing the manuscript.

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The Psychological and Social Impact of Covid-19: New Perspectives of Well-Being

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The recent Covid-19 pandemic has had significant psychological and social effects on the population. Research has highlighted the impact on psychological well-being of the most exposed groups, including children, college students, and health workers, who are more likely to develop post-traumatic stress disorder, anxiety, depression, and other symptoms of distress. The social distance and the security measures have affected the relationship among people and their perception of empathy toward others. From this perspective, telepsychology and technological devices assume important roles to decrease the negative effects of the pandemic. These tools present benefits that could improve psychological treatment of patients online, such as the possibility to meet from home or from the workplace, saving money and time and maintaining the relationship between therapists and patients. The aim of this paper is to show empirical data from recent studies on the effect of the pandemic and reflect on possible interventions based on technological tools.

Keywords: COVID-19, empathy, psychological disease, psychotherapy, social distancing, telepsychology

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INTRODUCTION

The Covid-19 pandemic led to a prolonged exposure to stress. As a consequence, researchers showed an increased interest in measuring social and community uneasiness in order to psychologically support the population. This increased attention might help in managing the current situation and other possible epidemics and pandemics. The security measures adopted in managing the pandemic had different consequences on individuals, according to the social role invested. Some segments of the population seem to be more exposed to the risk of anxious, depressive, and post-traumatic symptoms because they are more sensitive to stress.

The following article has two focuses of interest: (1) the evaluation of the psychological and social effects of the pandemic on the population, mostly children, college students, and health professionals; and (2) the identification of new perspectives of intervention based on digital devices and in line with the social security measures and mental health promotion. Telepsychology, for instance, is a valid tool, effective in taking charge of the psychological suffering caused by the pandemic and in preventing the chronicity of the disease. The prolonged stress could involve anxiety, depression, and the inability to manage traumatic and negative emotions. Furthermore, the constant fear of contagion affects daily life and leads to social isolation, modifying human relations.

COVID-19 AND AT-RISK POPULATIONS: PSYCHOLOGICAL AND SOCIAL IMPACT OF THE QUARANTINE

Studies of pandemics faced over time, such as SARS, Ebola, H1N1, Equine Flu, and the current COVID-19, show that the psychological effects of contagion and quarantine is not limited on the fear of contracting the virus (Barbisch et al., 2015). There are some elements related to the pandemic that affect more the population, such as separation from loved ones, loss of freedom, uncertainty about the advancement of the disease, and the feeling of helplessness (Li and Wang, 2020; Cao et al., 2020). These aspects might lead to dramatic consequences (Weir, 2020), such as the rise of suicides (Kawohl and Nordt, 2020). Suicidal behaviors are often related to the feeling of anger associated with the stressful condition widely spread among people who lived/live in the most affected areas (Miles, 2014; Suicide Awareness Voices of Education, 2020; Mamun and Griffiths, 2020). In light of these consequences, a carefully evaluation of the potential benefits of the quarantine is needed, taking into account the high psychological costs (Day et al., 2006; Mazza et al., 2020).

As reported in a recent survey administered during the Covid-19 pandemic, children and young adults are particularly at risk of developing anxious symptoms (Orgilés et al., 2020). The research involved a sample of 1,143 parents of Italian and Spanish children (range 3–18). In general, parents observed emotional and behavioral changes in their children during the quarantine: symptoms related to difficulty concentrating (76.6%), boredom (52%), irritability (39%), restlessness (38.8%), nervousness (38%), sense of loneliness (31.3%), uneasiness (30.4%), and worries (30.1%). From the comparison between the two groups—Spanish and Italian parents—it emerged that the Italian parents reported more symptoms in their children than the Spanish parents. Further data collected on a sample of college students at the time of the spread of the epidemic in China showed how anxiety levels in young adults are mediated by certain protective factors, such as living in urban areas, the economic stability of the family, and cohabitation with parents (Cao et al., 2020). On the contrary, having infected relatives or acquaintances leads to a worsening in anxiety symptoms. Furthermore, the economic problems and the slowdown in academic activities are related with anxious symptoms (Alvarez et al., 2020). In addition, an online survey conducted on the general population in China found that college students are more likely to experiencing stress, anxiety, and depression than others during the pandemic (Li et al., 2020). These results suggest monitoring and promoting mental health of youths in order to reduce the negative impact of the quarantine (CSTS, 2020; Fessell and Goleman, 2020; Li et al., 2020).

Health-care workers (HCWs) are another segment of population particularly affected by stress (Garcia-Castrillo et al., 2020; Lai et al., 2020). HCWs are at risk to develop symptoms common in catastrophic situations, such as post-traumatic stress disorder, burnout syndrome, physical and emotional exhaustion, depersonalization, and dissociation (Grassi and Magnani, 2000; Mache et al., 2012; Øyane et al., 2013). However, an epidemic presents different peculiarities compared to a catastrophic event, for instance, the stigmatizing attitudes in particular toward health professionals, who are in daily contact with the risk of infection (Brooks et al., 2020). During SARS, up to 50% of health-care professionals suffered from acute psychological stress, exhaustion, and post-traumatic stress, caused by the fear of contagion of their family members and the prolonged social isolation (Tam et al., 2004; Maunder et al., 2006).

As a consequence of the pandemic, the health professionals who were overworked suffered high level of psychophysical stress (Mohindra et al., 2020). Health professionals also lived/live in daily life a traumatic condition called secondary traumatic stress disorder (Zaffina et al., 2014), which describes the feeling of discomfort experienced in the helping relationship when treatments are not available for all patients and the professional must select who can access them and who cannot (Roden-Foreman et al., 2017; Rana et al., 2020). Data from a survey on 1,257 HCWs who assisted patients in Covid-19 wards and in second- and third-line wards showed high percentages of depression (50%), anxiety (44.6%), insomnia (34%), and distress (71.5%) (Lai et al., 2020). Also, the constant fear of contagion leads to obsessive thoughts (Brooks et al., 2020), increasing the progressive closure of the person and reducing social relationships. In line with these results, Rossi et al. (2020) evaluated mental health outcomes among HCWs in Italy during the pandemic, confirming a high score of mental health issues, particularly among young women and front-line workers. Furthermore, Spoorthy et al. (2020) conducted a review on the gendered impact of Covid-19 and found that 68.7–85.5% of medical staff is composed of women, and the mean age ranged between 26 and 40 years. Also, women are more likely to be affect by anxiety, depression, and distress (Lai et al., 2020; Zanardo et al., 2020). Liang et al. (2020) also found a relation between age and depressive symptoms associated with the pandemic. Indeed, the medical staff at younger ages (<30 years) reports higher self-rated depression scores and more concern about infecting their families than those of older age. Staff > 50 years of age reported increased stress due to patient's death, the prolonged work hours, and the lack of personal protective equipment. Cai et al. (2020) also found that nurses felt more nervous compared to doctors.

As emerged by the recent literature, the promotion of psychological interventions on the specific population who is more likely to develop pathologies and suffering is needed. The Lancet Global Mental Health Commission's observation (Patel, 2018) reported that the use of digital technologies can provide mental health interventions in order to reduce anxiety and stress levels and increase self-efficacy (Kang et al., 2020; Xiao et al., 2020).

TELEPSYCHOLOGY: TRAINING AND PROMOTION OF PSYCHOLOGICAL WELL-BEING

In order to reduce anxiety and depression symptoms widespread among the population, the World Health Organization (2019) and the Centers for Disease Control and Prevention (2020) proposed specific guidelines on the correct use of health

protection with the aim to minimize the distress associated with health-care professions.

At the same time, as a consequence of the emerging issues, psychotherapists provided psychological support online, addressing the technological challenge (Greenberg et al., 2020); Liu et al., 2020). In line with the technological progress, professional organizations promoted specific guidelines and policies related to customer protection, privacy, screening, evaluation, and development of self-help products (Duan and Zhu, 2020; Zhou et al., 2020). Technological development in mental health foreshadows future trends that include "smart" mobile devices, cloud computing, virtual worlds, virtual reality, and electronic games in addition to the traditional psychotherapy tools. In this perspective, it is important to help future generations of psychologists and patients to collaborate in the potential growth areas, through education and training on the benefits and effectiveness of telepsychology (Maheu et al., 2012).

Indeed, more awareness of the potentials of the online services is needed, exploring the main differences between the devices (chat, video-audio consultation, etc.) in order to use them in relation to the specific purposes identified by the professional. For example, the Italian Service of Online Psychology conducted a study based on a service of helpdesk on Facebook. This service guided people in asking for psychological help, working on their personal motivation. At the same time, another helpdesk on Skype provided some psychological sessions *via* webcam (Gabri et al., 2015). In this line, telecounseling is a diffuse online method used by counselors and psychologists during the recent pandemic (De Luca and Calabrò, 2020).

One of the future goals of public and private psychological organizations should be the promotion of specific training for psychologists and psychotherapists, with the following aims: (1) developing the basic skills in managing the effects of a pandemic and of emergency situations; and (2) sensitizing patients to online therapeutic relationship, providing the main rules and benefits of the process (Stoll et al., 2020; Joint Task Force for the Development of Telepsychology Guidelines for Psychologists, 2013). On this line, a significant example is the Virginia Commonwealth University (VCU) which proposed PhDs in telepsychology, with the aim of training future psychologists in managing the psychological effects of the pandemic through an online psychology service (Baylor et al., 2019). The service provided by the VCU had been effective in reducing anxiety, depression (Sadock et al., 2017), and hospital recoveries (Lanoye et al., 2017). As shown, telepsychology assumes a key role in the improvement of health care. Online psychological services avoid geographical barriers and are suitable to become a useful integrated tool in addition to traditional psychotherapy (APS, 2020; Perrin et al., 2020).

ADVANTAGES OF PSYCHOLOGICAL SUPPORT AND ONLINE PSYCHOTHERAPY

Online psychological services provide several advantages, especially in the current situation of pandemic. First of all, online services help people in a short period of time, reducing the risk of contagion and the strong feeling of anxiety in both psychotherapists and patients, who feel uncomfortable in doing traditional psychotherapy due to the pandemic (Békés and Aafjes-van Doorn, 2020). Furthermore, Pietrabissa et al. (2015) identified some of the main advantages of telepsychology, such as the decrease in waiting for the consultation, because it takes place from home or from the workplace, saving time and expense, less travel and rental costs for the office, for those who provide the service and for those who use it. As reported by the authors, online psychological services facilitate access to people who struggle to find support close to their social environment, avoiding difficulties related to mobility. Also, online services help people who have less confidence in psychotherapy. Indeed, mostly online psychotherapy takes place in one's comfort zone, facilitating the expression of problems and feelings.

According to the situations, online services could provide a different medium. For instance, the chat is a useful tool to establish a first assessment of a person who feels uncomfortable in using video. Indeed, the online psychotherapy is perceived as more "acceptable." Suler (2004) defined the term *online disinhibition effect* demonstrating how the web, unlike the real life, leads to the failure of the hierarchical relationship based on dominant-dominated among individuals; this aspect, according to the author, allows a greater sense of freedom in expressing oneself and less concern related to judgment (*ibid.*). Other researchers (Mantovani, 1995; Tosoni, 2004) have integrated to the construct of *online disinhibition effect* the concept of social space, emphasizing the role of the "situation," of the "social norms" (Brivio et al., 2010, p. 811), of the tools ("artifacts"), and of the cyberplace, which allow different levels of interaction. Each person has a different experience of the network and several levels of disinhibition. For instance, a mild disinhibition could be a person who chooses to ask for help talking with a psychologist about their problems; while a high disinhibition could be represented by flaming, an expression of online bullying or cyberstalking.

Online psychological services should be integrated with the various territorial services in order to provide the patients local references in relation to the specific health and economic needs. Finally, the possibility for the therapist and for the patient to record the sessions *via* chat and in audio/video mode—with the informed consent of the participants (Wells et al., 2015)—provides another useful tool to compare the sessions and to underline the positive outcomes and the effectiveness of the therapeutic process. According to this perspective, online psychological support and psychotherapy become a resource for psychotherapists and patients in a co-build relationship (Algeri et al., 2019).

PSYCHOLOGICAL AND SOCIAL SUFFERING AND THE EMPATHIC PROCESS

In analyzing the psychological impact of the quarantine, the importance for individuals to feel integral part of the society emerged, an aspect often undervalued in psychological well-being. Experts of public health believe that social distancing

is the better solution to prevent the spread of the virus. However, although it is not possible to predict the duration of the pandemic, we know very well the serious impact of these measures on the society, on relationships and interactions, in particular on the empathic process. In the early 90s, empathy was described as a form of identification in the psychological and physiological states of others. This definition led to a debate between the disciplines of philosophy of psychology and philosophy of the mind (Franks, 2010). Willard Van Orman Quine (1908–2000) renewed attention to the debate on empathy with a thesis on the development of language and mind in the analytical philosophy. According to Quine, the attribution of the so-called intentional states, through which the psychology commonly explains human behavior, is based on empathy (Treccani, 2020) and leads people to attribute beliefs, desires, and perceptions (Quine, 1990, 1992, Pursuit of Truth: Revised Edition, 1992). Analyzing this aspect within the recent situation of the pandemic, an increment of antithetical positions and attitudes could be noticed. On the one hand, people identify themselves with those who suffer (neighbors, friends, relatives who are living stressful events), promoting activities such as the so-called "suspended expenses." For instance, solidarity and humanitarian activities, food, and medicine delivery for people who are unable to go to the supermarket. On the other hand, there is a part of the population who experiences a feeling of "forced empathy." This aspect could be also emphasized by the use of technological devices that might lead to a depersonalization of relationships, forcing the sense of closeness, at least virtually. The hyperconnection of feelings becomes a way to reduce the self-isolation and its consequences, representing the contrary of the idea of Durkheim (1858–1917), who considered society as a specific entity, built on social facts (Durkheim, 1922). The sensation "to be forced to feel" could lead people to distance themselves from others after the emergency situation, incrementing social phobias.

Also, human communication is changing. The formal question "how are you?" at the beginning of a conversation is no longer just a formality, as before the pandemic. For example, the relationship between employee and the manager is different, leading to more responsibilities in listening and understanding feelings expressed during the video call, generating a forced reciprocity. Hence, the aforementioned "forced empathy" may be common in this period because the social distance and the emergency situation make people want to be heard and appreciated, and the simple question "how are you?" becomes an anchor to express fears and emotions (Pasetti, 2020).

DISCUSSION

The Covid-19 pandemic has affected the way people live interpersonal relationships. The lockdown was characterized of a different organization of daily life, with an incrementation of time at home and a reduction of distance through digital devices. This period was also seen as an evolution in the concept of empathy, producing new perspectives in the study of the phenomenon according to a sociological and neurological points of view. Indeed, empathy—defined as the ability to understand and share the feelings of another—involves several elements, such as: (a) social context and historical period of the individual, (b) neurological mechanisms, and (c) psychological and behavioral responses to feelings of others. The neuro-sociological perspective analyzes the mechanisms involved in the empathic process, focusing on human communication and interpersonal relationships (Singer and Lamm, 2009; Decety and Ickes, 2009). Specifically, in this historical period characterized by an increment in the man–machine relationship, neurosociology could become one of the principal sciences for the study of human relations and technology. "We live increasingly in a human–machine world. Anyone who doesn't understand this, and who is not struggling to adapt to the new environment—whether they like that environment or not—is already being left behind. Adapting to the new, fast-changing, technologically enhanced context is one of the major challenges of our times. And that certainly goes for education" (Prensky, 2012, p. 64).

According to the abovementioned considerations, our suggestion consists in:

Primary prevention. Studying the impact of the pandemic toward an at-risk population to reduce symptoms related to stress and providing specific online psychological counseling based on the target (students, medical staff, parents, and teachers).

Secondary prevention. Overcoming the limitations of the human interaction based on digital devices: (1) developing new spaces of inter- and intrasocial communication and new tools of support and psychological treatment, reproducing the multisensory experienced during the face-to-face interaction (Virtual Reality, holograms, serious game etc.); (2) training the next generation of psychotherapists in managing online devices and in implementing their adaptive and personal skills; and (3) sensitizing the general population on telepsychology and its advantages.

Research according to the neurosociological perspective. Studying human interaction mediated by new technologies and the role of empathy, associating neuroscience, sociology, and psychology.

AUTHOR CONTRIBUTIONS

VS, DA, and VA conceptualized the contribution. VS wrote the paper, reviewed the manuscript, and provided the critical revision processes as PI. All authors approved the submission of the manuscript.

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MINI REVIEW
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The Legacy of Sickness Behaviors

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Systemic infections of all types lead to a syndrome known as sickness behaviors. Changes in the behavior of febrile humans and animals formed the original basis for this concept. Body temperature is behaviorally regulated in both endotherms and ectotherms. However, infections cause other changes in body functions, including sleep disruption, anorexia, cognitive and memory deficits and disorientation. The brain mediates this entire cluster of symptoms, even though most major infections occur outside the brain. The true importance of sickness behaviors is not the numerous discoveries of symptoms that affect all of us when we get sick. Instead, the legacy of 30 years of research in sickness behaviors is that it established the physiologic importance of reciprocal communication systems between the immune system and the brain. This conceptual advance remains in its infancy.

Keywords: immune-brain communication, fever, systemic physiology, interleukin-1, motivated behaviors

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INTRODUCTION

It started with a fever. Well, really, it started with trying to understand fever. After all, pathogenic microbes like SARS-CoV-2 infect epithelial cells in the lungs as well as endothelial cells. Influenza also infects epithelial cells of the respiratory tract. Entry of SARS-CoV-2 and influenza into these cells establishes residence, as well as their ability to set up housekeeping outside the brain. Yet, a part of the brain known as the hypothalamus and higher brain centers control fever, not the lungs. This finding characterizes the research on fever and infectious diseases that long followed disparate paths. Lipopolysaccharide (LPS) is composed of a lipid and a polysaccharide expressed on the outer membrane of Gram-negative bacteria. Following the discovery that LPS acts as an adjuvant to enhance antibody responses, graduate students who studied immunology in the 1960s, 70s, and '80s were taught that the main target for LPS is B lymphocytes. This of course ignored the much earlier discovery in 1888 that injection of heat-killed gram-negative bacteria into rabbits causes fever (summarized by Cavaillon; https://www.lpsbiosciences.com/index.php/news-blog-3/lps-history). This simple example exemplifies the dichotomy in the relationship between studies in immunology and systemic physiology that continued until the end of the twentieth century.

This unrealistic state of affairs began to collapse in the late 1970s as a consequence of the purification, cloning and expression of the first cytokine, human interferon-α, in 1978. Six years later, the United States Food and Drug Administration approved interferon-α for clinical use. Advances in recombinant DNA technology and expression systems rapidly led to purification and sequencing of two more "substances" produced by leukocytes. Their biological activities defined their names: endogenous pyrogen and/or lymphocyte activating factor and T-cell growth factor. Time-consuming and costly biological assays were required for quantification. ELISA assays did not exist. The scientific community now defines these two substances as interleukin-1 (IL-1) and

interleukin-2 (IL-2), respectively. Thirty-five more cytokines and their receptors have been sequenced, cloned and expressed since the original discovery of IL-1 and IL-2.

All modern-day physiologists, immunologists, and neuroscientists who are engaged in temperature regulation research are now fully aware that in order to understand fever one needs to understand cytokines. They know that pathogens like gram-negative bacteria, SARS-Cov-2 and influenza lead to production of endogenous pyrogens in the periphery and the hypothalamus. In turn, these endogenous pyrogens alter the activity of warm- and cold-sensitive neurons in the preoptic area of the anterior hypothalamus. The result is the production of second messengers like prostaglandin E2 (PGE 2) and ceramide that initiate physiological changes leading to fever. But these scientists still want to know how something produced outside the brain communicates with structures inside the brain to cause fever. Circumventricular organs that possess permeable capillaries, blood-borne cytokines that activate cerebral microvascular endothelial cells, afferent neural connections from the periphery to the brain like the vagus nerve, entry of immune cells into the brain parenchyma via the choroid plexus and the recently discovered lymphatic drainage system in the meninges all have scientific support. But a precise and universally accepted roadmap of all of the specific routes of the communication networks that mediate not only fever but also the variety of other symptoms that accompany sickness still does not exist.

GROUNDWORK FOR THE DISCOVERY OF SICKNESS BEHAVIORS

Something From the Immune System Increases Glucocorticoids in Blood

Hans Selye advanced the concept of stress by showing that a variety of discomforting challenges in rats cause hypertrophy of the adrenals and involution of the thymus gland, one of the two primary lymphoid organs where lymphocytes are formed (1). Knowledge of the immune system was in its infancy at that time, but this discovery pointed scientists to a potential relationship between stress and immunity that occurred via a route that was later shown to travel through the brain (i.e., the hypothalamic-pituitary-adrenal axis). By the 1950s, the scientific community accepted that a part of the brain known as the hypothalamus was critical to stress responses. Noxious stimuli cause the hypothalamus to secrete corticotropin-releasing factor (CRF) into hypophyseal portal vessels that connect to the anterior pituitary gland. This causes release of pituitary-derived adrenocorticotropin hormone (ACTH) into the blood. Within an hour, there is an increase in systemic concentrations of the glucocorticoids corticosterone (rodents) and cortisol (humans). These early discoveries defined the hypothalamic-pituitary-adrenal axis.

In 1957, Wexler et al. established that injection of LPS peripherally causes an increase in plasma glucocorticoids (2). This led to the heretical idea that foreign antigens not only induce an immune response but also inform the brain that the body is experiencing an infection. But exactly how this occurred had to await the discovery of immune messengers that were cloned and expressed in the late 1970s and early 1980s. We now know these proteins as cytokines.

Systemic IL-1 Increases Both Adrenocorticotropic Hormone and Glucocorticoids

Besedovsky et al. reported the earliest and strongest evidence to establish that cytokines act as afferent signals that carry messages to the brain. His group injected supernatants from mitogen-stimulated spleen cells into the peritoneum of rats. This caused corticosterone in blood to rise (3) and norepinephrine in the hypothalamus and brain stem to decline (4). Professor Besedovsky, however, was not only a physiologist but also a scholar of immunology. He knew that glucocorticoids not only inhibit many actions of the immune system but were likely to also impair the production of the newly-discovered cytokine IL-1. His expertise in physiology led him to speculate that a negative feedback system existed between the immune system and the anterior pituitary gland (5). In this model, IL-1 released after a systemic infection would cause secretion of ACTH, a rise in plasma glucocorticoids and inhibition of the initiating immune response. He tested this hypothesis by isolating human white blood cells and exposing them to Newcastle disease virus. Supernatants from these cultures increased plasma glucocorticoids. Interferon-α was likely secreted into these supernatants. However, interferon-α is species-specific, so human interferon-α was unlikely to be the culprit when injected into rodents. Instead, he attempted to block the glucocorticoid-increasing activity by pretreating the supernatants with a neutralizing antibody to IL-1. This experiment established that supernatants treated with the IL-1 neutralizing antibody were unable to increase plasma glucocorticoids in rats. Professor Besedovsky went on to show that recombinant IL-1 increased corticosterone in nude mice that lack T cells. As such, the glucocorticoid-stimulating activity of IL-1 was unlikely to be a downstream product of T cell-derived cytokines such as IL-2. These experiments proved that IL-1 serves as an afferent signal from the immune system that subsequently increases both pituitary-derived ACTH and corticosterone from the adrenal gland.

Systemic IL-1 Acts in the Brain

The experiments described above were clever and ground-breaking, but no structure in the brain had yet been shown to be involved. Neurons from a part of the brain known as the paraventricular nucleus of the hypothalamus secrete CRF that causes release of pituitary-derived ACTH into the blood. But other possible sources of ACTH exist, such as a report showing that IL-1 induces release of ACTH directly from pituitary cells (6) and expression of the ACTH precursor gene, proopiomelanocortin, by leukocytes (7). Two back-to-back publications in *Science* magazine unequivocally proved that systemic administration of IL-1 increased release of CRF from hypothalamic neurons (8, 9). These data convincingly proved

that soluble substances produced by activated leukocytes could inform the brain that a perturbation has occurred in the immune system. This groundbreaking finding led others to ask if these same signals from the immune system affect other aspects of brain function, with a particular emphasis on behavior.

SICKNESS BEHAVIORS

Thermoregulatory Behavior Formed the Basis of the Concept of Sickness Behavior

The concept of sickness behaviors had its roots in a large literature on thermoregulatory behavior. By the 1980s, it was well-known that both endo- and ectotherms utilize a variety of behaviors to regulate body temperature. For example, ectotherms like reptiles estivate during the heat of the day to reduce water loss and prevent pathological damage caused by high body temperature. Endotherms like mammals and birds lower their metabolic load in hot weather by reducing foraging for food and seeking cooler environments (e.g., burrows or shade). In cold weather, both ectotherms and endotherms reduce their surface area to minimize heat loss, a behavior that often takes the form of huddling.

Benjamin Hart, a veterinarian at the University of California, Davis wrote a review article in which he connected the dots between fever and behavior (10). He noted that striking changes in behavior occur during fever, including reduced food consumption, animal grooming to promote evaporative heat loss and polydipsia, lethargy and insomnia. Professor Hart wrote, "…the behavior of sick animals and people is not a maladaptive response or the effect of debilitation, but rather an organized, evolved behavioral strategy to facilitate the role of fever in combating viral and bacterial infections." His paper extended ideas about fever to a variety of new and some previously unrecognized thermoregulatory behaviors. This review reshaped the landscape about immune system to brain communication. However, the focus was on fever and thermoregulatory behavior. It did not address the multiple aspects of sickness behaviors recognized today. These include symptoms such as inflammatory pain, a variety of mental health disorders and learning and memory deficits.

All new theories and concepts must be rigorously tested before they become facts. Cloning and expression of cytokines like IL-1, tumor necrosis factor (TNF), and IL-6 occurred in the early part of the 1980 decade. But most of the behavioral experiments with these recombinant cytokines were initially aimed at investigating their role as endogenous pyrogens that elevate the hypothalamic set point and lead to fever. Data from these experiments ultimately led to the realization that both IL-1 and TNF serve as endogenous pyrogens. However, motivated behaviors classically reside in other structures of the limbic system beside the hypothalamus. As such, the question arose as to whether cytokines would affect other brain regions like the limbic cortex, hippocampal formation and amygdala. In short, the Hart review that focused on the connection between disease and fever encouraged scientists to ask whether other behaviors induced by infections and the subsequent release of cytokines are mediated by higher-order brain structures.

Reduction in Motivated Behavior Is Independent of Fever

The first clue that cytokines are involved in human sickness behaviors came from phase 1 clinical trials for cancer. Systemic injections of interferon α, IL-1 and IL-2 all induced a variety of adverse effects, including inappetence, fever, headaches, fever, malaise, disorientation and somnolence (11). Many scientists argued that these CNS-mediated symptoms were due to toxicity caused by injection of high doses of cytokines into very sick patients. Clearly, these early data established that peripheral cytokines could have major effects on the brain. However, scientists considered the effects of systemic cytokines on the brain to be pure pharmacological rather than physiological effects. They did not seriously consider the possibility that physiologic concentrations of peripheral cytokines synthesized and released following exposure to infectious and non-infectious agents could communicate with the brain to induce sickness behaviors.

Professor Evelyn Satinoff at the University of Illinois Urbana-Champaign was a pioneer in the field of thermoregulation, which led her to investigate fever, infection and sleep and wakefulness. Stephen Kent earned his Doctorate of Philosophy under her guidance. In 1990, Steve accepted a post-doctoral position to work with both Professors Kelley and Dantzer using behavioral equipment that was available in Bordeaux, France. Steve designed and conducted clever experiments and published the data with Nancy Rothwell's group in Manchester, England. The goal was to determine if fever is responsible for the IL-1-induced reduction in food-motivated behavior (12). He used classic operant conditioning chambers in which hungry rats had to press a lever to obtain a small pellet of food. Rats were given an injection of recombinant IL-1 systemically (intraperitoneal, IP) or centrally (intracerebroventricular; ICV). Injection of the IL-1 receptor antagonist (IL-1RA) preceded injections. Food-motivated behavior, social investigation of a novel juvenile, body temperature and metabolic rate were the dependent variables.

As expected, IL-1 administered in either the peritoneum or brain ventricles increased body temperature (∼1.5 C) and oxygen consumption (∼18%) and reduced food-motivated behavior (∼90%) and social investigation (∼90%). Pretreatment with IL-1RA systemically followed by IL-1 given via the same peritoneal route reduced both body temperature and metabolic rate. However, when both compounds were administered ICV, IL-1RA failed to affect either of these two variables. The behavioral experiments provided considerably different results. Regardless of whether IL-1 was given IP or ICV, the IL-1RA antagonist injected by the same route blocked both the reduction in food-motivated behavior and social investigation. Pretreatment with IL-1RA given ICV followed by injection of IL-1 via the IP route yielded an unexpected result. Although the antagonist had no effect on either the rise in body temperature or metabolic rate, it blocked the reduction in both food-motivated and social behavior. This result established that rats with an elevated metabolic rate and fever are fully capable of engaging in motivational behaviors. As such, the data were interpreted

to indicate that the fever-inducing and the behavioral effects of IL-1 are medicated by different receptor mechanisms, all of which was summarized in a state-of-the-art review article (13). Subsequently, Fortier et al. (14) demonstrated that the febrile and anorexic effects of the viral mimic, polyinosinic:polycytidylic acid (poly I:C), are mediated via differing pathways. Similarly, Damm et al. (15) reported that LPS-induced sickness behaviors and fever can be disassociated. Importantly, Corrard et al. (16) reported similar results in feverish children with data showing a dissociation between a number of clinical sickness behaviors and the severity of fever. These human data are consistent with the original results of Kent et al. (12) by showing that clinical manifestations of sickness are independent of fever.

Experiments published more than 20 years after the initial reports of sickness behaviors have strengthened these early findings showing that fever can occur separately from sickness behaviors. For example, investigators interested in motivational theory have studied sickness behaviors. They asked whether physiological states like hunger, fear or libido affect any aspect of sickness behaviors. They found that sickness can either increase or decrease social behaviors [reviewed by (17)]. A recent paper reported that sickness behaviors and fever can be disassociated in LPS-injected guinea pig pups, depending upon whether LPS is injected with their mother nearby (18). Presence of the mother enhanced LPS-induced fever in the pups even though sickness behaviors were nearly absent. In humans, activation of the immune system with a typhoid vaccine increased negative mood and IL-6 in the absence of fever (19). Once again, exogenous stimuli as provided by stressful psychological tasks increased these differences, consistent with theories of motivation.

CODA

Prior to the beginning of the twenty-first century, naysayers argued that the immune and central nervous systems do not dialogue with one another. They advocated maintaining the distinct disciplines of immunology and neuroscience, with little to no communication between the two. But emerging data demanded a more innovative approach. Physiology, which is a truly integrative science that spans reciprocal regulatory control systems among all organ systems, was not seriously considered. The major reasons for the arguments of skeptics were the existence of the blood-brain-barrier (BBB), lack of CNS lymphoid vessels and paucity of antigen-presenting cells in the brain. The scientific community now accepts that the BBB is much more than a barrier, acting as a true interface between the blood and brain [BBI; (20)]. Secondly, a century of science was turned upside down by the discoveries of Louveau et al. (21) and Aspelund et al. (22) who showed convincing histological evidence and now the functional importance of the meningeal lymphatic system [reviewed by (23)]. Finally, it is well-documented that microglia, monocytes and dendritic cells in the brain parenchyma can express major histocompatibility antigens that present antigen to T lymphocytes [reviewed in (24)]. And of course the discovery and identification of 37 cytokines, their receptors and multiple chemokines ushered in a entirely new way of thinking about immune-brain networks.

As shown by the early experiments on sickness behaviors, systemic cytokines alert the brain that insults such as an infection or trauma have occurred in the periphery. Indeed, the brain can synthesize and express several cytokines. Many other fascinating discoveries have provided entirely new insights into brain-communication systems. They range from links between clinical depression and systemic inflammation [see reviews by (25, 26)] to the emerging roles of neurotransmitters such as acetylcholine and catecholamines in the development of bioelectronic medicine for treatment of diseases like rheumatoid arthritis and Crohn's disease [reviewed in (27)]. As such, nearly all of the naysayers have disappeared. The discovery of sickness behaviors in all forms established the powerful role of communication between the immune system and the brain. This is the true legacy of sickness behaviors.

AUTHOR CONTRIBUTIONS

The concept for this article was developed and proposed by KK and the article was jointly prepared by KK and SK. All authors contributed to the article and approved the submitted version.

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Aging as a Context for the Role of Inflammation in Depressive Symptoms

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Inflammation has been implicated in the pathogenesis and maintenance of depressive symptoms. The role of inflammation in depressive symptomatology may be complex, varying within endophenotypes and across the lifespan. Aging is associated with myriad changes in the structure and function of the brain. Yet, little attention has been given to the role of inflammation in depressive symptoms within a lifespan developmental framework. In this study, we examined whether the association between inflammation and depressive symptom domains varied by age. Participants were a community sample of individuals (N = 2,077, Range = 30–84) who participated in the Biomarker projects of the MIDUS2, MIDUS Refresher, or the MIDJA study. Inflammation was indexed by two inflammatory markers consistently implicated in depressed individuals, interleukin 6 (IL-6) and C-reactive protein (CRP), measured in blood. Depressive symptom domains, including depressed affect, anhedonia, somatic complaints, and interpersonal problems, were reported *via* the Center for Epidemiologic Studies—Depression Scale (CES-D). Inflammatory markers were associated with more somatic complaints, more interpersonal problems, and less anhedonia. Age moderated the relationship between inflammatory markers and two depressive symptom subscales. Specifically, the positive association between inflammation and somatic complaints and the negative association between inflammation and anhedonia increased with age. These observations offer preliminary evidence from a large community sample that aging may be an important context for the role of inflammatory signaling in different aspects of psychological and behavioral well-being.

Keywords: aging, depression, inflammation, lifespan, somatic complaints, anhedonia, immune system

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INTRODUCTION

Depression affects 264 million people globally every year including millions of Americans (1). Major depressive disorder (MDD) causes significant loss of productivity in the workplace and is the sixth costliest health condition in the U.S. (2–4). Indeed, the economic burden of depression is estimated at $210.5 billion in the U.S. alone (5). Depressed persons are also 20.9 times more likely to die by suicide and two times more likely to die prematurely due to other causes

(6). Yet, depression treatments with the most empirical support appear to have modest effectiveness (7). Thus, a better understanding of the factors that lead to depressive symptoms is needed in order to develop more effective treatments for this burdensome disease.

Inflammation has been linked to depressive symptoms in studies examining both exogenously-induced and naturally occurring inflammation (8, 9). Inflammation refers to the production of soluble proteins called cytokines by immune cells in response to potential threats (10). Inflammatory proteins play a key role in the communication between the immune system and other systems such as the central nervous system, which is the putative pathway that may lead to depressive symptoms (11–13). While short-term inflammatory activity serves a functional role in preventing disease, chronic systemic inflammation has been linked with increased morbidity and mortality (14–16). Indeed, the two most common markers of systemic inflammation, C-Reactive Protein (CRP) and interleukin (IL) 6, are consistently elevated among individuals with major depressive disorder relative to controls (12). Additionally, several studies have found that elevated inflammatory markers precede depressive episodes (17–19).

Depression is a heterogeneous disorder comprised of several endophenotypes, or domains of possible impairment that may be biologically distinct from one another (20, 21). Endophenotypes provide an intermediary link between genes and the visible consequence of those genes (phenotypes) (20). Common endophenotypes observed in individuals with depression are: negative emotionality and reactivity, impaired reward function, impaired learning and memory, impaired executive function, psychomotor slowing, and exaggerated stress sensitivity (21, 22). These depressive endophenotypes correspond to several depressive symptom domains: fatigue and psychomotor slowing correspond to somatic complaints, negative emotionality and reactivity correspond to depressed mood, and impaired reward function corresponds to anhedonia (22). Furthermore, previous research has shown that exogenous activation of the immune system leads to exaggerated reactivity to negative information, altered reward activity, and somatic complaints (22).

Signaling from the immune system to the brain *via* inflammation may be the biological basis of several depressive symptom domains (8, 9). Indeed, inflammation has been linked with somatic complaints (23–32), depressed affect (30, 33, 34), anhedonia (27, 35, 36), and interpersonal problems including feelings of social disconnection and troubled relationships (37–40). However, the observed association between inflammation and each of these symptom domains has been mixed, suggesting differential associations in older adults relative to healthy, young adults. Notably, a longitudinal study of older adults observed that sustained elevations in inflammation, as measured by CRP, were more robustly linked to somatic complaints than cognitive-affective depressive symptoms over time (41). Furthermore, the association between inflammation and positive affect, depressed affect or interpersonal problems has been less robust or not observed among samples in middle and later adulthood [c.f. (42–45)] In summary, inflammation has been linked to several commonly observed phenotypes in depression, though the literature reflects many apparent discrepancies involving the role of age.

There is a complex phenomenon that occurs during the aging process. Systemic inflammation increases with age (46). Yet, depressive symptoms follow a nonlinear trajectory; they are highest among young adults, decline across middle adulthood, then rise again among the oldest old (47). Indeed, older adults (ages 60+ years) experience relatively high rates of subthreshold depressive symptoms that are associated with clinically meaningful functional impairment (48–50). Suicide rates are also consistently higher in both late middle age (ages 45–59) and in older age (age 80 and above) than among young adults [see also (51) for a special issue on this topic; (52, 53)]. Despite this, rates of diagnosed depression tend to decline across middle adulthood (14, 54). Indeed, American adults aged 50 and over are 1.6 times less likely to be diagnosed with depression than adults aged 26–49 and 2.8 times less likely to be diagnosed with depression than young adults under age 25 (55). Thus, depression may be underdiagnosed in older populations, possibly due to differential symptom presentation with age. A plausible explanation for this phenomenon is that age modifies the sensitivity of the central nervous system to inflammatory signaling, such that immune activation leads to different depressive endophenotypes as the brain changes.

While systemic inflammation increases with age, the sensitivity of different neural circuits and their functional outcomes due to inflammation may vary across the lifespan. Indeed, systemic inflammation increases with age, leading to a heightened inflammatory state even in healthy older adults (46). There are also normative decreases in some brain structures and functions that begin as early as age 20 (56–58). Our central hypothesis is that changes to the structure and function of the brain that occur with age [see (56) for review] may alter the influence of inflammatory signaling on psychological phenomena, including many depressive symptoms. In the current study, we aimed to explore the potential moderating effect of age on the relationship between inflammation and depression endophenotypes. We expected that there would be a positive association between inflammation and somatic complaints, depressed affect, anhedonia, and interpersonal problems. Given the observations in the literature that older adults are more susceptible to somatic complaints while also less reactive to negative stimuli, we expected that the links between inflammation and somatic complaints would increase with age, while the links between inflammation and affective symptoms (depressed affect and anhedonia) would decrease with age (41). We did not formulate an a priori hypothesis about the moderating effect of age on the link between inflammation and interpersonal symptoms due to a lack of consensus in the existing literature.

METHODS

Participants

The present study includes data from a community sample of 2,077 individuals (54.3% female, 66.8% currently married; 90.3% Caucasian) between the ages of 30 and 84 who participated in

the Biomarker projects from the 2nd wave of the Midlife in the United States (MIDUS2) (n = 1,255), the refresher cohort of the Midlife in the United States (MIDUS-R) (n = 863), and the Midlife in Japan (MIDJA) (n = 382) studies. The MIDUS-R and MIDJA studies were conducted to increase the diversity of the overall MIDUS sample in order to allow tests of hypotheses about the role of psychosocial factors in the health (broadly defined) of mid- and later-life adults across multiple cultural contexts. The MIDUS2 and MIDUS-R samples were predominantly white, 93 and 82%, respectively, and more than 1/3 of the sample had attained a bachelor's degree or higher, while the MIDJA sample was uniformly Japanese and just under 1/3 of the sample attained a bachelor's degree or higher. Of the 2,500 participants who participated in one of these three studies, 2,428 (97.1%) had complete data for all of our primary variables and covariates. Consistent with consensus guidelines in research involving inflammatory markers (59, 60), as well as previous studies using data from MIDUS [e.g., (61)], 251 individuals were excluded for current smoking, 84 were excluded for likely infection (CRP $>$ 10 μg/mL), and 16 were excluded for both smoking and likely infection. Current smokers were excluded due to tobacco smoking being linked to increases in inflammatory markers such as IL-6 and CRP (59).

MIDUS2 participants originated from the Midlife in the United States study conducted from 1995 to 1996 and were recruited *via* random-digit dialing of potential respondents ages 25–75 across the 48 contiguous states. A diverse population of 7,108 participants included the respondents, eligible siblings, and twins. The MIDUS2 Biomarker project [2004–2009; (62)] included a total of 1,255 participants that stayed overnight at one of three general clinical research centers (GCRC) at the University of California Los Angeles (UCLA), the University of Wisconsin (UW), or Georgetown University (GU).

MIDUS-R participants were from a refresher study [MIDUS Refresher; (63)] conducted in 2011– 2014 to replenish the original MIDUS cohort with a new sample containing 3,577 participants ages 24–75. The MIDUS-R Biomarker project [2012–2016; (64)] included a total of 863 participants that stayed overnight at one of three GCRCs.

MIDJA participants were from the Midlife in Japan study [MIDJA; (65)], a sister study to MIDUS in 2008 comparing the psychosocial factors in the health of adults between Japan and the U.S. Participants ages 30–79 years old were randomly sampled from the 23 wards of Tokyo and were recruited *via* a "deliver-and-pick-up" method. Our analyses used a subset of participants from the MIDJA study that agreed to partake in the Biomarker project in 2009–2010. The MIDJA Biomarker project (66) included 382 participants that stayed overnight at a medical clinic near the University of Tokyo for biological assessments. MIDJA participants completed the same questionnaire battery as the MIDUS sample which was translated into Japanese.

Procedures

All study procedures for all included projects were approved by the Institutional Review Board at each site prior to data collection. Participation in the MIDUS2 and MIDUS-R Biomarker projects required a 2-day stay at one of the three GCRC's/CRU's. MIDUS2 participants completed a self-report questionnaire for demographics and psychosocial assessments. The second day involved a fasting blood collection at 6:30–7:00 a.m., as well as a physical exam. MIDUS-R participants underwent the same protocol, except participants completed the physical exam on the first day. Blood samples were processed at the GCRC/CRU, and then frozen and shipped to the MIDUS Biocore Labs at the University of Wisconsin and the University of Vermont for assay. Serum IL-6 was assayed at the University of Wisconsin, and plasma CRP was assayed at the University of Vermont.

Participants in the MIDJA Biomarker project completed their biological assessments during the day at a medical clinic near the University of Tokyo. At the clinic, a physical exam was administered, and then a non-fasting blood draw was completed. Blood samples were immediately processed at the University of Tokyo, sent to Syowa Medical services to be frozen until they were shipped to the Biocore lab in Madison, WI, USA to be assayed under the same protocols as the MIDUS2 and MIDUS-R Biomarker projects. Upon leaving the clinic, participants were given an at-home assessment packet that included psychosocial measures such as the CES-D. Once completed, the packet was mailed to Tokyo Women's Christian University.

Measures

Inflammation

Inflammation was measured *via* concentrations of CRP in plasma and IL-6 in serum. Plasma CRP was measured *via* a BNII nephelometer (Dade Behring Inc., Deerfield, IL) with a particle enhanced immunonepholometric assay. The range of detection for this assay was 0.175–1,100 μg/mL. CRP samples that fell outside the assay range were re-assayed *via* immunoelectrochemiluminescence using a high-sensitivity assay kit (Meso Scale Diagnostics #K151STG). Intra-assay CV ranged from 2.2 to 4.4% and inter-assay CV ranged from 2.1 to 5.7%. Serum IL-6 was assessed using a Quantikine high-sensitivity enzyme-linked immunosorbent assay kit (R & D Systems, Minneapolis, MN). The range of detection for this assay was 0.156–10 pg/mL. Intra-assay coefficient of variability (CV) was 3.2% and inter-assay CV was 12.3%.

Depressive Symptoms

Depressive symptoms were measured using the well-validated and widely used Center for Epidemiologic Studies—Depression Scale (CES-D) (67, 68). This 20-item questionnaire contains four subscales: depressed affect (7 items), positive affect (recoded as anhedonia; 4 items), somatic complaints (7 items), and interpersonal problems (2 items). For each item, participants were asked to rate how often they felt a certain way during the past week (e.g., "I felt depressed" and "I was bothered by things that usually don't bother me."). Respondents rated on a 4-point scale ranging from 0 (rarely or none of the time) to 3 (most or all of the time), and responses were summed to create total and subscale scores. The positive affect subscale was then reverse coded to reflect anhedonia. Total scores could range from 0 to 60, with higher scores indicating more depressive symptoms, and scores $>$15 indicating a likely major depressive

episode. CES-D scores have high construct validity in older adults (69, 70), and the Japanese version of the CES-D has shown specificity and external validity (71, 72), with a similar factor structure (73). Internal reliabilities of all subscales were good in this sample, $\alpha = 0.82–0.89$.

Data Analysis

All continuous variables were examined for normality and heteroscedacity. IL-6 and CRP were both transformed using the natural log transformation. Based upon best practices in research using inflammatory biomarkers (59), all analyses covaried for sex and body mass index (BMI). All analyses also covaried for the study from which the data was drawn (MIDUS2, MIDUS-R, or MIDJA) because the method of biomarker collection differed between the MIDUS and MIDJA samples, and there were significant differences between participants in MIDUS2, MIDUS-R, and MIDJA samples in age, $F_{(2,\ 2,074)} = 23.81$, $p < 0.001$, BMI, $F_{(2,\ 2,074)} = 202.07$, $p < 0.001$, IL-6, $F_{(2,\ 2,074)} = 112.33$, $p < 0.001$, CRP, $F_{(2,\ 2,074)} = 243.38$, $p < 0.001$, and depressive symptoms, $F_{(2,\ 2,074)} = 59.56$, $p < 0.001$.

To determine the main effect of CRP, IL-6, and age on depressive symptoms, we conducted multiple regression models predicting depressed affect, anhedonia, somatic complaints, and interpersonal problems separately from CRP and IL-6, as well as age, while accounting for our key covariates.

To determine whether age moderated the association between CRP or IL-6 and depressive symptoms, we used the PROCESS Macro for SPSS to estimate the interaction between CRP or IL-6 and age as a predictor of each depressive symptom domain (74), as well as to compute the association between CRP, IL-6, and depressive symptoms for individuals ±1SD from the mean age in our sample. All predictors were mean-centered for analyses, and all interaction models included key covariates. In models where the reliability of the estimated interaction was <0.10, we used the Johnson-Neyman method to determine the age at which the pattern of association between CRP or IL-6 and depressive symptoms reached significance. All *p*-values are reported for transparency and to facilitate comparison with other studies, but a *p*-value <0.05 is considered statistically reliable, and a *p*-value <0.007 corrected for multiple comparisons (75, 76).

TABLE 1 | Inflammatory markers and depressive symptom domains by age (Quartiles).

Quartile	1	2	3	4
Age (years)	**25–43**	**44–53**	**54–63**	**64–84**
n	515	522	509	531
Inflammation				
CRP (M ± SD)	1.83 (2.20)	1.88 (2.07)	1.92 (2.13)	1.84 (1.98)
IL-6 (M ± SD)	1.89 (1.82)	2.07 (2.01)	2.61 (2.45)	3.23 (2.91)
Depressive symptoms				
% Clinically elevated	21.0	19.0	13.9	8.7
Depressed affect (M ± SD)	2.30 (3.14)	2.24 (3.20)	1.49 (2.55)	1.16 (2.19)
Anhedonia (M ± SD)	3.71 (3.15)	3.22 (2.98)	3.28 (3.27)	3.39 (3.42)
Somatic complaints (M ± SD)	3.82 (3.35)	3.54 (3.11)	2.98 (3.27)	2.83 (2.61)
Interpersonal problems (M ± SD)	0.58 (0.95)	0.47 (0.87)	0.31 (0.76)	0.25 (0.63)

RESULTS

Depressive symptoms in the sample varied widely, such that total depressive symptom scores ranged from 0 to 55, and 15.6% ($n = 324$) of participants exceeded the clinical threshold on the CES-D, indicating possible Major Depressive Disorder. **Table 1** provides descriptive information about inflammatory markers and depressive symptoms by age quartiles. **Table 2** provides descriptive statistics for all key study variables and the bivariate correlations between them. As expected, both inflammatory markers were correlated with several depressive outcomes. CRP was associated with more somatic complaints and less anhedonia.

TABLE 2 | Descriptive statistics for key study variables and bivariate associations between them.

	M(SD)	Range	Correlations						
			1.	2.	3.	4.	5.	6.	7.
1. Age	53.80 (12.98)	25–84	1.00						
2. BMI	28.43 (6.61)	14.99–77.58	0.01	1.00					
Inflammatory markers									
3. CRP (μg/mL)	1.86 (2.09)	0.02–10.00	0.06**	0.53***	1.00				
4. IL-6 (pg/mL)	2.45 (2.40)	0.03–23.00	0.31***	0.44***	0.56***	1.00			
Depressive symptoms (CESD)									
5. Depressed affect	1.80 (2.84)	0–20	−0.17***	0.08***	0.06**	0.01	1.00		
6. Anhedonia	3.40 (3.22)	0–12	−0.02	−0.14***	−0.19***	−0.12***	−0.37***	1.00	
7. Somatic complaints	3.29 (3.04)	0–18	−0.13***	0.12***	0.11***	0.07**	0.64***	0.22***	1.00
8. Interpersonal problems	0.40 (0.82)	0–6	−0.17***	0.07**	0.04	0.02	0.42***	0.19***	0.41***

***p < 0.01, ***p < 0.001; BMI, body mass index; IL, interleukin; CRP, C-reactive protein; CESD, Center for Epidemiological Studies—Depression scale.*

Higher IL-6 was associated with more somatic complaints, less anhedonia, and more interpersonal problems.

Inflammatory Markers as a Predictor of Depressive Symptoms

After adjusting for sex, BMI, and study, CRP was associated with more somatic complaints, $b = 0.18$, $SE = 0.07$, $p = 0.008$, $R^2 = 0.04$, $F_{(5, 2,071)} = 16.66$, $p < 0.001$, and less anhedonia, $b = -0.43$, $SE = 0.07$, $p < 0.001$, $R^2 = 0.04$, $F_{(5, 2,071)} = 18.90$, $p < 0.001$. CRP was not associated with depressed affect, $b = 0.07$, $SE = 0.06$, $p = 0.25$, $R^2 = 0.04$, $F_{(5, 2,071)} = 17.69$, $p < 0.001$, or interpersonal problems, $b = 0.02$, $SE = 0.02$, $p = 0.27$, $R^2 = 0.03$, $F_{(5, 2,071)} = 13.88$, $p < 0.001$. After adjusting for sex, BMI, and study, IL-6 was associated with more somatic complaints, $b = 0.32$, $SE = 0.10$, $p = 0.002$, $R^2 = 0.04$, $F_{(5, 2,071)} = 17.26$, $p < 0.001$, less anhedonia, $b = -0.28$, $SE = 0.11$, $p = 0.01$, $R^2 = 0.03$, $F_{(5, 2,071)} = 12.54$, $p < 0.001$, and greater interpersonal problems, $b = 0.06$, $SE = 0.03$, $p = 0.018$, $R^2 = 0.03$, $F_{(5, 2,071)} = 14.79$, $p < 0.001$. IL-6 was not associated with depressed affect, $b = 0.14$, $SE = 0.09$, $p = 0.13$, $R^2 = 0.04$, $F_{(5, 2,071)} = 17.90$, $p < 0.001$.

Age as a Moderator of Inflammation on Depressive Symptoms

Table 3 provides coefficient estimates from the interaction models predicting depressive symptom domains as a function of CRP, age, their interaction, and our covariates (sex, BMI, and study). **Figure 1** illustrates the association between CRP and each depressive symptom domain as a function of age.

Age significantly moderated the association between CRP and both somatic complaints and anhedonia. There was a significant interaction between CRP and age when predicting somatic complaints, $b = 0.011$, $SE = 0.004$, $p = 0.01$. Specifically, CRP was associated with more somatic complaints among older participants (>66 years), $b = 0.32$, $SE = 0.09$, $p < 0.001$, and average aged participants (41–66 years), $b = 0.18$, $SE = 0.07$, $p = 0.006$, but not younger participants (<41 years), $b = 0.04$, $SE = 0.09$, $p = 0.67$. Using the Johnson-Neyman technique, the association between CRP and greater somatic complaints was significant and positive after about age 51. There was also a significant interaction between CRP and age when predicting anhedonia, $b = -0.013$, $SE = 0.005$, $p = 0.006$. Specifically, the negative association between CRP and anhedonia was stronger with increasing participant age; younger participants (<41 years) $b = -0.27$, $SE = 0.09$, $p = 0.003$, average aged participants (41–66 years) $b = -0.43$, $SE = 0.07$, $p < 0.001$, and older participants (>66 years) $b = -0.60$, $SE = 0.09$, $p < 0.001$. Using the Johnson-Neyman technique, the association between CRP and anhedonia emerged after about age 37 and increased in magnitude throughout the lifespan.

Table 4 provides coefficient estimates from the interaction models predicting depressive symptom domains as a function of IL-6, age, their interaction, and our covariates (sex, BMI, and study). **Figure 2** illustrates the association between IL-6 and each depressive symptom domain as a function of age. Age did not significantly moderate the association between IL-6 and any symptom domains.

There was a non-significant interaction between IL-6 and age when predicting somatic complaints, $b = 0.01$, $SE = 0.01$, $p = 0.10$. Specifically, IL-6 was associated with more somatic complaints among older participants (>66 years), $b = 0.46$, $SE = .13$, $p < 0.001$, and average aged participants (41–66 years), $b = 0.32$, $SE = 0.10$, $p = 0.001$, but not younger participants (<41 years), $b = 0.18$, $SE = 0.13$, $p = 0.16$. Using the Johnson-Neyman technique, the association between IL-6 and somatic complaints was significant and positive after about age 46. There was also a non-significant interaction between IL-6 and age when predicting interpersonal problems, $b = -0.003$, $SE = 0.002$, $p = 0.06$. Specifically, IL-6 was associated with more interpersonal problems among younger participants (<41 years), $b = 0.11$, $SE = 0.04$, $p = 0.003$, average aged participants (41–66 years), $b = 0.06$, $SE = 0.03$, $p = 0.02$, but not older participants (>66 years), $b = 0.02$, $SE = 0.04$, $p = 0.59$. Using the Johnson-Neyman technique, the association between IL-6 and greater interpersonal problems was significant and positive up to about age 56.

DISCUSSION

The complex relationship between aging, inflammation and depressive symptoms may reflect a dynamic developmental process by which the brain becomes differentially susceptible to

TABLE 3 | Estimated coefficients predicting depressive symptoms and phenotypes from CRP, age, and their interaction.

	Depressed affect		Anhedonia		Somatic complaints		Interpersonal problems	
R^2	0.04***		0.05***		0.04***		0.03***	
Predictor	***b (SE)***	***p***	***b (SE)***	***p***	***b (SE)***	***p***	***b (SE)***	***p***
Intercept	1.53 (0.11)	<0.001	3.27 (0.13)	<0.001	3.00 (0.12)	<0.001	0.42 (0.03)	<0.001
CRP	0.07 (0.06)	0.25	−0.43 (0.07)	<0.001	0.18 (0.07)	0.008	0.02 (0.02)	0.28
Age	−0.04 (0.005)	<0.001	−0.001 (0.005)	0.83	−0.03 (0.005)	<0.001	−0.01 (0.001)	<0.001
CRP x age	−0.002 (0.004)	0.55	−0.013 (0.005)	0.006	0.01 (0.004)	0.01	−0.002 (0.001)	0.20
Covariates								
Female	0.44 (0.12)	<0.001	−0.05 (0.14)	0.72	0.37 (0.13)	0.006	−0.03 (0.04)	0.38
Sub-study	0.05 (0.07)	0.50	0.21 (0.08)	0.007	0.09 (0.07)	0.22	0.01 (0.02)	0.58
BMI	0.03 (0.01)	0.01	−0.03 (0.01)	0.006	0.04 (0.01)	<0.001	0.005 (0.003)	0.11

****p < 0.001.*

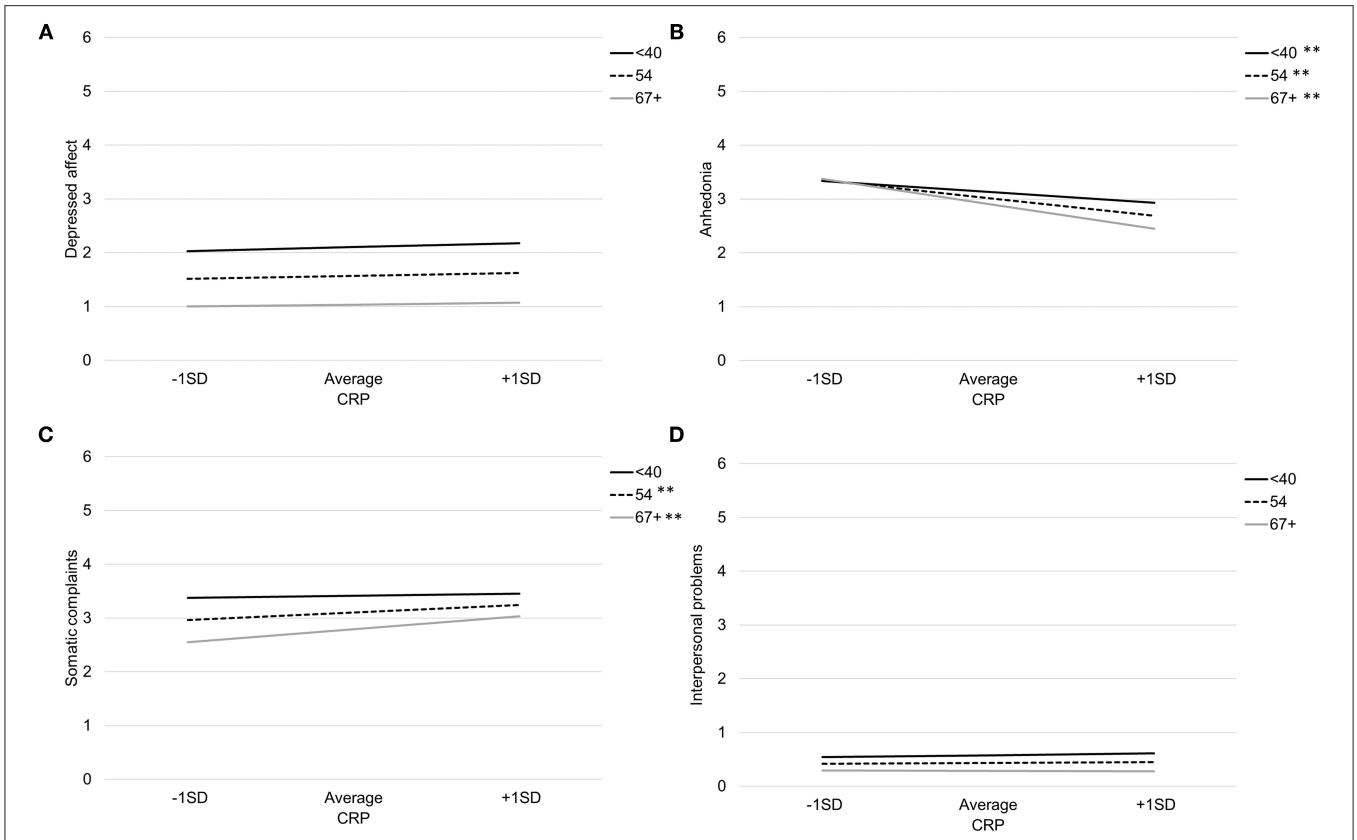

FIGURE 1 | Association between CRP and depressed affect **(A)**, anhedonia **(B)**, somatic complaints **(C)**, and interpersonal problems **(D)** by age. Note: $^{**}p < 0.007$, $^{*}p < 0.05$.

TABLE 4 | Estimated coefficients predicting depressive symptoms and phenotypes from IL-6, age, and their interaction.

	Depressed affect		Anhedonia		Somatic complaints		Interpersonal problems	
R^2	0.04***		0.03***		0.04***		0.036***	
Predictor	***b (SE)***	***p***	***b (SE)***	***p***	***b (SE)***	***p***	***b (SE)***	***p***
Intercept	1.46 (0.12)	<0.001	3.46 (0.14)	<0.001	2.80 (0.13)	<0.001	0.39(0.04)	<0.001
IL-6	0.14 (0.09)	0.13	−0.28 (0.11)	0.01	0.32 (0.10)	0.0015	0.06 (0.03)	0.019
Age	−0.03 (0.01)	<0.001	0.005 (0.007)	0.50	−0.04 (0.01)	<0.001	−0.01 (0.002)	<0.001
IL-6 x age	−0.006 (0.006)	0.32	−0.005 (0.01)	0.48	0.01 (0.01)	0.10	−0.003 (0.002)	0.06
Covariates								
Female	0.44 (0.12)	<0.001	−0.14 (0.14)	0.31	0.40 (0.13)	0.002	−0.03 (0.04)	0.37
Sub-study	0.05 (0.07)	0.46	0.24 (0.08)	0.002	0.07 (0.07)	0.34	0.01 (0.02)	0.47
BMI	0.03 (0.01)	0.01	−0.06 (0.01)	<0.001	0.04 (0.01)	<0.001	0.004 (0.003)	0.26

$^{***}p < 0.001$.

the behavioral effects of inflammation. In this large, community sample, the association between inflammation and depressive symptoms varied as a function of age and domain of impairment, particularly with respect to anhedonia and somatic complaints. Specifically, inflammation was associated with more reported somatic complaints and less anhedonia as age increased. We observed this association most robustly using CRP as an inflammatory biomarker and observed similar, but non-significant patterns using IL-6. A conceptual figure summarizing the observed associations between inflammation and each symptom domain as a function of age is shown in **Figure 3**. These findings have important implications for developmental immunology and neuroscience, as well as the conceptualization of somatic complaints among older adults.

More CRP was associated with less anhedonia in our sample, an effect which grew in magnitude with age. The present findings provide promising preliminary evidence that aging is an important context to consider in the role of inflammation

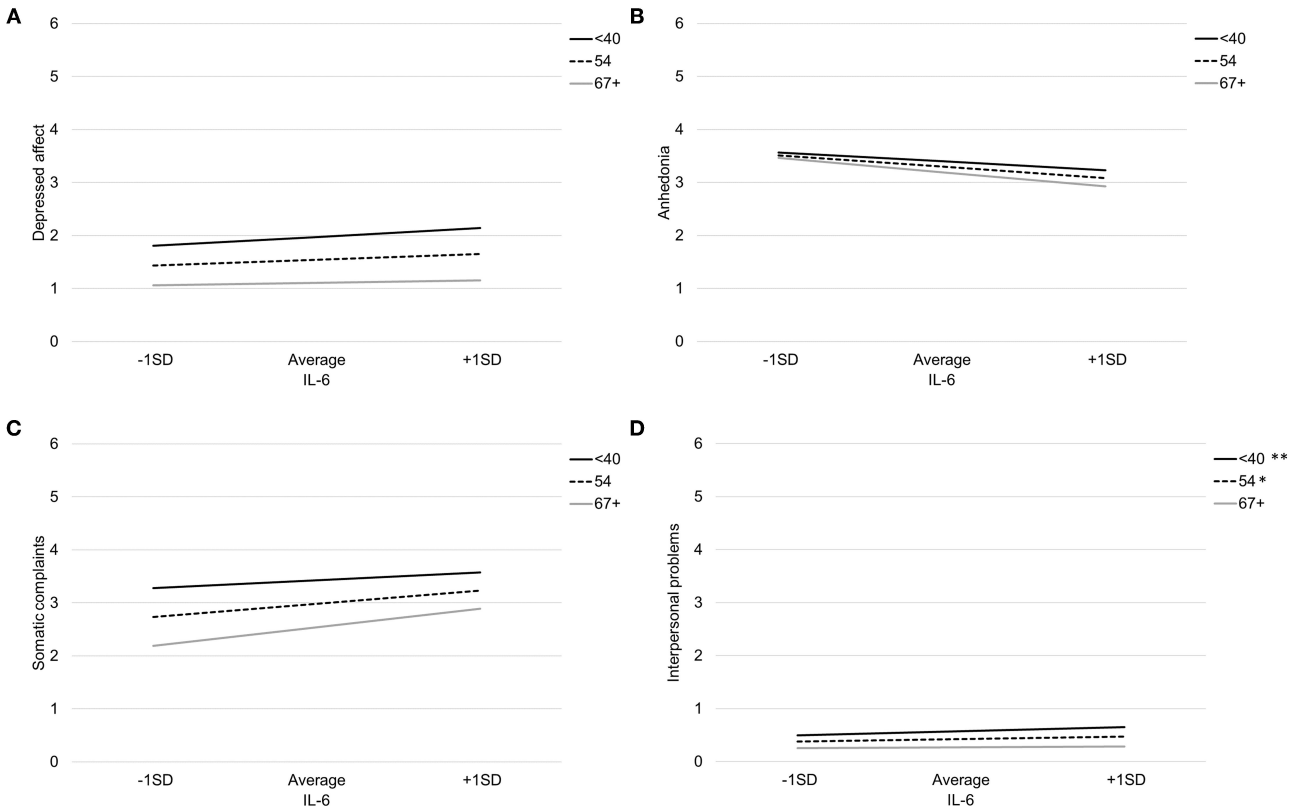

FIGURE 2 | Association between IL-6 and depressed affect **(A)**, anhedonia **(B)**, somatic complaints **(C)**, and interpersonal problems **(D)** by age. Note: $^{**}p < 0.007$, $^{*}p < 0.05$.

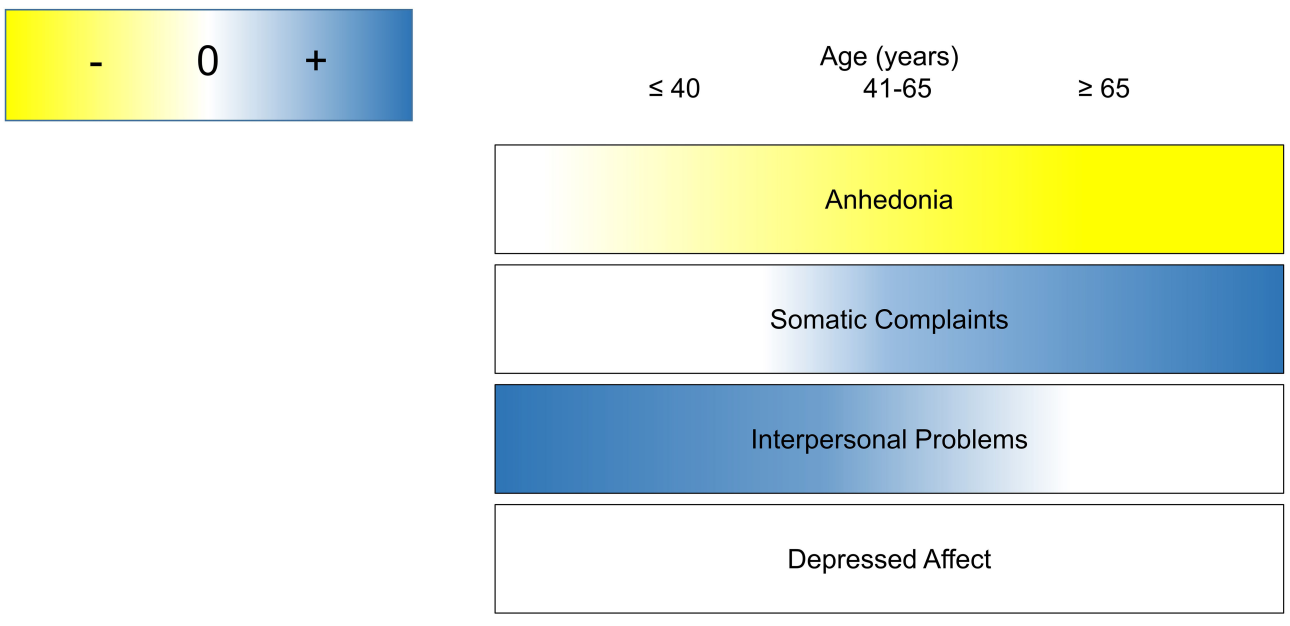

FIGURE 3 | Conceptual summary of age as a context for the role of inflammation in depressive symptom domains.

in anhedonia, the neural mechanisms of which warrant further investigation. Indeed, in a study conducted with another subset of MIDUS participants, higher inflammation was associated with lower limbic reactivity to positive affective images and greater connectivity between the limbic system and prefrontal cortex (77). Inflammation affects reward learning, sensitivity, and motivation through frontostriatal circuit function in many ways, including interfering with dopamine synthesis (78). Additionally, the brain undergoes many changes across the lifespan, including decreases in white matter, gray matter, the volume and structural integrity of the striatum, a critical reward related region, as well as a reduction in dopaminergic receptors (56, 79–81), and declines in the frontostriatal circuit (82, 83). Inflammation may have a disproportionate impact on reward processing depending on the structural and functional integrity of reward circuits in the brain. In the current study, the negative association between CRP and anhedonia was somewhat unexpected given previous studies showing that inflammation can attenuate positive affect and psychological processes associated with reward (42–44, 84, 85). Yet, mild immune activation with acute laboratory stress or a vaccine can increase reward learning and motivation in the short-term (86, 87). The complexities of reward processes, which are comprised of learning, motivation, and sensitivity, must also be considered when thinking about how reward neurocircuitry relates to self-reported symptoms of anhedonia. The anhedonia subscale on the CES-D corresponds to subjective positive appraisals of one's life, happiness, and worth, which may more accurately reflect higher order psychological states than transient positive emotions measured in many studies (88). It is also possible that our negative association between inflammation and anhedonia was influenced by the very low incidence of anhedonia in our sample, and thus this finding should be interpreted with caution until it can be replicated within a clinical sample.

There was a stronger association between inflammation, as measured by CRP, and somatic complaints with increasing age. Of note, we observed this sensitivity consistently among individuals over the age of 51 for CRP, with a similar but non-significant inflection point using IL-6. Importantly, this interaction was significant after accounting for the unexpected, inverse association between age and somatic complaints. Somatic complaints on the CES-D include an increase in irritability, decrease in appetite, trouble with concentration, fatigue, sleep difficulty, and lack of motivation. Normative changes in structure within the aging brain may explain an increasing sensitivity of aging individuals to inflammation in relation to somatic complaints. This may also involve dopaminergic processes because inflammation interferes with the synthesis, transmission, and re-uptake of dopamine (89, 90), which has profound implications for many psychological phenomena, including somatic complaints such as fatigue. Indeed, the most consistent causal evidence linking inflammation to depressive endophenotypes exists for somatic complaints such as fatigue, sleep disturbance, and subjective cognitive difficulties (22). Studies examining correlates between inflammation and the structure and function of neural circuits implicated in different endophenotypes of depression could further elucidate how the context of aging affects the relationship between inflammation and depressive symptom domains.

Finally, it is important to note that we did not observe a link between inflammation and depressed affect in our sample, which is consistent with prior literature (42, 77, 91, 92) but often neglected in research on the role of inflammation in depressive symptoms. To our knowledge, the only studies which have found a significant link between inflammation and depressed affect have involved presenting the immune system with a short-term, strong inflammatory challenge which produces brief, high levels of inflammation in some individuals (22, 27, 30). Along these lines, it is also important to note that each of our models only accounted for between 3 and 5% of variance in symptoms. This is consistent with previous studies examining the association between inflammation and depressive symptoms (17, 93, 94). Depressive symptoms are largely heritable; with estimates ranging between 23 and 71% (95–98). Further, these models were based on observations within a community sample, not a clinical sample. These factors may have limited the between-subject variability to account for in our data. Whether inflammation accounts for more variance in symptom domains within clinical samples or after heritability is covaried out remains important to determine. Even so, characterizing the role of modifiable factors, such as inflammation, in health outcomes such as depression is critical to intervention development and healthcare practices.

Future Directions

Normative changes in the structure and function of the human brain with increasing age may mitigate or exacerbate the effect of inflammation on some affective and behavioral outcomes. In addition to the increasingly negative association between inflammation and anhedonia, we observed a non-significant trend that the link between inflammation and interpersonal problems weakened among older individuals. These findings may indicate a reduced susceptibility to some of the detrimental effects of systemic inflammation with age. Normative age-related changes in the function and structure of the brain are complemented by the many psychological and social resources that continue to amass throughout the lifespan which may further buffer older individuals against the deleterious influence of inflammation on emotional well-being. For example, older adults experience less limbic activation when presented with negative stimuli and recall positive memories more easily than negative memories (99, 100).

One strength of this study was its use of a large, epidemiological sample with participants from two nations (USA and Japan). Given the diversity of the combined samples, these observations may generalize across a wide range of individuals and societies which will be exciting to explore. However, the methodological differences in recruitment and data collection between the studies (MIDJA, MIDUS2, MIDUS-R) impeded our ability to account for the role of racial or ethnic background above and beyond the study from which the data was drawn. For example, it is possible that the role of aging in the association between inflammation and depressive symptom domains may differ between Asian and Caucasian individuals, yet any variable indicating race or ethnicity would be entirely confounded by

the study. While the CES-D has been validated as a measure of depression and depressive symptoms among Japanese adults (72), there is evidence that the factor structure of depressive symptoms using this measure differs from that observed in the U.S. such that the interpersonal problems subscale does not warrant its own symptom domain (73). It is also plausible and likely that the context of aging in immune to brain communications has different implications for our Japanese (MIDJA) and U.S. samples (MIDUS2 and MIDUS-R). Cross-cultural comparisons between aging Japanese persons and aging Americans have shown that both of these groups report similar levels of increased well-being with age (101). It is also noteworthy that our study found a non-significant trend between IL-6 and interpersonal problems in our combined sample, even though IL-6 was lower in the MIDJA sample compared to the MIDUS sample overall (102). To our knowledge, no studies have examined neurodevelopmental or aging-related inflammatory differences between American and Japanese samples. These studies would be a valuable follow-up to the present findings.

Limitations

These results should be considered in the context of the study's limitations. First and foremost, these data are cross-sectional and cannot be used to infer causality. Our model focuses on the influence of inflammation on depressive symptoms, although the relationship between inflammation and depression can be characterized as bidirectional (93, 94, 103, 104). Longitudinal studies can provide relevant information to inform future interventions. Second, it is important to note that our outcome measure was depressive symptoms rather than depressive episodes examined within a community sample where the prevalence of major depression was likely low. Yet, functional impairment increases linearly with depressive symptoms, even at subthreshold levels and particularly in the elderly, underscoring the clinical utility of understanding the pathogenesis of depressive symptoms regardless of diagnostic status (49, 50, 105, 106). Nevertheless, replication within clinical or treatment-seeking samples is needed, particularly in a sample with elevated somatic complaints. With respect to measurement of different domains of depressive symptoms, each domain differed in its potential sensitivity. Specifically, the interpersonal problems subscale of the CES-D is only comprised of 2 items, which may have limited our ability to detect associations with this construct.

Further, inflammation is a dynamic and multifaceted biological process that can be measured at the intracellular, cellular, molecular, and neural levels. In the present study, we have focused only on two common circulating markers of inflammation, which yielded similar patterns. However, there were only reliable associations with CRP not IL-6. One possible explanation for this observation in our data was that IL-6 appeared to increase with age while CRP did not (see **Table 1**), leaving more potential variance for CRP to explain in our depressive symptom domains. The more robust association between CRP, relative to IL-6, and depressive symptoms is consistent with observations in longitudinal studies of depression (19), though the broader literature shows a consistent association between IL-6 and depression as well (12). This particular distinction between CRP and IL-6 may or may not be meaningful. CRP and IL-6 are related inflammatory markers, as CRP is stimulated by IL-6. Clinically speaking, CRP is already used in other fields of medicine which increases its potential for adoption in psychiatry, and it is already being used to inform depression treatment [c.f. (107)]. Examination of whether age moderates the association between other inflammatory markers and depressive symptoms is needed. This will be particularly important in future work that takes the source of inflammation into consideration. In the present study, we were somewhat agnostic to the cause of inflammation (e.g., stress, injury, illness), though many inflammatory proteins have specific signaling functions that most certainly vary in their influence on the central nervous system. Finally, the moderating role of age in the link between inflammation and different depressive symptom domains may indicate that age is a proxy for several developmental processes. Here, we focused on the combined, non-specific biological and psychosocial developmental processes that occur with chronological age, but these phenomena may not unfold along the same time course and may be interdependent.

Conclusions

Inflammation is a well-established causal mechanism in the development of many depressive symptoms (8, 13, 22). Yet, little attention has been given to the stability of this phenomenon across the human lifespan. Given our vast and growing knowledge of how the human brain changes across the lifespan, there are likely to be periods of greater susceptibility and periods of relative protection from these putative effects. These preliminary observations suggest that the association between inflammation and somatic complaints is stronger, while the association between inflammation and anhedonia is weaker, among older adults. If corroborated with experimental evidence, these findings may have important implications for the conceptualization of somatic complaints among older adults within healthcare settings. Indeed, individuals above the age of 65 are disproportionately diagnosed with high rates of inflammatory physical disorders and low rates of depression (54). At the same time, older adults are also more likely to die by suicide than younger adults [see (51) for a special issue on this topic; (52, 53)]. It is possible that treatment-seeking older adults with somatic complaints could benefit from some of the well-established treatments for depression. These patients may be exhibiting a differential presentation of depressive symptoms than their younger counterparts. Indeed, there is evidence that the same pharmacological treatments most effective for treating depressive symptoms also provide relief for somatic symptoms experienced by older adults (108, 109). Our preliminary observations may inform important modifiable factors that can be used for novel pharmacological and behavioral intervention development for older adult populations.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: https://doi.org/10.3886/ICPSR29282.v9;

https://doi.org/10.3886/ICPSR36901.v6; https://doi.org/10.3886/ICPSR34969.v4. For more information, you can visit the MIDUS Study website: http://www.midus.wisc.edu/.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University of California Los Angeles IRB, University of Wisconsin IRB, Georgetown University IRB, and the University of Tokyo IRB. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KS and KK contributed conception and design of the secondary data analysis. M-LT retrieved and organized the database. KK conducted the data analyses and interpretation of the data. All authors contributed to the writing and revision of the manuscript.

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Sickness and the Social Brain: Love in the Time of COVID

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As a highly social species, inclusion in social networks and the presence of strong social bonds are critical to our health and well-being. Indeed, impaired social functioning is a component of numerous neuropsychiatric disorders including depression, anxiety, and substance use disorder. During the current COVID-19 pandemic, our social networks are at risk of fracture and many are vulnerable to the negative consequences of social isolation. Importantly, infection itself leads to changes in social behavior as a component of "sickness behavior." Furthermore, as in the case of COVID-19, males and females often differ in their immunological response to infection, and, therefore, in their susceptibility to negative outcomes. In this review, we discuss the many ways in which infection changes social behavior—sometimes to the benefit of the host, and in some instances for the sake of the pathogen—in species ranging from eusocial insects to humans. We also explore the neuroimmune mechanisms by which these changes in social behavior occur. Finally, we touch upon the ways in which the social environment (group living, social isolation, etc.) shapes the immune system and its ability to respond to challenge. Throughout we emphasize how males and females differ in their response to immune activation, both behaviorally and physiologically.

Keywords: social behavior, infection, sex differences, social stress and social support, immune

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INTRODUCTION

During this historic moment, humanity is faced with a global pandemic of the novel coronavirus SARS-CoV-2 which causes COVID-19. As a result, we must grapple not only with an enormous infectious challenge, but also with social distancing, isolation, and the fragmentation of social networks. This increased social distance is necessary to prevent viral transmission, but long-term social separation is likely to adversely impact mental health outcomes far into the future. As a highly social species, inclusion in social networks and the presence of strong social bonds is critical to our health and well-being (1–3). Early studies suggest that loneliness and psychological distress have increased significantly during the COVID-19 pandemic as compared to before it began (4, 5) and that this loneliness and perceived social isolation are predictive of increased anxiety, depression, and suicidal thoughts (5, 6). Devastatingly, the populations that appear to be most vulnerable to COVID-19 are also those that bear the greatest burden of psychosocial stress. Specifically, COVID-19 infection and COVID-19-related deaths are highest in minority and low socioeconomic status (SES) populations both in the United States and worldwide (7–10). Importantly, social isolation and social stress—at either the level of the individual or the social group—have been shown to negatively impact immune function, while positive social relationships and higher status within social hierarchies enhance many aspects of immune defense and thus may protect against infection, across a wide array of infectious disease (11, 12).

Across the evolutionary continuum, as more complex social structures have evolved, so too has the risk of pathogen exposure. Therefore, immune responses to infection and social systems are inextricably linked. In the context of COVID-19, as well as other infectious diseases, it is critical that we understand the complex interplay between the immune system and the social brain.

Numerous studies from countries including China, Italy, and the United States have found that there is a sex difference in COVID-19 disease prognosis and mortality, with men being more vulnerable than women (13–19). Immune responses to infection, including COVID-19, differ between men and women. For instance, men appear to have higher circulating cytokines such as Interleukin (IL)-8 and IL-18 following COVID-19 infection, while women mount a greater T lymphocyte response (20). These findings are in line with a large body of previous literature demonstrating sex differences in the immune response to a variety of infectious agents, with women typically displaying lower susceptibility to infection, but higher rates of autoimmune diseases [for review see (21, 22)]. In addition, men may be more likely than women to be adversely impacted by social isolation and stress as a result of the pandemic. For example, in a study of 4,000 elderly men and women, loneliness was predictive of mortality at a 10-year follow up in men, but not women (23). Similarly, in a meta-analysis of published studies, Roelfs et al. (24) found that mortality risk is higher under conditions of underemployment and this effect is 37% higher in men than in women (24). In non-human animals, sex differences in social behavior abound, and males and females often differ in their response and susceptibility to social stress. These findings highlight the need to better understand the ways in which sex differences in social behavior and susceptibility to social stress may contribute to sex-specific vulnerability and resilience in the face of infectious agents.

In this review, we will reflect on the bi-directional relationship between social behavior and the immune system, with an emphasis on how it differs between the sexes. First, we will review the acute effects of infection, either bacterial or viral, on social behavior in both humans and other animal species and how these behavioral effects differ between males and females. We will also discuss the neuroimmune mechanisms that have been posited to underlie these behavioral changes. While many studies demonstrate that maternal infection (or immune activation more broadly) during pregnancy and early life infection can impact social behavior later in life, here we will focus largely on acute adult infection for the sake of scope. Next, we will explore the ways in which the social environment (group living, social isolation, social status, etc.) and perceptions of social connectedness shape the immune system and its ability to respond to challenge in males and females across species. Finally, we will touch on the mechanisms by which this social context is encoded in immune function. Together, we hope to highlight that group living and pathogen defense go hand-in-hand, and that neither can be completely understood without consideration of the other **Figure 1**.

HOW DOES INFECTION CHANGE SOCIAL BEHAVIOR?

Early observations of the behavior of sick animals and humans noted a constellation of behavioral changes that have been termed "sickness behavior." These behaviors include lethargy, anorexia, and social withdrawal and are not simply negative effects of the pathogen, but critical adaptive responses on the part of the host aimed at recuperating and reducing the spread of infection to other individuals (25, 26). Sickness behavior comes at a cost; lethargy, anorexia, and social withdrawal weaken the individual, increase risk of predation, and limit social opportunities such as in the context of mate selection and parental care (27, 28). Therefore, the display of sickness behavior represents an inherent trade off. Several theories as to the utility of sickness behavior have been proposed. Lethargy likely conserves energy in order to mount and maintain a fever response [critical to fighting off invading pathogens; (25)], while the entire suite of behaviors serves to protect the individuals' kin by reducing physical contacts, decreasing environmental contamination, and signaling illness to other individuals (27). Indeed, several studies have shown that individuals of many species are capable of recognizing, and avoiding interaction with, sick conspecifics (29–32).

In Humans

In humans, recent studies have provided a nuanced view of the ways in which infection and inflammation alter social behavior [for comprehensive review see (33)]. Much of this work has been conducted in laboratory settings using an experimental challenge with the bacterial mimetic Lipopolysaccharide (LPS). Participants treated in the lab with LPS report increased feelings of social disconnection, loneliness, and social sensitivity as compared to control-treated participants (34–36). These findings are aligned with the idea that individuals withdraw from social contact when ill. However, in some instances, it might be adaptive to approach others during sickness so that they can provide care and support. Inagaki et al. (37) found that participants reported an increased desire to be with close others (spouses or family members) following LPS administration. Similarly, positive social feedback from an unfamiliar peer appears to be more rewarding following LPS as compared to control treatment (38). Eisenberger et al. (33) posits that heightened sensitivity to social information (either positive or negative) following infection may underlie these findings and be adaptive because it facilitates the rapid identification of, and discrimination between individuals who may or may not provide aid during the recuperative process.

Sex Differences in Humans

Are there sex differences in social withdrawal in humans? Few studies have directly compared social outcomes in both males and females following immune challenge in humans (39). However, Moieni et al. (35) found that females reported higher social disconnectedness scores than males following an LPS challenge. In contrast to females, however, males reported lower subjective social status following LPS administration than at baseline (40). (32) observed that while both men and women

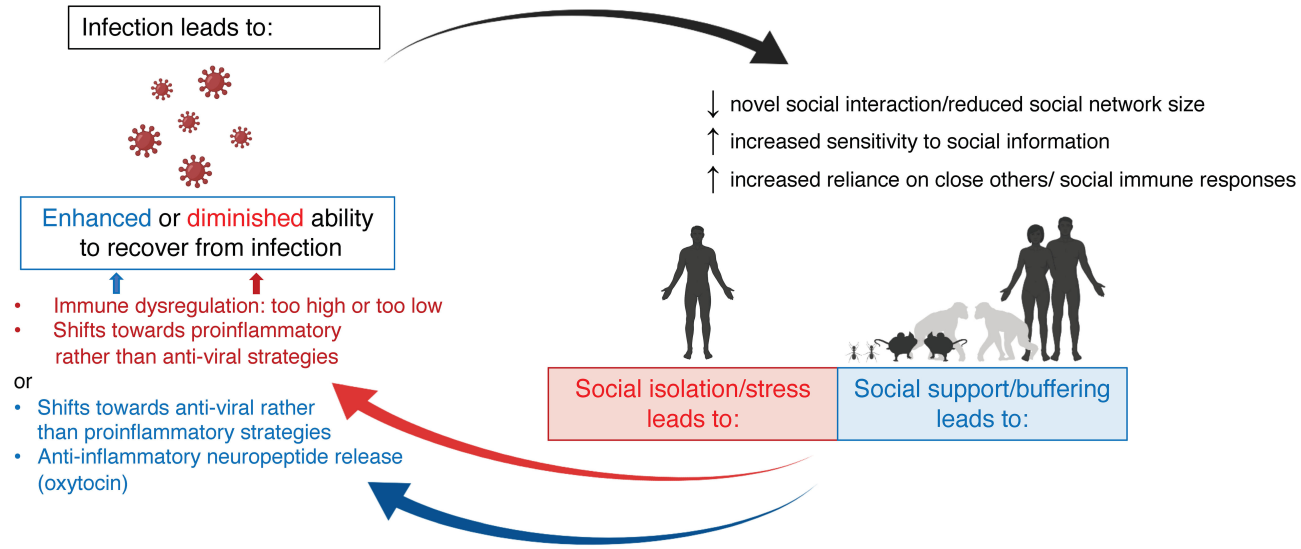

FIGURE 1 | The bi-directional relationship between infection and social behavior. Infection (either viral or bacterial) induces social withdrawal and decreases social network size, across species. Infection also increases sensitivity to social information and increases social interactions with familiar peers and family members. Together, these changes in social behavior aim to reduce disease transmission while promoting individual recovery. Social context can also impact immune function. Social isolation, social stress, or low position within a social hierarchy all lead to immune dysfunction—often shifting immune responses toward pro-inflammatory rather than anti-viral strategies. Conversely, strong social bonds and high social status are associated with a shift in immune responses toward anti-viral strategies and higher oxytocin release, which may act as an anti-inflammatory mediator. Created with BioRender.com.

complain about symptoms with similar frequency following LPS challenge, men were more likely to emit vocalizations, such as sighs and deep breaths, that might still signal illness to others, than women (32). These findings provide evidence in humans that males and females may manifest changes in social behavior differently during an acute immune challenge. It is important to note, however, that many factors - including those that are often gendered - can influence the display of sickness behavior in humans. Highlighting this, in a separate study, (41) found that how sick participants anticipated becoming predicted how sick they actually became (41). Similarly, in a retrospective self-reported study of sickness behavior, familism, or the valuation of family above the individual, was associated with stronger sickness behavior in men than in women (42). Thus, sociocultural influences may make it difficult to determine biological sex differences in the sickness response in humans.

In Animal Models

Social withdrawal following an LPS challenge has also been observed in a wide array of non-human animal species **Box 1**. Vocalizations are used by many species to communicate across social networks and to find and engage with potential mates. Such social contacts are reduced following LPS administration in passerine bird species (54, 55), vampire bats (56), and field crickets (57), among others. Wild barn mice decrease their social contacts and limit the size of their social network following an LPS challenge (58). Similarly, LPS administration to dominant mice promotes hierarchy destabilization in laboratory settings (59). Several studies have found decreases in direct social interaction between novel conspecifics following LPS administration in adult male rats and mice (60–63). Yet, consistent with studies in humans, many instances have been found in which animals prefer or increase social contact following immune challenge—particularly with familiar peers. In rhesus macaques, LPS administration increases time spent engaging in affiliative behavior in both males and females and this effect persists for 24 h after the stimulation (64). Similarly, LPS administration increases social interaction and huddling in male and female rats (65) and enhances partner preference in female prairie voles (66). In vampire bats, LPS administration decreases social grooming between conspecifics, but this effect is minimal for maternal grooming of infants (56). Together, these findings indicate that changes in social behavior following infection are highly context- and social partner- specific. This specificity is likely related to the inherent trade-offs in sickness behavior discussed above. For instance, individuals may limit social interactions with novel individuals in order to reduce disease spread, but maintain, or even enhance interactions with familiar conspecifics to promote self/kin survival. Aspects of the social context, such as whether or not an individual is currently rearing offspring, may shift the risk vs. benefit of suppressing or engaging in sickness behavior, thereby altering the degree to which changes in social behavior are displayed following infection (67).

Notably, while the effects of the viral mimetic Polyinosinic:polycytidylic acid (Poly I:C) on social behavior have been extensively characterized during the perinatal period (68–70), much less is known as to how it effects social behavior

BOX 1 | The relationship between infection and social communities.

In addition to changes in social behavior at the level of the individual, infection, or the risk thereof, often changes social behavior at the community level. These "social immune responses" are especially common in animal species that live in large, complex social groups where risk of infection and transmission is high, such as eusocial insect species (43, 44). They consist of behaviors aimed at reducing exposure to pathogens in the environment and limiting the establishment and transmission of pathogens once the community has been infected (45). For example, honeybees respond to invasion of the hive by the heat-sensitive fungus *Ascosphaera Apis* which causes "chalkbrood disease" by generating a behavioral fever (rise in hive temperature) which is protective against infection (46). Several insect species, including honeybees and wood ants, secrete antimicrobial molecules or collect antimicrobial resins from the environment which they incorporate into the building of their nests (47, 48). Furthermore, infected individuals are often either forcibly or voluntarily excluded from the colonies to limit pathogen transmission. Indeed, in the ant species *Temnothorax unifasciatus*, worker ants leave the nest to die in isolation following infection, presumably to limit risk to kin (49). Finally, social grooming is used in insect species including ants, earwigs, and honeybees to transfer antimicrobial or immune mediators between individuals and between parents and offspring (50–52). In a wide-scale study of 11 distinct insect lineages (some eusocial and some non-eusocial), Lopez-Uriba et al. (53) used phylogenetic mixed linear models to test whether colony size predicted cellular immune response. They found that cellular immune responses were lower in larger colonies (53). This finding may suggest that behavioral adaptation, rather than increased cellular immunity, is the most critical defense against the increased risk of infection that comes with community living in such insect species.

acutely in adulthood. Several studies have shown that Poly I:C increases sickness behavior in adult mice and rats, but none of these studies assessed social interaction (71–73). Further characterizations of the effects of viral challenges on acute sickness responses in adults would add greatly to this body of literature.

Sex Differences in Animal Models

Despite this abundance of studies, there is a paucity of direct comparisons of social responses to acute immune challenge between adult males and females. One study in adult rats found that LPS administration decreased social interaction but increased huddling with familiar cage mates in both males and females, but with stronger effects observed in females (65). In line with this finding, sexual behavior and sexual receptivity are inhibited following LPS injection in female, but not male rats (74). It has been posited that such sickness-induced decreases in sexual behavior may serve to reduce conception and pregnancy while females are ill (75). In contrast, recent studies suggest that males exhibit more sickness behavior than females following adult administration of LPS, the viral mimetic Poly I:C, or influenza viral infection, but these studies did not include the assessment of social behavior [(76, 77), Sharma et al., 2019]. This, along with sex differences in the neural mechanisms underlying changes in social behavior following infection, remains an important area for future research.

WHAT ARE THE NEUROIMMUNE MECHANISMS MEDIATING THE RELATIONSHIP BETWEEN SOCIAL BEHAVIOR AND THE IMMUNE SYSTEM?

The process by which changes in social behavior are induced following infection requires highly coordinated and brain-region specific neuroimmune interactions [see review by (39)]. Bacterial and viral infections activate the innate and adaptive immune systems in the periphery. A large body of work shows that toll-like receptor activation in innate immune cells triggers the release of pro-inflammatory cytokines such as IL-1β, IL-6, and tumor necrosis factor (TNF) α which then act in social neural circuits to shift behavior (78–80). Below, we review the brain regions and neuroimmune mechanisms which have been shown to be most critical.

The Prefrontal Cortex, Amygdala, and Mesolimbic Reward System as Key Neural Substrates for Immune-Driven Changes in Social Behavior

The amygdala, prefrontal cortex (PFC), and mesolimbic reward system stand out as neural structures that have been implicated in both the human and animal literature as important neural mediators of infection-induced changes in social behavior. All are core nodes of the "social decision-making network" which regulates social behavior across vertebrate animals (81). Each likely plays a unique role within these networks. As a "salience detector," the amygdala is critical to the identification and decoding of social stimuli (82). This information is relayed to the PFC, which is critical to social decision-making (83–85), as well as (both directly and indirectly) to the mesolimbic system [consisting largely of projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAc)] to drive behavior—either approach or avoidance (86–88).

Findings in humans suggest that changes in amygdala activity may serve to increase sensitivity to potential social threats when sick. In a randomized controlled trial, LPS administration increased amygdala activation in response to threatening faces as compared to placebo control and this increase was associated with increased feelings of social disconnection (89). Multiple studies have found increased activity of the subgenual anterior cingulate cortex (sACC; a sub-region of the PFC) following immune activation. Specifically, administration of the typhoid vaccine increased activity of the sACC during an emotional face processing task in male participants and increased circulating levels of pro-inflammatory cytokines such as IL-6 (78). Furthermore, the functional connectivity of the sACC with the amygdala, nucleus accumbens, and other regions of the PFC was reduced by this exposure and this effect was mediated by peripheral IL-6 levels (78). Finally, ventral striatum activity is increased in response to images of support figures, but not strangers, following LPS administration in human study participants and this increase is correlated with circulating levels of IL-6 in circulation (37). Together, these studies provide evidence from human studies that the amygdala, PFC, and NAc

may be key brain regions in which cytokines act to alter social behavior following infection.

Findings in the animal literature also support the importance of these brain regions as sites of neuroimmune mediation of social behavior. In adult male mice and rats, LPS administration increases the expression of c-Fos (a marker of neural activity) in the amygdala, as well as IL-1β and IL-6 mRNA in the amygdala (90–92). Interestingly, healthy male rats avoid social interaction with conspecifics that have received an LPS challenge, and this effect is dependent on vasopressin signaling in the medial amygdala (93), lending further support for the role of the amygdala in social information processing following infection. LPS administration also increases mRNA for IL-1β, TNFα, and IL-6 in the PFC of adult male rodents (94). As will be discussed in more detail below, microglia, the resident immune cells of the brain are key responders to peripheral cytokines following infection (95). Peripheral LPS administration alters microglial morphology in the PFC (often used as an indicator of function), increasing microglial soma size and decreased process length (96, 97).

Several studies suggest that dopamine signaling in the mesolimbic system may be particularly important for linking infection and social behavior [for complete review see (87)]. Immune challenge has been shown to impact dopaminergic signaling in the context of reward and motivation, albeit not in the social domain (98–100). Activation of VTA projections to the NAc facilitates social interaction (101) and activation of dopamine D1 receptors in the NAc increases social play behavior (102). Work from our laboratory recently showed that in healthy male (but not female) rats, microglial, complement-dependent phagocytosis of D1 receptors in the NAc is required for the normal developmental decline of social play behavior between adolescence and adulthood (103). Intriguingly, Ben-Shaanan et al. (104) found that chemogenetic activation of dopaminergic projections from the VTA to the NAc increased social interactions with familiar cage mates and improved the innate immune response to E. coli infection—decreasing bacterial load (104). This finding is in line with those from human studies suggesting that activation of the ventral striatum (of which the NAc is a component) may increase social interactions with familiar peers, and thus, buffer against infection. Of note, however, some findings are counter to this hypothesis, suggesting that dopamine may increase neurotoxicity following infection (87, 105).

Immune Mediators of Social Behavior

As evidenced by the studies discussed above, increases in the pro-inflammatory cytokines IL-1β, TNFα, and IL-6 are often associated with changes in social behavior following immune activation and/or with activity in social circuits in the brain (37, 78, 90–92, 94, 106). Several studies provide a causal link between these cytokines and social behavior. For example, in adult male rats and mice, peripheral or central administration of an IL-1 receptor antagonist attenuates the suppressive effects of LPS or IL-1β on social behavior (61, 107, 108). Interestingly, IL-1 receptor blockade also reduces the effects of TNFα on social behavior (79, 80), suggesting synergism between these cytokines. Finally, central administration of either LPS or IL-1β fails to induce social withdrawal in IL-6 KO mice (63). Cumulatively, these studies provide compelling evidence for a causal role of these cytokines in the induction of social withdrawal following infection.

Microglia, the resident immune cells of the brain, are also important mediators of the relationship between infection and social behavior. Peripheral LPS injection increases IL-1β and TNFα mRNA in microglia (109–111). Since LPS does not cross the blood brain barrier, it is likely that local cytokine release by microglia at least partially mediates the impact of immune activation on social behavior. In support, aberrations in microglial function, including chemogenetic manipulation and elevated protein synthesis, disrupt social behavior, and prevent immune activation-induced changes in social behavior (112–114).

Finally, lymphocytes have also been implicated in the neural control of social behavior. SCID mice, which lack mature B and T lymphocytes and are thus deficient in adaptive immunity, have deficits in social behavior that can be restored by lymphocyte repopulation (115). Moreover, mice deficient in interferon-γ (produced by T cells) display social deficits (115). Interestingly, both SCID mice and IFN-γ knock-out (KO) mice also display hyperactivity of the PFC in response to social stimuli. This finding is well-aligned with the human studies demonstrating increased activity of the PFC in response to social information following infection.

Sex Differences in the Neuroimmune Mechanisms Mediating Social Behavior Following Infection

The vast majority of the work detailed above was conducted only in male animals. However, the studies that have been performed in both sexes indicate potential avenues for further investigation. In humans, in a double-blind, placebo controlled clinical trial on the relationship between cytokines and social behavior, LPS administration increased both circulating IL-6 and TNFα, as well as depressed mood and feelings of social disconnection in male and female participants (35). Interestingly, cytokine increases were greater in females than in males and behavior correlated with cytokine measures in females only (35). In female, but not male rats, IL-1β inhibits sexual behavior (116). In mice, Sharma et al. (73) found sex differences in cytokine mRNA expression in the brain following LPS challenge in adulthood, with males having more IL-1β mRNA expression and females having higher TNFα mRNA expression; however social behavior was not assessed.

In many of the studies discussed earlier, females exhibited greater social behavior changes following infection than males (40, 65, 74). One possibility is that this might reflect better behavioral adaptation in females. In general, males tend to fair worse in the face of infection [for review see (21, 22)], while females tend to mount greater adaptive immune responses to viral infection—as is the case in COVID-19 (19, 20). One obvious mechanism by which sex-specific susceptibility/responsivity might be generated is via sex differences in steroid hormone

exposures. In line with this idea, both androgens and estrogens have been shown to influence immune function (117), with broad theories suggesting that testosterone is immunosuppressive while estrogen enhances immune function (118, 119). It has also been proposed that exposure to androgens, in either males or females, may increase susceptibility and variability in responses to challenges (120), lending itself to greater male vulnerability. Less is known regarding the specific role of steroid hormones in *social behavior* changes following infection. However, evidence supports their possible involvement. For example, IL-1β administration increases anxiety-like behavior in female rats in estrus, but not those in non-estrus (121). Moreover, IL-1β administration also increases anxiety-like behavior in ovariectomized females treated with progesterone (121). During healthy brain development, VanRyzin et al. (122) recently showed that testosterone drives increased microglial phagocytosis of newborn neurons in the male brain, contributing to the masculinization of social play behavior (122). Further research is needed to determine the contribution of steroid hormones to changes in social behavior following an acute infection in adulthood.

Microglia represent another particularly attractive candidate to mediate sex differences in the impact of infection on social behavior. Indeed, microglial biology is replete with sex differences during both homeostatic and disease conditions (22, 103, 122–124). For instance, recent work from our lab using RNA sequencing demonstrated that microglial gene expression and morphology differs between males and females at baseline (125). Furthermore, based on a novel "microglial developmental index" based on gene transcription, adult female microglia appear to be more mature than male microglia and acute LPS challenge accelerates microglial development in males only (Hanamsagar et al., 2018). Intriguingly, we have also recently found that microglial pruning of dopamine D1R receptors in the NAc is critical to the normal development of social play behavior in males, but not females (103). It is therefore possible that sex differences in the impact of immune stimulation on microglial function is a route by which sickness leads to sex-specific behavioral responses.

HOW DOES SOCIAL CONTEXT SHAPE IMMUNE FUNCTION?

Group living inherently increases individual exposure to pathogens and parasitism, but also provides opportunities for the evolution of collective social responses to protect against infection/parasitism. A large body of literature across species suggests that social isolation and social stress may impair immune function, while strong social bonds may buffer against infection.

Social Isolation and Immune Function

Early research into the effects of social isolation on immune function revealed striking decreases in pathogen resistance in isolated animals. For example, mice that were housed in individual cages reached 85% mortality following West Nile Virus infection, as compared to only 50% in socially housed mice (126). This was driven by enhanced viral proliferation and mass loss of the spleen and thymus in isolated mice. IL-6 expression in response to either the viral mimetic Poly I:C or LPS is increased in isolated mice as compared to those that were socially housed (71, 127). Social isolation also increases the blood trafficking of leukocytes and monocytes (128) and decreases anti-inflammatory IL-10 mRNA and protein in the blood and brain (129). Wound healing is impaired to a similar extent in male and female mice following social isolation (130, 131), indicating some similarity between the sexes in this outcome.

Findings in humans echo this animal work. In an extreme example, social isolation during space flight or terrestrial preparation for space flight, led to damped immune responses to viral infections and reactivation of latent viral infections such as herpesviruses (132). More frequently, isolation is assessed based on loneliness or "perceived social isolation" in humans. In psychiatric inpatients, reported loneliness was found to be associated with lower immunocompetence (133). Healthy participants (male and female) who reported greater loneliness mounted a greater TNFα, and IL-6 response to an acute LPS challenge than those that did not (134). Similarly, trait sensitivity to social disconnection is associated with a greater inflammatory response (as evidenced by TNFα and IL-6) to LPS challenge, (35). On the other hand, in a recent study of almost 9,000 adults over the age of 50, social engagement and cohabitation were associated with lower levels of pro-inflammatory factors including fibrinogen, C-reactive protein, and white blood cell count, irrespective of sex (135). Thus, whether increases or decreases in inflammatory markers is observed likely depends very much on the specific context and endpoint in question. Furthermore, too little or to great an immune response can have detrimental consequences for the ability to overcome infection. For instance, excessive cytokine release can increase mortality following infection by damaging host tissues, as is the case of the "cytokine storm" observed in some patients with COVID-19 (136).

Many of the same neural structures that mediate the effects of infection on social behavior, also mediate the effects of social context on immune function. PFC gene expression analyzed postmortem indicated that loneliness in the 5 years anti-mortem was associated with an enrichment for immune related genes (137). Greater feelings of loneliness are associated with greater ventral striatum activity (138) suggesting convergence of inflammation and social isolation effects on the ventral striatum. Blocking opioids with the opioid receptor antagonist naltrexone increases feelings of social disconnection (138), suggesting that opioids may play a role in these effects.

Social Stress and Immune Function

A wealth of studies has shown that social stress, in the form of social defeat stress in rodents, low social rank within a hierarchy in non-human primates, and low socioeconomic status in humans, has severe negative consequences for immune function [for excellent reviews see: (139–141)].

In brief, in male rodents, social defeat increases pro-inflammatory cytokines including IL-6, TNFα, and IL-1β, but

decreases the anti-inflammatory cytokine IL-10 in the brain (94, 142–144). Social defeat also exaggerates the impact of an immune challenge with LPS on cytokines production, microglial activation, and monocyte infiltration to the brain (145). Of particular relevance to the current COVID-19 pandemic, lung inflammation is also increased in mice exposed to social stress (146). Until recently, social defeat paradigms were used almost exclusively in male animals, for the simple reason that it was harder to elicit aggression in females. However, recent work has overcome this hurdle by using DREADD technologies to induce aggressive behavior toward females in male rodents (147). In this study, the authors found that social defeat induced similar increases in pro-inflammatory cytokines and monocyte infiltration into the brain (147), albeit without direct comparison between the sexes. Still, it represents an important step toward the inclusion of females in studies of adult susceptibility to social stress.

In primates that live in hierarchically organized social groups, several studies suggest that social status shifts immune function. In female rhesus macaques, the effects of LPS administration on pro-inflammatory gene expression are higher overall in low-ranking vs high-ranking individuals. Furthermore, gene expression patterns are shifted such that low-ranking females up-regulated genes related to bacterial defense, while high-ranking females upregulated more genes related to viral defense (148, 149). The same group has also shown that in wild male and female baboons, males up-regulate many more genes than females in response to LPS and that some of these genes include those that were up-regulated in low-ranking females (150). It is important to note however, that the authors determined that in males, immune gene transcription was a precursor to social status, suggesting that immune function may contribute to social rank (150). This is in line with the idea of a "conserved transcriptional response to adversity" (CTRA) in which adversity biases gene expression toward pro-inflammatory gene expression and away from anti-viral and antibody production genes (151, 152). Similar CTRA gene expression shifts have also been demonstrated in leukocytes from humans exposed to social stress, i.e., low socioeconomic status (153, 154). In a study of peripheral cytokine expression and cognitive function following a flu vaccine in human (largely female) volunteers, participants who had experienced early life social stress displayed more strongly associated changes in IL-6 and depressed mood (155), providing evidence in humans for long lasting effects of social stress on immune responses.

Neuroimaging studies suggest that the PFC and amygdala may be critical to the effects of social stress on immune function. Lower perceived social status is associated with an increased pro-inflammatory response to a social evaluation stress test and greater dmPFC activity during negative social feedback (38). In a study of young women, this social stress task increased serum cytokine levels, amygdala activity, and functional connectivity between the amygdala and the dorsolateral PFC (156). Moreover, this increased connectivity was associated with increased feelings of social rejection (156).

Social Buffering and Immune Function

While social isolation and social stress potentiate inflammatory responses, social bonds and supportive social networks can also have powerful stress buffering and anti-inflammatory functions (157, 158). In social species, strong social bonds decrease stress and enhance immune function (159, 160). For example, socially monogamous prairie voles exhibit stronger immune responses than socially promiscuous meadow voles (161). In infant Bonnet macaque monkeys exposed to maternal separation, the presence of juvenile conspecific (friend) prevented mitogen-induced increases in leukocyte activation (162). Furthermore, the frequency of affiliative interactions with this companion were positively associated with natural cytotoxicity (162). Similarly, in a study of adults who experienced low socioeconomic status (SES) as children, those who reported high levels of maternal warmth exhibited lower IL-6 responses following stimulation of peripheral blood mononuclear cells [PBMCs; (163)]. Finally, in a study of adult men, perceived social support at home was associated with higher levels of natural killer (NK) cells and a higher INFγ/IL-4 cytokine ratio (164).

As discussed earlier, activation of the mesolimbic reward system, and dopamine signaling in particular, may represent a potential mechanism by which positive social interactions might boost immunocompetence (87, 104). Another potential candidate is the oxytocin (OT) system. Oxytocin is a highly evolutionarily-conserved neuropeptide that mediates social behavior and is released during a variety of social encounters (165). Of particular interest here, OT appears to have anti-inflammatory capacities as well (166, 167). In a randomized controlled trial in adult men, intravenous oxytocin administration blunted LPS-induced increases in a number of immune molecules, including TNFα (168). In singly housed female Siberian hamsters, stress impairs wound healing, but this effect is absent in socially housed hamsters or singly housed hamsters treated with OT (169). Furthermore, OT receptor antagonism delayed wound healing in socially housed hamsters (169). In male mice, *in vivo* systemic treatment with LPS increased TNFα and IL-1β in the PFC 24 h later, but this increase was attenuated by intranasal OT administration (Yuan et al., 2016). *In vitro*, OT also dampened the response of both primary microglia and BV-2 cells to LPS treatment (Yuan et al., 2016). Together, these studies provide evidence in both male and female animals that OT is anti-inflammatory and, thus, of great interest to understanding how social support systems may buffer against immune challenge (158). Importantly, however, direct comparisons between the sexes were not made in these studies. Many studies have shown that OT is an important regulator of social behavior in both males and females (170, 171). Yet, the OT system is also replete with sex differences (172, 173). OT and OTR expression are regulated by steroid hormones (174–176). Therefore, it is highly likely that sex differences in the OT system might contribute to sex differences in the degree to which social interactions can provide buffering in the face of immune challenge.

CRITICAL PERIODS AND CHRONIC ILLNESS: THE BREAKDOWN OF ADAPTIVE RESPONSES

Shifts in social behavior are a critical part of the adaptive host response to infection. However, when immune challenges occur during developmental critical periods or lead to chronic inflammation, they can have long-lasting and maladaptive consequences for social dysfunction—even after the acute illness has passed (95, 177). Immune challenges during the perinatal period disrupt adult social functioning in both males and females, but these effects appear to depend on a variety of factors including developmental timing of the challenge, drug dose, and the nature of the challenge itself (30, 68, 69, 111, 178, 179). For instance, maternal immune activation with influenza virus (70) or Poly I:C during pregnancy leads to social deficits in adult offspring in both rodents and primates (68, 70, 180–182). Several studies have investigated the effects of Poly I:C administration during early to mid-gestation on social behavior in both male and female offspring and observed social deficits only in males (180, 183). Interestingly, late gestational Poly I:C (on the last day of pregnancy) induces social deficits in both male and female offspring (184), which may suggest that sex-specific vulnerability is sensitive to gestational age. Similarly, in rodents, administration of a low dose of LPS between postnatal days (PND) 3–5 has been shown to decrease social behavior in both males and females in adolescence (30, 178) and only in females in adulthood (111), while a high dose of LPS administered at PND 9 only decreases social behavior in adulthood in males (69). Thus, either a viral or bacterial infection may alter social behavior in males and females, but the magnitude of these effects differs between the sexes and changes along developmental trajectories.

Adolescence is a developmental phase during which social motivation is heightened and social interactions are particularly important for the development of appropriate adult social behaviors. It is also a period of sensitivity to immune challenges (185, 186). Several recent studies have taken great strides toward characterizing sex differences in neuroimmune interactions during adolescence as well as their implications for social behavior (73, 76, 103, 187, 188). It appears that while males and females respond differently to immune challenges during adolescence, the pattern of sex differences is often specific to a given neuroimmune endpoint. In line with this idea, Cai et al. (76) found that females mounted greater IL-1β and IFN-γ responses to an LPS challenge than males during adolescence but this was the opposite during adulthood (76). In contrast, IL-6, IL-12, and TNFα responses are similar between males and females during both adolescence and adulthood (76). Finally, male microglia appear to be more amoeboid and less ramified than female microglia in the PFC during adolescence (187). This "activated" morphology is often used as a proxy (albeit a limited one) for microglial functional state as it is observed following immune challenge and correlates with pro-inflammatory cytokine expression (125, 189, 190). Similarly, in the NAc, microglia play a critical role in sculpting social circuits in males but not females (103).

Sex differences in susceptibility to social isolation and social stress are also observed during the adolescent period. In humans, adolescent girls are more likely than adolescent boys to be sensitive to social stress, become depressed, or to engage in self-injurious behavior following stress in peer and/or family relationships (191, 192). In adolescent male mice, social isolation during adolescence leads to impaired social recognition memory in adulthood (193). Furthermore, chronic social stress during adolescence leads to social deficits that are transmitted to the next generation as well (194). In Syrian hamsters, deprivation from social play during adolescence increased social avoidance following social defeat in both males and females but had opposite effects in males and females on aggressive behavior during the social defeat exposure itself (195).

These findings highlight the long-term impact of infection and social stress on social behavior when these challenges occur during developmental critical periods. In these cases, changes in social behavior shift from being acute adaptive responses to an immediate context, but rather a developmental organization of neuroimmune interactions and behavior that can become maladaptive.

CONCLUSIONS: THE IMPORTANCE OF SOCIAL CONTEXT WHEN IT COMES TO COVID-19

In conclusion, we have highlighted the intimate relationship between immune function and the social landscape. Infection can shift social behavior either for the benefit of the host or for the invading pathogen. Similarly, social context can make individuals either more vulnerable to infection, as in the case of social isolation or psychosocial stress, or it can provide social buffering and promote resilience, as in the presence of strong social bonds. As the scientific community, and the world at large, works to promote resilience in the face of COVID-19, social context must be a major consideration. Furthermore, our synthesis of the literature on infection and social behavior suggests that sex differences in this relationship *in adulthood* remain vastly understudied. Overall, both males and females respond to infection and social isolation, but the few studies that have been conducted suggest nuanced sex differences in the nature of these responses. Given the male bias in susceptibility to COVID-19 and other infectious diseases, it is critical that we understand the sex differences in neuroimmune function that may impart vulnerability and protection to males and females, respectively. Age at infection is also of critical importance. Indeed, it is possible that COVID-19 infections in children that elicit even a mild immune response could have long-lasting impacts on social circuit development. Finally, we must emphasize the ameliorative power of social connection and work to better understand and promote those connections in this era of social distancing.

AUTHOR CONTRIBUTIONS

CS and SB conceived of and wrote the manuscript together. All authors contributed to the article and approved the submitted version.

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Peripheral Lipopolyssacharide Rapidly Silences REM-Active LH^{GABA} Neurons

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Immune factors (e.g., cytokines, chemokines) can alter the activity of neuronal circuits to promote "sickness behavior," a suite of adaptive actions that organisms exhibit in response to infection/injury in order to maximize their chances of recovery (i.e., return to homeostasis). This includes drastic alterations in sleep/wake states, locomotor activity, and food intake, among other behaviors. Despite the ample evidence highlighting interactions between the brain and systemic immunity, studies on how immune challenges alter the activity of genetically defined cell populations controlling arousal states are scarce. As the lateral hypothalamus (LH) serves a major integrative function in behavioral arousal, food intake, and monitoring and responding to changes in systemic physiology, we investigated how GABAergic neurons within this brain region alter their activity across normal sleep/wake states and in response to a peripheral immune challenge with bacterial endotoxin [lipopolysaccharides (LPS)]. Using fiber photometry (GCaMP6s Ca^{2+} signal) in tandem with electroencephalogram (EEG)/EMG recordings to determine arousal states, we observed that population activity of GABAergic neurons in the lateral hypothalamus (LH^{GABA}) is highest during rapid-eye-movement sleep (REM), and this activity changes drastically across spontaneous arousal state transitions, with the lowest activity observed during non-REM sleep. Upon intraperitoneal LPS challenge, LH^{GABA} neurons rapidly decrease their activity in tandem with elimination of REM sleep behavior (characteristic of cytokine-induced sickness). Together, these data suggest that peripheral immune challenges can rapidly (in $<$ 40 min) alter subcortical neuronal circuits controlling arousal states. Additionally, we demonstrate that fiber photometry offers a sensitive and cell-type specific tool that can be applied to study the neuronal substrates of sickness behavior.

Keywords: lipopolysaccharides, *Escherichia coli*, sleep, lateral hypothalamus, fiber photometry, GABA, VGAT

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INTRODUCTION

Sickness behavior is characterized by acute and protracted changes in sleep/wake states, appetitive, sexual, and social behavior, among other changes (Dantzer and Kelley, 2007; Dantzer et al., 2008; Myers, 2008). This suite of adaptive behaviors is largely conserved across the phylogenetic tree, including in humans (Shattuck and Muehlenbein, 2015). Changes in behavior in response

to infection/injury can be attributed to neuroimmune crosstalk among peripheral and central cytokines, endothelial cells, glia, and neurons (Henry et al., 2008; Jin et al., 2016). In response to acute inflammatory challenges, such as bacterial endotoxin [lipopolysaccharides (LPS)] exposure, mice increase their time spent in non-rapid-eye-movement (NREM) sleep at the expense of rapid-eye-movement sleep (REM) sleep, with corresponding decreases in wakefulness. These inflammatory signals in the periphery are partially transduced to the brain *via* vagal afferent nerve fibers (Opp, 2005; Zielinski et al., 2013; Borniger et al., 2017). During extended periods of immune activation (e.g., in neurodegenerative disease), sleep becomes fragmented and is accompanied by protracted insomnia (Toth and Krueger, 1988; Dauvilliers, 2007; Irwin and Opp, 2017). The biological substrates that drive this phenomenon remain to be fully identified and characterized, although myeloid cell (microglia/macrophage) interactions with neurons seem to be predominant drivers of infection-associated sleep disruption (Toth and Hughes, 2004). Significant progress has been made in recent years in identifying neural ensembles underlying inflammation-associated changes in feeding behavior (Chaskiel et al., 2016, 2019; Liu et al., 2016; Wang et al., 2019). However, additional work is required to understand how neurons controlling feeding, arousal, and motivational states integrate various inflammatory inputs to induce changes in overt behavior.

The first experimental evidence for humoral (and potentially immune) regulation of sleep/wake states came over a century ago from the Japanese physiologist Kuniomi Ishimori, who demonstrated that cerebrospinal fluid (CSF) from sleep-deprived dogs powerfully induced sleep in naïve recipient dogs (Kubota, 1989; Krueger et al., 2001). Subsequent studies from Fencl et al. (1971) confirmed this finding by injecting CSF from sleep-deprived goats into recipient rats and observed marked increases in sleep. Pappenheimer, Krueger and colleagues subsequently followed up on these findings and termed the mysterious sleep-inducing substance in CSF "Factor S." Factor S was later determined to be muramyl peptide, a component of bacterial cell walls. Injections of low doses of muramyl peptide or another bacterial cell wall component, LPS, powerfully induced slow wave sleep (SWS) with high amplitude delta (δ) waves (0.5–4 Hz) in the electroencephalogram (EEG) of cats (Krueger et al., 1982, 1984, 1986; Krueger, 1985; Cady et al., 1989). Why would a piece of bacterial cell walls have any influence on mammalian sleep? The evidence thus far supports the hypothesis that the immune response elicited by a bacterial infection indirectly regulates the activity of neuronal structures that control sleep/wake states to putatively overcome the infection/injury and return to homeostasis. In short, the immune system engages sleep circuitry in order to promote rest and recovery.

The hypothalamus represents a key biological substrate underlying the expression of sickness behavior. It controls virtually all homeostatic processes that become dysregulated upon infection/injury, including sleep/wake states, food intake, sexual/social behavior, body temperature, and stress responses, among others (Saper and Lowell, 2014; Bonnavion et al., 2016; Scammell et al., 2017). GABAergic neurons within the lateral division of the hypothalamus (LH^{GABA}) represent a heterogenous population of cells that differentially contribute to sleep/wake control. Indeed, single cell RNA sequencing (scRNA-seq) demonstrated that at least 15 sub-populations of GABAergic neurons exist within the lateral hypothalamus (LH) alone (Mickelsen et al., 2019). Major sub-populations include those that express the long-form leptin receptor (LepRb), neurotensin (NTS), or cocaine and amphetamine related transcript (CART) (Bonnavion et al., 2015, 2016; Mickelsen et al., 2019). Whether these subpopulations play similar or differing roles in sleep/wake control is an active area of investigation, but collectively this GABAergic population seems to promote rapid arousal out of NREM, but not REM sleep (Herrera et al., 2016; Venner et al., 2016). Early single-unit electrophysiological studies suggested that LH^{GABA} neurons are active during sleep, with a large proportion active during REM states compared to NREM sleep and wakefulness (Hassani et al., 2010). More recent work demonstrated that approximately 34% of LH^{GABA} neurons are maximally active during REM sleep, and function to reinforce and stabilize hypothalamic representations of feeding behavior (Oesch et al., 2020). Additionally, early studies suggested that LH^{GABA} neurons are preferentially responsive to the inflammatory cytokine IL-1β(De et al., 2002), suggesting that they may play a role in regulating sickness responses governed by the hypothalamus. Further, work has demonstrated that sleep deprivation enhances mRNA expression of a bacterial peptidoglycan recognition protein (PGRP), suggesting a link between bacteria, the hypothalamus, and sleep (Rehman et al., 2001). We aimed to build upon this work by examining population wide LH^{GABA} Ca^{2+} activity during spontaneous arousal state transitions and in response to peripheral endotoxin (LPS) administration. We hypothesized that LH^{GABA} neurons alter their activity across discrete brain states and predicted that we would observe high Ca^{2+} activity during REM sleep, consistent with prior observations. Because of the strong REM-suppressive actions of bacterial endotoxin, we reasoned that LH^{GABA} neurons would drastically alter their activity across arousal states during the inflammatory response.

MATERIALS AND METHODS

Mice

Heterozygous VGAT-IRES-Cre mice (N = 5; male, >8 weeks old; JAX # 028862) were used in these experiments, housed with *ad libitum* food and water at room temperature (22 ± 2°C). The dental cement headcap of one mouse became disconnected (and therefore required euthanasia) between initial recordings and subsequent LPS experiments, so N = 4 for the LPS data. These mice were bred in-house and maintained on the c57bl6 background for >10 generations prior to use. Cre + mice were used for all experiments, and genotyping was done using tail gDNA and primers targeting Cre sequences (Cre_F: GGGATTGCTTATAACACCCTGTTACG; Cre_R: TATTCGGATCATCAGCTACACCAGAG). All experimental protocols were approved by the Stanford University IACUC prior to beginning these studies (protocol #18787).

Surgery

Electroencephalogram/EMG electrodes were custom made as in previous work (Carter et al., 2012; Eban-Rothschild et al., 2016, 2020). Mice were deeply anesthetized with ketamine/xylazine (90 mg kg^{-1}/10 mg kg^{-1}, respectively), and then their head was shaven and cleaned with betadine/EtOH. Mice were then positioned on a stereotaxic frame for surgery and administered prophylactic analgesia (buprenorphine SR; 1 mg kg^{-1}; SC). Mice were maintained on a low-power heating blanket during surgery to prevent hypothermia. The skin on the head was cut from the posterior margin of the eyes until the midpoint of the scapulae, and then cleaned using H_2O_2 and sterile saline. Three holes were drilled into the skull. Two holes (one at 1.5 mm AP, 1 mm ML; the other on the contralateral hemisphere at −2 mm AP, −1.5 mm ML) were to be used for placement of cortical electrodes for EEG measurement, and the last hole was used for viral injections into the LH (−1.2 mm AP, ± 0.89 mm ML, −5.3 mm DV). A Hamilton syringe (0.36 mm outer diameter; 28 gauge) loaded with 300 nl AAV-DJ-DIO-ef1α-GCaMP6s [titer > 1×10 (Dauvilliers, 2007) vg/ml; Stanford Viral Vector Core] was slowly lowered to these coordinates and virus was injected unilaterally at 100 nl/min. Following injection, the syringe was left in place for an additional 10 min to prevent backflow, then the syringe was slowly removed. A 400 μm diameter fiber optic (Doric Lenses; 6 mm in length) was slowly lowered to just above the virus injection coordinate (−5.2 mm DV) and then cemented into place using Metabond (Parkell, Inc.) and UV-curable dental resin. EMG leads were inserted and secured in the trapezius muscles, and EEG screws were cemented into place. After fiber and EEG/EMG placement, any surgical openings were sutured closed, and then the mice were given supplemental warmth (heating pad) and hydration (0.4 ml saline, SC) until mobile. Mice were allowed to recover for at least 3 weeks before starting experiments (to allow for adequate transgene expression). Before starting recordings, mice were separated and allowed to acclimate to a specialized (open top) sleep recording chamber, EEG/EMG tethers, and the fiber optic patchcord for at least 3 days.

LPS Administration

Mice were administered 0.5 mg kg^{-1} LPS (serotype O111:B4; Sigma-Aldrich) in sterile saline (intraperitoneal; IP) as in prior work (Borniger et al., 2017) at zeitgeber time (ZT) 4, when sleep pressure has mostly abated. Forty minutes later, photometry and EEG signals were collected for an additional 40 min to monitor LH^{GABA} Ca^{2+} activity in tandem with sleep/wake states. For control/baseline recordings, mice were administered sterile saline vehicle alone (200 μl; IP). We chose to record 40 min after IP injections to reduce the influence stress had on the neural/sleep phenotype.

Fiber Photometry

Fiber photometry is an increasingly common method within the neuroscience community by which an optic fiber is placed near a brain region of interest and light is delivered and collected from the fiber tip. Cells within the target area are engineered (e.g., *via* viral transfection) to express a fluorescent protein (e.g., GCaMP6s) that, upon light excitation, transduces Ca^{2+} activity (a proxy of neural activation) into a high-temporal resolution fluorescent signal that is collected by the optic fiber, converted into a voltage signal, and subsequently analyzed. Because of the small and lightweight design of optic fibers, these recordings can be done in freely moving mice, as in the present study. In line with this, fiber photometry experiments were conducted as previously (Eban-Rothschild et al., 2016; Giardino et al., 2018; Li et al., 2020). In brief, we modulated blue light from a 470-nm excitation LED (M470F3, ThorLabs, NJ, United States) at 211 Hz, using a custom MATLAB program (MathWorks, Natick, MA, United States) and a multifunction data acquisition device (NI USB-6259, National Instruments, Austin, TX, United States). Blue light was passed through a GFP excitation filter (MF469-35, ThorLabs), bounced off a dichroic mirror (MD498, ThorLabs), and then coupled using a fiber collimation package (F240FC-A, ThorLabs) into a low-fluorescence patch cord (400 μm, 0.48 NA; Doric Lenses) *via* a zirconia sleeve (Doric). GCaMP6s fluorescence was collected through the excitation patch cord, where it traveled through a GFP emission filter (MF525-39, ThorLabs), and focused onto a photodetector with a lens (Model 2151, Newport, Irvine, CA, United States; LA1540-A, ThorLabs). The signal was relayed to a lock-in amplifier (30-ms time constant, Model SR830, Stanford Research Systems, Sunnyvale, CA, United States) that was synchronized to 211 Hz. Amplified signals were collected at 1 kHz using custom MATLAB code and a multifunction data acquisition device (National Instruments).

EEG/EMG

Sleep/wake states were assessed *via* EEG/EMG. These biopotentials were sampled at 256 Hz with VitalRecorder (Kissei Comtec Co.) software, and then passed through an amplifier (Grass Instruments). Raw EEG/EMG voltage data were exported (.txt) into MATLAB (MathWorks, Natick, MA, United States) and analyzed using custom scripts [as in Li et al. (2020)]. Wake was defined as low amplitude, high frequency EEG oscillations with prominent EMG signal. NREM sleep was characterized by large amplitude, low frequency delta oscillations in the EEG, with little or no EMG signal. REM sleep was identified based on a predominant theta (θ) component of the EEG, with no EMG activity reflecting complete motor atonia. Behavioral states (wake, NREM, or REM sleep) were assessed blind to the time-locked photometry signal or experimental manipulation (LPS or saline).

Histology

After completion of experiments, mice were deeply anesthetized using ketamine/xylazine and then perfused (transcardial) with ice-cold 1x PBS followed by 4% paraformaldehyde (PFA). Brains were dissected and post-fixed in 4% PFA at 4°C overnight, followed by cryoprotection in 30% sucrose for 2–3 days until sunk. Serial sections were cut on a cryostat (Leica Microsystems) at 30 μm and placed into 24-well plates containing 1x PBS + 0.1% NaN_3, covered with aluminum foil, and maintained at 4°C until histology/immunohistochemistry. Validation of GCaMP6s viral transduction and fiber placement was confirmed *via* confocal

microscopy (Excitation λ: 488 nm; Emission λ: 509 nm; LSM-710; Zeiss).

Data Analysis and Statistics

Electroencephalogram/EMG data and time-locked photometry data were analyzed using custom MATLAB code. In brief, photometry data was corrected for linear or exponential decay in the trace [as in Eban-Rothschild et al. (2016) and Eban-Rothschild et al. (2020)], which occurred in a minority of recordings. Photometry data was down sampled to 256 Hz in order to match the EEG signal sampling rate. Data from each arousal state transition (i.e., wake-to-NREM, NREM-to-wake, NREM-to-REM, and REM-to-Wake) were analyzed for the mean and max fractional fluorescence change (dF/F) in each state, and then time series were generated for 10 s preceding and 10 s following each transition. Differences among experimental groups was assessed using one-way ANOVA, followed by Tukey's HSD *post hoc* test. For analysis of GCaMP6s spectral data, 2-way repeated measures ANOVAs were used with treatment and frequency bin as independent factors, followed by Šidák's multiple comparisons *post hoc* test.

RESULTS

LH^{GABA} Neurons Are Predominantly REM-Active

We monitored LH^{GABA} Ca^{2+} activity during natural arousal state transitions. These neurons exhibited marked changes in GCaMP fluorescence across arousal states, with the highest mean fractional fluorescence change (ΔF/F or dF/F) during REM sleep compared to wakefulness or NREM sleep (**Figure 1**). Additionally, these neurons were intermediately active during wakefulness compared to REM and NREM sleep, respectively (**Figure 1D**; One-way ANOVA $F_{2,591} = 438.1$; $p < 0.0001$; Tukey's *post hoc* wake vs. NREM: $q = 10.72$, adjusted $p < 0.0001$; wake vs. REM: $q = 35.58$, adjusted $p < 0.0001$; NREM vs. REM: $q = 41.84$, adjusted $p < 0.0001$). In contrast, NREM sleep and wakefulness showed similar maximal ΔF/F values, but REM sleep reached upward of 20–30% ΔF/F state (**Figure 1E**; One-way ANOVA $F_{2,591} = 212.9$; $p < 0.0001$); (Tukey's *post hoc* wake vs. REM: $q = 27.29$, adjusted $p < 0.0001$; NREM vs. REM: $q = 28.45$, $p < 0.0001$). These results indicate that LH^{GABA} Ca^{2+} activity peaks during REM sleep, suggesting that this

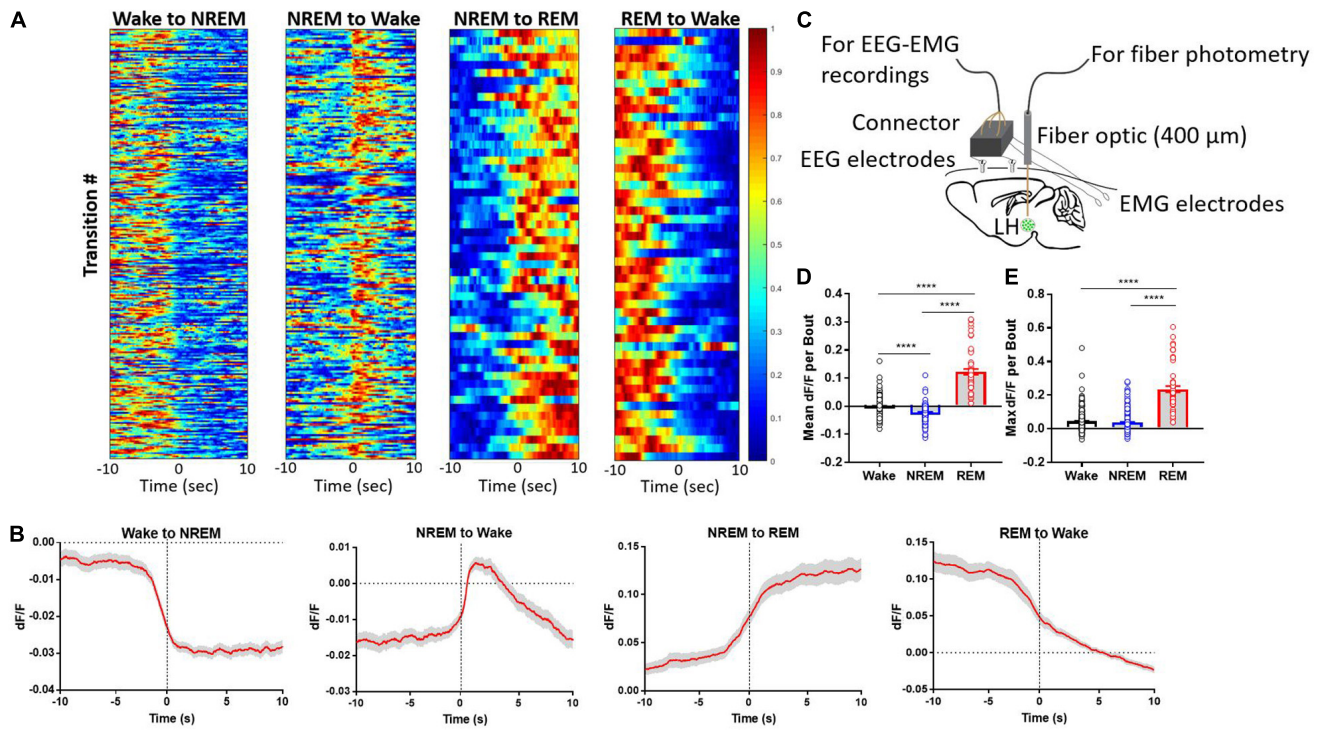

FIGURE 1 | Lateral hypothalamic GABAergic neurons are wake- and REM sleep-active. **(A)** Heatmaps showing GCaMP6s signal across arousal state transitions (Wake-to-NREM (256 transitions), NREM-to-Wake ($n = 208$ transitions), NREM-to-REM ($n = 60$ transitions), and REM-to-Wake ($n = 57$ transitions), with transition number on the y-axis and time on the x-axis; GCaMP6s signal is reflected in the colormap. **(B)** The same data as in panel **(A)** but collapsed into the average signal time series across arousal state transitions. **(C)** Experimental design describing the set up for simultaneous recording of EEG/EMG + fiber photometry signal from freely moving mice. **(D)** mean dF/F of LH^{GABA} neuronal activity per bout of each arousal state (One-way ANOVA $F_{2,591} = 438.1$; $p < 0.0001$); (Tukey's *post hoc* wake vs. NREM: $q = 10.72$, adjusted $p < 0.0001$; wake vs. REM: $q = 35.58$, adjusted $p < 0.0001$; NREM vs. REM: $q = 41.84$, adjusted $p < 0.0001$). **(E)** max dF/F of LH^{GABA} neuronal activity per bout of each arousal state (One-way ANOVA $F_{2,591} = 212.9$; $p < 0.0001$); (Tukey's *post hoc* wake vs. REM: $q = 27.29$, adjusted $p < 0.0001$; NREM vs. REM: $q = 28.45$, $p < 0.0001$). Error bars represent S.E.M., $N = 5$ mice, ****$p < 0.0001$, One-way ANOVA followed by Tukey's HSD *post hoc* test).

heterogenous subset of neurons likely plays a role in REM sleep-related phenomena.

Endotoxin Rapidly Silences LH^{GABA} Neurons

Upon injection of LPS, mice rapidly entered NREM sleep at the expense of REM sleep. This was associated with widespread silencing of LH^{GABA} neurons throughout the entire recording session (**Figures 2A–D**; mean dF/F per bout between baseline and LPS groups (wakefulness: t-ratio = 8.239, adjusted $p < 0.0001$; NREM sleep: t-ratio = 6.057, $p < 0.0001$); max dF/F per bout between baseline and LPS groups (NREM sleep: $t = 4.020$, $p < 0.001$) (Multiple t-tests, Holm–Sidak method). Upon closer inspection of the data, we noted that the GCaMP6s signal showed reductions primarily in the lower frequency ranges (<10 Hz), where large, coordinated bursts of calcium activity (and putatively neuronal activity) occur (**Figures 2E,F**; 2-way RM ANOVA main effect of LPS treatment $F_{1,6} = 11.85$, $p = 0.0138$; main effect of frequency $F_{240,1440} = 24.74$, $p < 0.0001$; interaction of treatment × frequency $F_{240,1440} = 11.44$, $p < 0.0001$). Šidák's multiple comparisons *post hoc* tests identified all frequency bins below 4.25 Hz were significantly different between groups (0.25 Hz frequency steps; **Figure 2F**). There was no compensation in higher frequency ranges, suggesting the effect we observed was due to a reduction in coordinated firing rather than simple desynchronization of the local LH^{GABA} network. These data link inflammation-induced suppression of REM sleep to the silencing of hypothalamic neurons that regulate arousal states.

DISCUSSION

Our experiments identify LH^{GABA} neurons as putative central sensors of peripheral immune activation. We observed that LH^{GABA} neurons are primarily REM-active, an arousal state powerfully inhibited by acute immune challenge (i.e., with LPS). Prior work demonstrated that these neurons are integrated into arousal circuitry in a unique way. Optogenetic stimulation of LH^{GABA} neurons during NREM, but not REM sleep, rapidly induces wakefulness (Herrera et al., 2016). This aligns with our observations of maximal LH^{GABA} Ca^{2+} activity during REM sleep, which may represent a physiological "ceiling" that further optogenetic stimulation cannot break.

GABAergic neurons in the lateral hypothalamus provide powerful inhibitory control over GABAergic neurons within the thalamic reticular nucleus (TRN). Direct activation of TRN neurons results in diverse electrocortical and behavioral outputs, which are largely dependent on the stimulation frequency and modality (e.g., electrical vs. optical). These effects range from

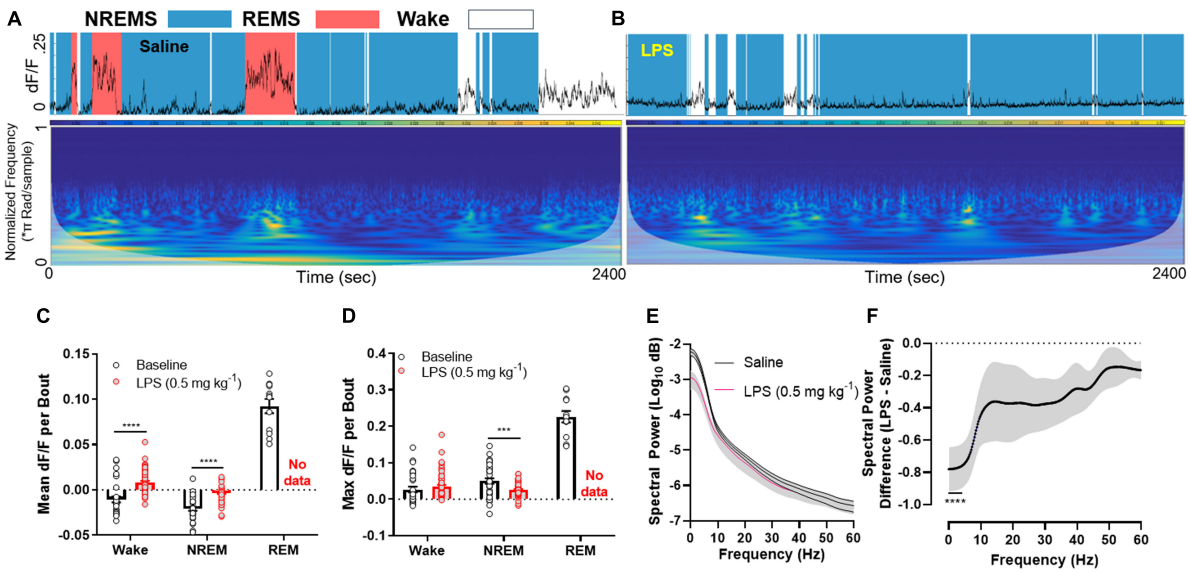

FIGURE 2 | LPS rapidly silences LH^{GABA} neurons. **(A)** Representative GCaMP6s trace and scaleogram from a mouse 40 min following a saline injection. The trace is shaded by the arousal state the animal was in at the time (based on EEG/EMG recordings), where blue = NREM sleep, red = REM sleep, and white = wakefulness. The colormap for the scaleogram represents the power. **(B)** representative GCaMP6s trace and scaleogram from the same mouse 40 min following a 0.5 mg kg^{-1} LPS IP injection. Note the absence of high amplitude GCaMP signal in tandem with loss of REM sleep. **(C)** quantification of all data in the experimental set showing the mean dF/F per bout between baseline and LPS groups (wakefulness: t-ratio = 8.239, adjusted $p < 0.0001$; NREM sleep: t-ratio = 6.057, $p < 0.0001$). **(D)** quantification of all data in the experimental set showing the max dF/F per bout between baseline and LPS groups (NREM sleep: $t = 4.020$, $p < 0.001$) (Multiple t-tests, Holm–Sidak method). **(E)** Mean spectral power of the GCaMP6s signal among the entire experimental set for saline and LPS treated mice. Note the disparity in power at the lower (<10 Hz) frequencies. **(F)** The same data as in panel **(E)** except the difference is calculated for ease of viewing (2-way RM ANOVA main effect of LPS treatment $F_{1,6} = 11.85$, $p = 0.0138$; main effect of frequency $F_{240,1440} = 24.74$, $p < 0.0001$; interaction of treatment × frequency $F_{240,1440} = 11.44$, $p < 0.0001$; individual data points were analyzed using *post hoc* Sidak's multiple comparisons test (significance denoted by **** where all values are significant until 4.25 Hz on the x-axis). Note a ∼80% decrease in low frequency power in response to LPS treatment. Error bars represent S.E.M., ****$p < 0.0001$, ***$p < 0.001$, and **$p < 0.01$; $N = 4$ mice.

increases in cortical gamma (∼30–150 Hz) (Macdonald et al., 1998), NREM spindles (Halassa et al., 2011; Kim et al., 2012), and EEG slow waves (Kim et al., 2012). A few years ago, Herrera et al. (2016) identified LH^{GABA} neurons as a major source of inhibitory input to TRN^{GABA} neurons, directly linking a feed forward inhibitory circuit to dynamic changes in behavior and cortical activity. This positioned LH^{GABA} neurons as major players in sleep/wake state transitions and overall arousal state. Our data extend these findings and suggest that immune-mediated modulation of this neuronal population may play a role in the regulation of arousal in response to infection/injury, although this remains to be tested empirically. It is relevant that other hypothalamic populations, including the sleep-regulating preoptic neurons, seem to be disposable in mediating the effect of inflammation (muramyl dipeptide) on sleep (Shoham et al., 1989). This lends credence to the idea that discrete cell populations within this brain structure enact a coordinated response to inflammatory signals, rather than a general and non-specific response.

Another major aspect of sickness is a change in the expression of motivated behavior (Lasselin et al., 2017), which is naturally intertwined with arousal. An important characteristic of a motivational state is that it competes with other motivational states for behavioral output. The normal expression of behavior re- quires a hierarchical organization of motivational states that is continuously updated according to the circumstances. When an infection occurs, the sick individual is at a life or death juncture and his/her physiology and behavior must be altered so as to overcome the disease. However, this is a relatively long-term process that needs to make room for more urgent needs when necessary. It is easy to imagine the following [from Dantzer (2001)]: "if a sick person lying in his/her bed hears a fire alarm ringing in his/her house and sees flames and smoke coming out of the basement, he/she should be able to momentarily overcome his/her sickness behavior to escape danger"(Dantzer, 2001). In motivational terms, fear competes with sickness, and fear-motivated behavior takes precedence over sickness behavior. An example of this competition between fear and sickness is provided by the observation that the depressing effects of IL-1β on behavior of mice are more pronounced when experimental animals are tested in the safe surroundings of their home cage than when they are placed into a new environment (Propes and Johnson, 1997; Dantzer, 2001). As LH^{GABA} neurons regulate diverse motivated behaviors, in part *via* their projections to the midbrain dopaminergic system (Nieh et al., 2016), future work should examine how inflammatory signaling alters their activity across various motivational states.

Our findings on LH^{GABA} dynamics during immune challenge are especially relevant given the role these neurons play in appetitive and consummatory behaviors dysregulated during sickness. Seminal studies from the middle of the 20th century revealed that electrical stimulation of the LH (and putatively GABA neurons) promotes voracious feeding and appetitive reward-related behaviors (Hoebel and Teitelbaum, 1962; Margules and Olds, 1962), while lesioning this area elicited aphagia and subsequent emaciation (Anand and Brobeck, 1951; Hoebel, 1965). Subsequent work demonstrated that the actions of the LH on consummatory/appetitive behavior are conserved across evolutionary time and persist in humans (Quaade et al., 1974; Molina-Borja and Gómez-Soutullo, 1989). Stuber and colleagues used cell-type specific tools to bolster these early findings and identified LHGABA neurons as major drivers of feeding and reward behavior (Jennings et al., 2015). Optogenetic stimulation of these neurons (20 Hz) increased the time mice spent in a designated food area, enhanced food consumption, and promoted a preference for the location that was previously paired with food consumption. Reciprocally, photoinhibition of these neurons elicited opposite phenotypes, where mice reduced food consumption and time spent in a location paired with optical inhibition. Appetitive and consummatory behaviors toward food are powerfully suppressed during immune activation (O'Reilly et al., 1988; Langhans et al., 1990), and hypophagia/anorexia is a hallmark of sickness behavior (Dantzer and Kelley, 2007; Pecchi et al., 2009). Our data support the notion that LHGABA neurons are critical regulators of sickness-induced sleep. However, it remains to be determined whether this same cell population links immune activation to reductions in food intake. If true, augmentation of LH^{GABA} activity may ameliorate several aspects of sickness behavior.

Our study has a few key limitations that are worth discussing. We did not measure EEG/EMG and photometry signals during the entire course of LPS-induced sickness (up to 24 h). This was done due to the potential of constant illumination to photobleach the GCaMP reporter, which would prevent appropriate interpretation of the data. Therefore, it remains unclear whether LH^{GABA} neurons recover their normal activity prior to the resolution of overt sickness behavior. Additionally, we cannot make causal inferences from these data, as the contributions of other neuronal populations on LH^{GABA} neuronal activity and sleep/wake states was not eliminated (e.g., hypocretin/orexin neurons) (Bonnavion et al., 2015). Indeed, LPS was shown to powerfully suppress hypocretin/orexin and histaminergic neuronal activity (cFos immunolabeling) during the dark phase in rats, when wakefulness and cellular activity are highest (Gaykema and Goehler, 2009). Comparative studies in mice with intact hypocretin/orexin neurons and those lacking this cellular population (ataxin-3 mice) demonstrated that LPS powerfully inhibited hypothalamic hypocretin expression in both genotypes but was only completely abolished in ataxin-3 mice. LPS also suppressed a potential compensatory increase in histamine decarboxylase-positive cells within the hypothalamus of ataxin-3 mice, which implies the involvement of multiple neuromodulator systems in inflammation-associated sickness (Tanaka et al., 2016). A major caveat that may influence the conclusions that we draw from these data are that bulk photometry recordings cannot delineate whether LPS silenced all LH^{GABA} neurons equally [as there are many subtypes (Mickelsen et al., 2019)], or whether their firing rates were fundamentally unchanged and simply desynchronized in their output. However, spectral analysis of the GCaMP signal (**Figure 2**) suggests that LPS reduced low frequency/high amplitude calcium waves, without additional increases in higher frequency oscillations, suggesting a net reduction in coordinated neuronal output rather than desynchronization.

Subsequent miniscope or single unit electrophysiological studies will be needed to definitively answer these questions. We also did not measure the extent of neuroinflammation induced by the fiber optic surgery itself, which may have influenced the somnogenic and neuromodulatory properties of LPS. In line with this, to provide a comprehensive picture of LH^{GABA} responses to LPS, multiple doses should be used in future studies. Finally, the downstream outputs of these neurons driving sickness behavior was not examined, and the effects of LH^{GABA} neurons may be secondary to a different population within the LH or other nuclei. Viral-mediated tract tracing studies and genetic ablation techniques will help to answer these questions.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The animal study was reviewed and approved by Stanford University IACUC.

AUTHOR CONTRIBUTIONS

JB: experimental design, performed experiments, analyzed data, wrote manuscript, and edited manuscript. LL: experimental design, study supervision, supplied critical resources/tools, and edited manuscript. Both authors contributed to the article and approved the submitted version.

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CONCEPTUAL ANALYSIS
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So Many Faces, Phases, and Facets, Sickness Behavior Beyond Disciplines

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Animals, including human beings, modify their behavior when they fall sick. Interestingly, sociology, biology, and psychology have at different times in their history developed constructs of illness or sickness behavior. The aims of the present paper are to consider sickness behavior in animals and humans and to evaluate to what extent the notions of sickness behavior would allow for interdisciplinary research. After distinguishing disease, illness, and sickness, the case will be made that illness behavior and sickness behavior can be considered heuristically as synonyms given the existence of some fluidity between the notion of illness and sickness. Based on this, different faces, phases, and facets of sickness behavior will be presented before addressing the question of how integration of constructs of sickness behaviors would be possible across biology, medicine, psychology, and sociology. It is concluded that interdisciplinary research on sickness behavior between biology, psychology, and sociology is possible and called for with regard to constructs, methods, and explanations, while keeping in mind differences in perspectives, for example between acute and chronic sickness behavior.

Keywords: biopsychosocial medicine, disease, health, illness, interdisciplinarity, sickness behavior

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INTRODUCTION: SICKNESS AS AN EXPRESSION OF HEALTH AND DISEASE

Even though philosophers of medicine may recently have seemed to agree to disagree on the possibility of consensus definitions of health and disease (1), the American Veterinary Medical Association has approved in 2008 the "One Health" imperative to promote collaboration between several disciplines "to attain optimal health for people, animals, and our environment" ((2), p. 13). This global perspective of health begs the question of how health relates to sickness and disease. One of the best illustrations of a face of sickness is *The sick child* painted several times by Edvard Munch between 1885 and 1926 that features his sister suffering from tuberculosis. Since then, there have been many debates, both in society and within academia, about what health, sickness, and disease would, could, or should be. This is important to keep in mind when discussing sickness as it is often positioned or described relative to health and disease. Here we will first consider a few descriptions of sickness in relation to health and disease before discussing differences in more detail.

The normal and the pathological published by the French physician and philosopher of medicine Georges Canguilhem during WWII is an interesting starting point because this scholar

distinguished "the experience of being sick" from disease, alluded to changes in behavior during sickness, and linked the possibility "to fall sick" to "good health." According to Canguilhem, medical science should not aim to generate a general disease concept but rather "determine what are the vital phenomena with regard to which men call themselves sick" ((3), p. 122). He further pointed out that different conceptions of disease based on deficiency, infection, or dysfunction on the one hand, and "the experience of being sick" on the other hand have in common the idea of "an internal struggle between opposing forces" ((3), p. 41). Within this general framework, Canguilhem drew attention to changes in "the sick person's personality" in that he or she can have "reactions which never turn up in the normal subject in the same form and in the same conditions," but that "are not the result of an impoverishment or diminution" ((3), p. 184). Such changes in behavior, which are readily observed during inflammation when "the anti-infectious defense is mobilized," implied for him that "[t]o be in good health means being able to fall sick and recover" ((3), p. 199).

Some years after Canguilhem, the American internist and psychiatrist George Engel proposed to link different levels of organization and various responses observed after bacterial infection. At the tissue level, this results in an inflammatory response while at the level of the whole organism it can give rise to a profound alteration of physiology (4). However, Engel noted that "we also see psychologic defenses, illustrated by such phenomena as regression, increased dependence, withdrawal of interest in the outer world" ((4), p. 55). Finally, he remarked that institutionalized medical care and social help can be solicited (4). In his later work, Engel tried to articulate these different responses and he put forward that "[a]s various systems of the body are brought into action to cope with the local process [of infection], this eventually influences total behavior" and that with the activation of "central neuro-humoral systems … must … come an impact on systems of internal perception of the mental apparatus indicating the change in the bodily status" ((5), p. 50). In turn, this is perceived "as an affect, a general sense of malaise, fatigue, restlessness, uneasiness, [or] vague anxiety" ((5), p. 50). In his subsequent biopsychosocial model of medicine, Engel argued that disease is a term that refers to objective phenomena, while other terms have been used to express personal experience "associated with impairment or discomfort" ((6), p. 130). He then insisted that "[p]sychological and social factors" are important "in determining whether and when patients with the biochemical abnormality of diabetes or of schizophrenia come to view themselves or be viewed by others as sick" to make the point that "boundaries between health and disease, between well and sick, are far from clear and never will be clear" ((6), p. 132). He thus indicates that it is not necessarily because an individual has been diagnosed with a disease by a physician by establishing a plausible cause for some clinical findings that that person feels sick or is considered sick by his environment. An attempt to provide some more clarity on the distinctions between disease, illness, and sickness will nevertheless be undertaken in the next section.

Distinctions Between Disease, Illness, and Sickness

In the mid-1970s, 2 years before Engel's proposal for biopsychosocial medicine, the philosopher of medicine Christopher Boorse put forward a distinction between disease and illness. According to him, disease "applies indifferently to organisms of all species" and "it is to be analyzed in biological … terms" ((7), p. 56). Instead, illness is a disease for which "its owner deserv[es] special treatment and diminished moral accountability" ((7), p. 56). That same year, the general practitioner and professor of medicine Marshall Marinker provided a further distinction between disease as "a pathological process, most often physical," illness as "a feeling, an experience of unhealth which is entirely personal" and sickness as "the external and public mode of unhealthy" ((8), pp. 82–83).

The philosopher of medicine Bjørn Hofmann has more recently noted that the notions of disease, illness, and sickness have been "more strictly defined …, but also fundamentally challenged" in "medical sociology, medical anthropology, and philosophy of medicine" ((9), p. 651). Thus, the sociologist Talcott Parsons already indicated in 1951 four societal expectations "relative to the sick role," namely, (1) "the exemption from normal social role responsibilities," (2) "the sick person cannot be expected by "pulling himself together" to get well," (3) "the state of being ill [i]s itself undesirable with its obligation to want to "get well," and (4) "the obligation … to seek technically competent help, namely, in the most usual case, that of a physician and to cooperate with him in the process of trying to get well" ((10), pp. 436–437). Later, the sociologist Andrew Twaddle suggested that adaptation could be a more appropriate characterization of the sick role than Parson's deviance framework ((11), p. 260, p. 270). Hofmann has argued that Twaddle's own triad of disease, illness and sickness is related to the World Health Organization's definition of health as "a state of complete physical, psychological and social well-being" ((9), p. 655) and thus reflected a perspective different from that of Parsons. These considerations led Hofmann to his own definitions according to which disease corresponds to "negative bodily occurrences as conceived of by the medical profession," illness to "negative bodily occurrences as conceived of by the person himself" and "sickness [to] negative bodily occurrences as conceived of by the society and/or its institutions" ((9), p. 657).

While it is understandable that there has been substantial interest in studying disease, illness, and sickness affecting human beings, it is also important to keep in mind that animals other than human beings can fall ill and are diagnosed with diseases by veterinarians. Animals have been used as work force, life stock, experimental subjects, and pets by man, and it is in these relationships that animals have been considered as victims of disease and sometimes as patients (12). In the 19th century, the physician and pathologist, Rudolf Virchow emphasized "that there is no scientific barrier, nor should there be, between veterinary medicine and human medicine" as "the experience of one must be utilized for the development of the other" (cited in Bollinger (13), p. 7). However, even though it is impossible to have access to their experience, humans have long recognized sick

animals, often because they were not performing the behaviors of interest to man, and tried to identify diseases. It has been argued that the existence of two roles of animals, namely, as subjects of veterinary care and as objects of medical and zoological research, has allowed for connections to occur between these fields and to have thus favored the development of the "multifaceted domain of 'agricultural [and veterinarian] science"' ((12), p. 105, p. 107). After remarking that the behavioral symptoms of disease, such as lethargy and reduced food intake, are not specific to a particular species and referring to studies showing that both fever and reduced food intake can favor survival of infected animals (14, 15), the veterinarian Benjamin Hart proposed at the end of the 1980s the concept of sickness behavior as "a highly organized behavioral strategy" with a "biological basis" ((16), p. 123).

The aims of the present work are therefore to consider sickness behavior both in humans and other animals and to evaluate to what extent the notion of sickness behavior would allow for interdisciplinary research. In the remainder of this introduction, and after having distinguished disease, illness, and sickness, some fluidity between the latter terms will be pointed out to make the case that illness behavior and sickness behavior can be considered heuristically as synonyms. Based on this, the second part of the paper will present different faces, phases, and facets of sickness behavior before addressing the question of how integration of constructs of sickness behaviors would be possible across biology, medicine, psychology, and sociology.

Some Fluidity Between Illness and Sickness

Interestingly, and after spelling out differences between these terms, Bjørn Hofmann also admitted that there are conditions that are considered disease and illness, but not sickness, others that are deemed disease and sickness, but not illness, and still other conditions that are viewed as sickness and illness but not disease. Among the latter would be fibromyalgia and chronic fatigue syndrome (9), in which individuals feel ill and are often recognized as being sick by their immediate environment and more or less by the societies in which they live, but do not have a disease as long as medical science has not identified plausible causes for these syndromes. In addition, there seems to be some porosity between illness and sickness in the ways they are employed in academia. Indeed, if according to Hofmann illness corresponds to "negative bodily occurrences as conceived of by the person himself" and sickness to "negative bodily occurrences as conceived of by the society and/or its institutions" ((9), p. 657), then it would be hard to understand why Talcott Parsons has used illness and sickness as synonyms, for example, when he wrote that "medical practice may be said to be oriented to coping with disturbances to the 'health' of the individual, with 'illness' or 'sickness"' ((10), p. 429). Another sociologist, David Mechanic, has elaborated on Parsons' sick role by proposing the term illness behavior to describe the ways symptoms can be interpreted differently and result in different kinds by various individuals ((17), p. 189). Thus, illness for Mechanic is not just a state but also a way of coping that determines, in part, if and how the individual appeals to modes of care, including those offered by society (18). Finally, and although the terms "illness" and "illness behavior" can be found regarding animals, the term "sickness behavior," proposed in 1988 by the veterinarian Benjamin Hart, is most prevalent.

Interestingly, typing "sickness behavior" in the Medical Subject Headings (MeSH) database on PubMed takes one to illness behavior. On PubMed, illness behavior is, since 2009 described as a "[c]oordinate set of non-specific behavioral responses to non-psychiatric illness" that "may include loss of appetite or libido, disinterest in activities of daily living or withdrawal from social interaction" (https://www.ncbi.nlm.nih.gov/mesh/?term=%22sickness+behavior%22). Of note, between 1975 and 2008, prior to the current heading of illness behavior, this term was indexed under "sick role" (https://www.ncbi.nlm.nih.gov/mesh/?term=%22sickness+behavior%22). Importantly, interrogating PubMed with "illness behavior" as a keyword set gives twice as many results as "sickness behavior." Similarly, searching for "illness behavior" on the American Psychological Association (APA) PsychInfo database results in almost 10 times more articles than searching for "sickness behavior." This difference between the PubMed and PsychInfo databases may be explained, in part, by the fact that illness behavior has been part of the APA Thesaurus of Psychological Index Terms since 1982 and is defined as "behaviors, attitudes, and emotions exhibited by individuals during the course of a physical or mental illness," whereas "sickness behavior" is not part of this index. Finally, typing "sickness behavior" as a search topic on the Web of Science (WoS) Core Collection yields more hits than "illness behavior." This suggests that overall in WoS-indexed articles "illness behavior" and "sickness behavior" are used differently than in articles found on PubMed and PsychInfo. Given this varying and somewhat liberal use of both terms, sickness behavior will be considered heuristically here as a synonym of illness behavior.

A final note of clarification concerns the distinction between syndrome and disease, which are sometimes used "improperly and ambiguously" (19). A syndrome can be defined as "a recognizable complex of symptoms and physical findings which indicate a specific condition for which a direct cause is not necessarily understood" while the term disease is employed when "medical science identifies a causative agent or process with a fairly high degree of certainty" (19). In keeping with the overall distinctions related above and the spirit of a syndrome as a collection of symptoms and physical findings, while recognizing that the causes for many of the disease that are accompanied by illness or sickness behaviors are known, different kinds of syndromes can be distinguished. Thus, (1) an illness-sickness syndrome could be conceived of as a collection of feeling cold, having a fever, fatigue, sleeping more, lower appetite, reduced food intake, wanting to be alone, and not engaging in social activities; (2) a sickness response syndrome would tentatively include all observable or measurable responses like a fever, increased time sleeping, lower food intake and less social interactions; and (3) a sickness behavior syndrome would be a syndrome of behaviorally observable changes, such as sleeping more, reduced food intake and not engaging in social activities.

DIFFERENT FACES, PHASES, AND FACETS OF SICKNESS BEHAVIOR

Without attempting to give an exhaustive overview of the various authors, periods, and aspects that can be distinguished regarding concepts of illness/sickness behavior, the idea here is rather to highlight some developments in different lines and traditions of research in sociology, biology, and psychology.

Sociology: The Sick Role and Illness Behavior in Medical Practice

The first line of research has been sociological and comprised the study of the so-called sick role and illness behavior. In 1951, Talcott Parsons considered that in Western societies illness is motivated as it comes with "the exemption from normal social role responsibilities" that may constitute a "secondary gain" ((10), pp. 436–437). Later, Parsons acknowledged that this line of thinking was inspired by the prevalent idea in the 1930s that psychological factors play an important role in somatic disease ((11), p. 258). He made a parallel with "accident-prone people" who are at increased risk of having an accident, but for whom the consequences of such accidents should not be considered from a point of view of motivation to argue that "similar considerations apply to such fields as infections, and … cancer" ((11), p. 260). Finally, Parsons also distinguished acute illness during which the individual is fully engaged "to coping with the state of illness" and chronic illness, which necessitates "only a very partial attention on the part of the patient" ((11), p. 269). David Mechanic also seemed to have put Parsons' early ideas into some perspective by pointing out that some individuals "may be motivated to adopt the sick role to obtain release from various kinds of responsibilities," but other individuals "who fear the dependence of the sick role or who are suspicious of physicians and avoid seeking medical advice even when serious symptoms appear" ((17), p. 190). Thus, in North-American sociology of the 1950s and 1960s, the constructs of the sick role and illness behavior were clearly linked to motivation but in different ways.

At the end of the 1960s, the South-African physician Issy Pilowsky introduced the notion of abnormal illness behavior to qualify a situation in which the patient does not seem to agree with the physician's diagnosis and proposed solution for the problem that the patient expressed (20). Another point of Parsons' "sick role" that has been discussed is that of the individual's responsibility. The Canadian sociologist Alexander Segall has proposed to distinguish between physical conditions for which Parson's sick role including the lack of responsibility of the ill individual would hold and a psychological conditions for which "the question of personal responsibility arises" ((21), pp. 163–164). The philosopher of science William Bechtel has wondered if, in the light of certain cultural changes that have taken place in Western societies since Parsons' publications of the 1950s, and in particular given the "growing sentiment that in many cases an individual is responsible for being sick," the concept of the sick role needs to be revised ((22), p. 131).

It is therefore not that surprising to see Pilowsky propose the "Illness Behavior Questionnaire" in the 1980s with subscales assessing hypochondria and the "psychologic versus somatic perception of illness" (23). Around that time, the Mexican-American sociologist Angelo Alonzo judged that even though the concepts of the sick role and illness behavior have motivated numerous studies in medical sociology, this had not led to a better understanding of social behavior in the context of illness and disease (24). His aim was therefore to propose an integrated behavioral model that can be used by different disciplines to further "understanding, assessing and intervening in social behavior surrounding disease and illness" ((24), p. 499). Adopting a "situational-adaption perspective to health and illness," Alonzo distinguished "everyday, acute, chronic and life threatening" illness behaviors ((24), p. 508). He also seemed to agree with David Mechanic that illness and behavior are not necessarily dependent in the sense that "some individuals seek medical care at the slightest health deviation [and] others must be coerced by law to present themselves for evaluation and treatment" ((25), p. 160). More recently, a plea was made to describe abnormal illness behaviors taking into account types of illnesses and to be generally cautious when using the label abnormal in these cases (26). Finally, some authors have proposed that illness behavior may integrate "lines of research [that] have been concerned with illness perception, frequent attendance at medical facilities, health care-seeking behavior, treatment-seeking behavior, delay in seeking treatment, and treatment adherence" ((27), p. 74).

Biology: Sickness Behavior as an Adaptive Regulated Response to Infection

The second line of research has been biological and driven by the idea that sickness behavior is an adaptive regulated response to infection. In his 1988 review that introduced the term "sickness behavior" for animals, Benjamin Hart provided a table of infectious diseases affecting domestic animals and human people that have been reported to be accompanied by fever, reduced food intake and behavioral depression (16). As indicated above, he considered that the behavioral symptoms of disease are not specific to a particular species and that fever is an adaptive response favoring survival of infected animals. Accordingly, Hart argued that anorexia reduced the likelihood of an animal engaging in locomotor activity to search for food and thus allowed to preserve the body's energy stocks that are needed to increase body temperature and mount a fever response (16). Similarly, he pointed out that curling up during an infectious disease reduced the surface area of the body and thus attenuated heat loss (16). In addition, Hart related findings indicating that the pro-inflammatory cytokine interleukin-1 (IL-1) not only is an endogenous pyrogen but also reduces food intake and locomotor activity as well as induces sleep in animals and humans (16). Not surprisingly, he concluded that fever and the behavioral symptoms of disease are brought about in a coordinated manner through the action of IL-1 as part of "an evolved disease-fighting strategy" ((16), p. 131).

One of the ways in which Benjamin Hart described sickness behavior was in terms of motivation (16). This question has been picked up and expanded by the French veterinarian Robert Dantzer who hypothesized that reduced appetite, reduced

activities, and social withdrawal typical of sick animals are the expression of changes in motivational priorities. The findings of his group showing that that sickness behavior in rodents, provoked by systemic injection of bacterial lipopolysaccharide (LPS), occurred as a function of external conditions, for example temperature and food availability (28, 29) corroborated the idea that sickness behavior is the expression of a motivational state. It has been also argued that increased sensitivity to pain or hyperalgesia typical of inflammation may be adaptive by avoiding the use of the painful body part and attending to it and should be "viewed as a part of sickness behavior" ((30), p. 96). Given that motivated behaviors are regulated by the central nervous systems, this opened new research avenues proposing several immune-to-brain signaling pathways and brain circuits mediating sickness behavior in the 1990s and 2000s (31). Finally, and over the past decade, various interventionist approaches have allowed to describe neurobiological mechanisms underlying reduced food intake of rodents in response to the administration of bacterial LPS or pro-inflammatory cytokines in quite some detail (32–35).

Psychology: Sickness Feelings and Cues

Psychology has picked up on the theoretical motivational framework laid down by the sociologists Tascott Parson and David Mechanic and studied the behavior of individuals with chronic medical condition in the context of coping styles. Thus, in adult cancer patients, protective buffering, which includes withholding or denying hiding cancer-related thoughts and concerns (36), was found to be motivated in large part by protection of one's partner (37). While many scholars trained in psychology also participated in the biological approach to sickness behavior by providing their expertise in animal behavioral testing, a third and psychological line of research on sickness behavior emerged after it was shown that the administration of bacterial LPS in humans also induces a transient systemic inflammatory response (38, 39). The first studies addressing LPS-induced sickness behavior in humans concerned phenomena previously established in rodents, namely, increased non-Rapid-Eye Movement sleep, conditioned aversion, and hyperalgesia (40–43). Moreover, and just as animal locomotor activity is reduced after LPS administration, LPS was found to lower walking speed in human volunteers (44). Interestingly, in terms of motivation, LPS injection to healthy volunteers has been reported to decrease "acceptance rates of high-effort options," but to increase "incentive motivation when the effort is deemed worthwhile" (45, 46). Other early studies have tested cognitive functions, thus also expanding work done in animals, and found that LPS administration decreased memory function (47, 48).

Furthermore, these and follow-up studies assessed emotions and mood, which is notoriously difficult or impossible to do in animals, and reported increased anxiety and depressed mood (47–49). In addition, a mainly feelings-based "sickness questionnaire" has been developed "to assess sickness behavior" in humans (50). Interestingly, recognition of a sick person by non-medical professionals did not require a questionnaire and could be made based on gait and facial cues (44, 51). Although there is a substantial number of articles that have applied functional brain imaging approaches to LPS-injected animals by detecting Fos transcription factors, these approaches are limited by the long-time window between the stimuli of interest and increased Fos expression indicating genomic activation and the fact that they require the animal to be sacrificed (52, 53). With the advent of wider implementation of functional brain imaging approaches in human, like Blood Oxygen Level-Dependent Magnetic Resonance Imaging, stimuli and metabolic activation could be studied in conscious subjects. Such studies have shown increased activation of right inferior orbitofrontal cortex in response to emotional visual stimuli after LPS administration (54) and increased functional connectivity between the left anterior insula and left midcingulate cortex (55). Thus, it has become possible to relate feelings, perception of cues or task performance, and metabolic cerebral activation patterns during sickness.

INTEGRATION OF CONSTRUCTS OF SICKNESS BEHAVIORS ACROSS DISCIPLINES IN BIOPSYCHOSOCIAL MEDICINE?

Epidemiology has a respectable historic tract record in pointing out potential causal relationships, for example between smoking and lung cancer, to biomedical disciplines that can mobilize intervention strategies to test the causality of the relationship (56). While sociology has the potential to play a similar role, this turned out to be more complicated perhaps because sociology is overall a less quantitative discipline than epidemiology and because of the increased focus on personal responsibility in disease between the 1950s and 1990s (57, 58). As a result, the influence of sociology on biomedical sciences may have depended more on scientific constructs, concepts, and ideologies. In spite of this, the very term medical sociology has moved from the cover of a book by David Mechanic in 1968 to a presently theory-rich sub-discipline of sociology (58). Finally, it has also been argued that epidemiological reasoning has been modified by sociological evidence, for example related to the notion of stress (59). Regarding illness/sickness behavior, it seems indeed that sociology was first to develop constructs under that banner. However, it does not seem to be the case that this was then passed on or seeped through to psychology and biology. Instead, while the construct of illness/sickness behavior developed in sociology inspired part of psychology, biology appeared to have developed its own construct, which then, in turn, influenced another part of psychology.

Biopsychosocial Medicine

Given that concepts of illness/sickness behavior have been developed in biology, psychology, and sociology, one may wonder to what extent these constructs are similar or compatible and what, if any, role illness/sickness behavior plays in the so-called biopsychosocial model of medicine. Indeed, George Engel, who proposed the biopsychosocial model of medicine in the 1970s expressed the hope that the study of all contributing factors would allow to explain "why some individuals experience

as 'illness' conditions which others regard merely as 'problems of living"' ((6), p. 133). He envisioned his "biopsychosocial concept of disease" as an approach allowing for the study of disease and medical care as interconnected phenomena ((6), p. 134). Engel emphasized that the first source of clinical information for a physician is the patient between his or her reported feelings, sensations, and thoughts and observable behavior and signs and that clinical study starts "within a two-person system, the doctor-patient relationship" ((60), p. 108). He thus encouraged physicians to acquire information and skills from "the psychosocial areas" in order "to have a working knowledge of the principles, language, and basic facts of each relevant discipline" ((60), p. 121). Moreover, for a biopsychosocial physician and in the interest of the patient, Engel recommended that "higher system level occurrences must be approached with the same rigor and critical scrutiny that are applied to systems lower in the hierarchy" ((60), p. 121). The reference framework here is systems theory according to which different levels of organization are hierarchically connected "so that change in one affects change in the others" ((6), p. 133). Within this framework, Engel placed the individual's experience and behavior between the two-person level, for example the patient–physician interaction, and the nervous system (60).

Although the biopsychosocial model of medicine has in large part been practice-oriented, several interdisciplinary fields, such as psychoneuroendocrinology, psychoneuroimmunology, and, more recently, microbiota–gut–brain research, have been presented as research fields relevant to, expression of, or even as validation of the biopsychosocial model (61–65). However, the anthropologist Margot Lyon has pointed out that even though psychoneuroimmunology claims to embrace more than biology and puts forward the role of behavior in health and disease, "the problem of the representation of situatedness is the primary axis of tension in current research and writing in psychoneuroimmunology" ((66), p. 77). According to her, losing "the situatedness of understanding" may occur when representations in science are considered disconnected from context, and thus oppose the traditions of hermeneutics, emphasizing the importance of interpretation, and phenomenology ((66), p. 91). While admitting that efforts to think in terms of interactions between the immune, endocrine, and nervous system have the potential "to represent the organism simultaneously in its psychosocial and biological context," Lyon also expressed the concern that, given the complexity of the psychosocial and biological as well as of the interactions between them, scientists are faced with "the problem of incalculable variables which cannot be experimentally eliminated" ((66), p. 91). According to her, the only ways to deal with these forms of complexities are either "through radical reduction, or through vast multidisciplinary studies which can bring many research strategies to bear on a single problem" ((66), p. 91).

Cross-, Multi-, and Interdisciplinarity: Integration and Incompatibilities

In present-day academia, there are many calls and some incentives to engage in more multi- or interdisciplinary research and it is therefore worthwhile to get a better idea of what may be behind these terms. The social scientist Patricia Rosenfield in an article discussing the possibilities of "transdisciplinary research" to foster and further "the links between the health and social sciences" indicated that multidisciplinary research typically occurs when there is "a common problem or set of problems, [but] each discipline works independently and the results are usually brought together only at the end" ((67), p. 1351). In her perspective and in the case of interdisciplinary research, the "different disciplines use their techniques and skills [together] to address a common problem" ((67), p. 1351). Finally, according to Rosenfield, transdisciplinary research can lead to more complete understanding by encouraging scientists of several disciplines "to transcend their separate conceptual, theoretical, and methodological orientations in order to develop a shared approach to the research" and thus foster shared concepts ((67), p. 1351).

While the term multidisciplinary refers to less methodological and knowledge integration than that of interdisciplinary, it has been proposed that both can be grouped under the term cross-disciplinary ((68), p. 1938). The philosophers Michael O'Rourke and Stephen Crowly have made the case that philosophy can streamline the interaction of disciplines independently from the level of integration and have proposed a toolbox approach to do so (68). This approach is based on answers to two categories of questions, namely, "what we are like that we may know the world and what the world is like that we may know it" ((68), p. 1943). The confirmation section of the former category, for example, then invites scientists from different disciplines to indicate to what extent they agree or disagree with statements like "unreplicated results can be validated if confirmed by a combination of several different methods" ((68), p. 1952).

Interestingly, regarding health and disease, the philosopher and psychologist Derek Bolton together with the philosopher and neurosurgeon Grant Gillett has recently made a plea for more cross-disciplinarity arguing that "[t]here is simply too much going on for one disciplinary approach alone" ((69), pp. 100–101). According to these authors, part of the problem is that the disciplines that make up the biopsychosocial model slow down the ongoing "biopsychosocial/environmental transdisciplinary revamp across the life and human sciences" ((69), p. 101). One of the examples Bolton and Gillette provided to illustrate the need for such a transformation is relevant for sickness behavior. These authors indicated that reduced activity can be a consequence of illness or injury, which are experienced as pain and distress to make the point that "even these subjective experiences turn out to be thoroughly biopsychosocial" ((69), p. 117). Indeed, the pain field has long acknowledged that self-reports of pain also depend social factors and that pain-free injury can exist (70). Similarly, reduced activity during illness sickness or after injury also depends on psychological and sociological factors. Thus, it has been argued that understanding the functional limitations and reduction in the ability to engage in everyday activities of people with chronic osteoarthritis pain requires to take into account how people manage risks of falls and social isolation within their socio-environmental contexts (71). Most recently, income below the national US mean was found to be positively

associated with sickness behavior in men as assessed with the Sickness questionnaire mentioned above (72). So, transcending disciplines may also require some deconstruction of disciplinary perspectives and approaches and getting acquainted with those of other disciplines.

However, transcending disciplinary traditions may not be that straightforward regarding illness/sickness behavior because, as pointed out by David Mechanic, "social scientists sought to depict the extraordinary variability of behavior, [whereas] physicians sought criteria to define 'abnormal illness behavior'" ((18), p. 1208). Along these lines, it may also be telling that even in an attempt to unify the concept of illness behavior, Sirri and colleagues have proposed a framework that does not at all include the biological perspectives developed by Benjamin Hart and Robert Dantzer (27). This seems most of all to reflect mutual ignorance between disciplines employing seemingly related constructs. As indicated above, philosophy, medicine, sociology, psychology, and biology have all put forward ideas about health, disease, illness, and sickness in general and illness and sickness behavior in particular. However, this then begs the question of whether or not any attempt of integration should encompass all these ideas. In this context, it is important to keep in mind that (1) interdisciplinarity does not necessarily take place between high-level theories and can involve lower-level concepts or constructs, explanations, and methods (73) and (2) that different academic disciplines have different objectives. Concerning the latter point, it has been proposed that philosophers are typically interested in theories, whereas scientists care more about constructs and measures ((74), p. XXXI). Thus, philosophers study a theory's essential properties, for example by specifying necessary and sufficient conditions, while psychologists often use constructs that are thought to have observable and measurable expressions that can be assessed, for example by the use of questionnaires ((74), p. XXXI). Indeed for the philosopher Anna Alexandrova, constructs and measures should be closely related in the sense that "measures must reliably track constructs" ((74), p. XXXII).

These considerations seem to apply to health, disease, illness, and sickness behavior as well. On the one hand, philosophy has been highly active in trying to develop general theories of health and disease but has paid less attention to illness/sickness behaviors, not to mention on how to measure these. On the other hand, biology, psychology, and sociology have been more involved in trying to measure illness/sickness behavior without being that much concerned about a general theory. Thus, several constructs of illness and sickness behavior may have been put forward in sociology, psychology, and biology. Here it is important to keep in mind that constructs of the same name can be described differently depending on the domain. Indeed and as outlined above, illness behavior is described on the biomedical database PubMed as a "[c]oordinate set of non-specific behavioral responses to non-psychiatric illness" that "may include loss of appetite or libido, disinterest in activities of daily living or withdrawal from social interaction," whereas on the APA database PsychInfo it refers to "behaviors, attitudes, and emotions exhibited by individuals during the course of a physical or mental illness."

Furthermore, we have recently pointed out that under the same banner of sickness behavior, biology relates behavioral measures in animals while psychology mostly uses questionnaires addressing feelings in humans, even though behavioral observations are possible (75). Indeed, regarding the requirement that "measures must reliably track constructs" ((74), p. XXXII), several disciplines often follow different paths. However, beyond behavior as such, which can be observed both in animals and humans, there is a growing interest in the mental states that accompany sickness behaviors. However, biologists and veterinarians do not have a direct access to the mental states of animals, the way psychologists and physicians can rely on verbal report of mental states in humans. Nevertheless, concluding as to the mental state of hunger or appetite when animals ingest more food than after a period of restricted access or to those of pain or nausea based on their facial expressions (76–78) seems rather straightforward. The critical point here is the interpretation of the behavioral observations in the process of making inferences about the mental states of animals. For example, rodent tests based on the time spent in open well-lit spaces or immobile in inescapable situations to assess anxiety or depression constructs have been criticized (79–82). These examples suggest that different research traditions can lead to diverse constructs even when the latter go by under similar names.

Stress Test for Interdisciplinarity

A historic example of diverse constructs used in different research traditions that have the same name is stress. The Hongro-Canadian physician Hans Selye is often credited for having given contents to the term stress in the life sciences. Indeed, he has proposed to coin his general adaptation syndrome to different adverse situations, stress (83), and to include infections under "systemic stress" ((84), p. 190). However, Selye has also attempted to progressively provide terminological clarity and to reserve the term stress to biological responses and that of stressors to the diverse stimuli and to distinguish between eustress and distress (85). Interestingly, early on George Engel made it clear that chemical, physiological, psychological, and social means can be mobilized to cope with stress(ors) and illustrated this with bacterial infection of a human being as an example (4). In this case, both a local inflammatory reaction and an overall modification of physiology can be observed as part of the host defense ((4), p. 55). However, Engel emphasized that "we also see psychologic defenses," such as "increased dependence [and] withdrawal of interest in the outer world" ((4), p. 55). Finally, he pointed out that, in addition, social and institutional resources can be mobilized (4). Based on this example, Engel seemed to consider biological, psychological, and sociological responses as different ways to deal with the stress(or) of an infection. In his later work, however, he also stated that "the need of the patient is to be relieved of 'distress' rightly or wrongly attributed to 'illness'" ((86), p. 102), suggesting that distress corresponds to the psychological state of an ill individual. Within the context of sociology, several scholars have studied "families under stress" after the Second World War (87, 88). While the sociologist David Mechanic judged that "The concept of stress has not been adequately or precisely defined in the behavioral sciences," he

proposed that is a state related to "anxiety, discomfort, emotional tension, and difficulty in adjustment" ((89), p. 51). He mostly referred to "perceived stress" and saw stress as a psychological state that can modulate illness behavior. Indeed, Mechanic found that individuals with reported "high stress," as measured by frequency of loneliness and nervousness, were significantly more likely to use medical facilities than persons with lesser "stress" ((17), pp. 191–192).

The philosopher Wim van der Steen considered in 1993 that in the beginning the investigation of stress took place in separate disciplines without much interaction (90). He credited Selye's physiological research for having "discovered that many adverse conditions produced the same kind of physiological responses in organisms," which was then "called the stress response" ((90), p. 263). However, Van der Steen also remarked that around the same time psychologists studying stress "were primarily interested in stimuli and in internal states of organisms, psychologically characterized" ((90), p. 263). Thus, physiologists have used the term stress for response whereas psychologists have employed the same to refer to stimuli and internal states. For Van der Steen, this is confusing and counterproductive given that independent descriptions of stimuli and responses are required for sound empirical research to take place (90).

If interdisciplinary research fields such as psychoneuroendocrinology and psychoneuroimmunology have over the past 25 years widely employed the terms stressor and stress response and have often distinguished physiological from psychological stress, the danger of confusing stimuli, internal states, and responses may be present for more recent interdisciplinary domains less aware of this historic debate. With respect to illness/sickness, one could specify that bacterial LPS fragments constitute a physiological stressor for animals and illness/sickness behavior is part of the stress response. To what the (di)stressed state of an infected organism (or experimental model thereof) corresponds is still a matter of active research, but anxiety may be a good candidate (49). However, although the very name of illness/sickness behavior seems to indicate a response of the organism, the risk is still present that various disciplines consider this differently. For example, the sickness behavior questionnaire mentioned above contains mainly questions about how the subject feels and seems to address less how the subject engages or not in daily activities (50).

Motivation as a Bridge Between Disciplines?

Interestingly, the notion of motivation has been mentioned in the context of illness/sickness behavior in sociology, biology, and psychology. Thus, the sociologist Talcott Parsons remarked that illness was motivated, but considered it a kind of "deviant behavior" ((10), p. 285). This latter qualification should probably be seen in the light of Parsons' hypothesis that the advantages and relief of responsibilities for the sick could constitute a "secondary gain" that can motivate an individual to become or remain sick ((10), p. 437). Several decades later, David Mechanic seemed to put this in a broader and different perspective by indicating that clinical practice learns that there are also many individuals, who, even when afflicted with disease, manage to work or have other activities precisely because they are motivated (18). Interestingly, neither the illness behavior questionnaire nor a recent article proposing to unify illness behavior mentioned motivation (23, 27). The notion of motivation can, however, be encountered regarding health-related choices, for example when it comes to those of former smokers. In this context, maintenance of non-smoking has been proposed to involve "motivational … mechanisms of self-change" ((91), p. 943). So despite the fact that motivation was an important topic to position the sick role and illness behavior concepts, it seems to be considered in different contexts in present-day medical sociology, even though its study in relation to medically unexplained chronic symptoms, such as pain and fatigue, will likely continue to prove to be relevant, for example in post-Covid-19 infection.

Benjamin Hart clearly worked from an evolutionary background for sickness behavior when he proposed that an infected animal that is sleepy or inactive "is less motivated to move about using energy that could fuel metabolic increases associated with fever" ((16), p. 129). Although a veterinarian by training, Robert Dantzer referred to psychology to define motivation "as a central state that reorganizes perception and action" using fear as an illustration and to emphasize that states of motivation allow to dissociate perception and action depending on the circumstances and do therefore not given rise to a fixed behavioral response ((92), p. 14). This specification served as rationale for the work of Aubert cited above showing that injection of a dose of LPS injection to lactating mice did not result in nest building when pups were placed throughout the cage at 20°C, but did induce nest building after pups were dispersed at 4°C (92). Thus, Dantzer concluded that "sickness behavior appears to be the expression of a central motivational state" ((92), p. 7, p. 20). It remained to be seen for him, however, if the sickness motivational system can account for all of the responses of an organism after activation of the innate immune system or if it "must be included in another more basic motivational system, such as the pain defense system" ((93), p. 155). One aspect of animal sickness behavior that can be considered from a motivational standpoint is behavioral expression in a social context. Interestingly, reduced agonistic behaviors have been reported in dominant mice, but not in submissive animals, after LPS administration, a finding that can be interpreted to indicate "that the expression of sickness-associated behaviors relies on a motivational reorganization and change in priorities that should differ according to social rank" ((94), pp. 114–115).

A classic theme in health psychology is that of coping with chronic disease. In this context, it is considered that social support can promote the adoption of adequate coping strategies by improving understanding and increasing motivation (95). It is important to emphasize here that coping can involve "approaching or avoiding the demands of chronic disease" and that the positions adopted by individual on this continuum involve motivations (95). More recently and regarding the acute disease model of LPS administration to young healthy volunteers, Lasselin and colleagues have reported an increased motivation to opt for the "high-effort/high-reward mode of

response, but only when the probability to win [a monetary reward] was the highest" ((49), p. 801). Others have promoted the idea of a so-called behavioral immune system that represents "a unique motivational system" and is closely associated with disgust ((96), p. 251). Thus, infections result in the emotion of disgust, which, in turn, leads to motivated "behavioral avoidance" ((97), p. 6). Interestingly, these considerations have been put forward within the context of "an evolutionary approach to socio-ecological psychology" ((97), p. 6). As indicated above, some psychologists have recently shown how gait and facial cues allow subjects to recognize a sick person (44, 51). It would thus be interesting to study if and how these social cues affect motivation.

CONCLUSION

On the one hand, many of the interdisciplinary initiatives involving sociology and medicine, like social medicine, the sociology of health and disease, and the biopsychosocial model of medicine, have emphasized the importance of a holistic approach and of considering multiple factors (6, 98). On the other hand, numerous interdisciplinary research efforts mobilizing psychology and biology have been done within the framework of evolution. This then allows, following Ernst Mayr, to distinguish how and why questions about, proximate causation relative to causal mechanisms operating within the life of the organism and ultimate causation regarding adaptation or drift over evolutionary time (99). When it comes to the possibility of an interdisciplinary approach of illness/sickness behavior, this means that multiple causes would need to be considered from the perspective of the organism. It seems that the notions of stressor, between infection as a physiological stressor and dominance as a psychosocial stressors, and of motivation as a state offer opportunities for biology, medicine, psychology, and sociology to communicate and collaborate to further our understanding of illness/sickness behaviors in particular those accompanying chronic conditions. So it seems that interdisciplinary research on illness/sickness behavior between biology, psychology, and sociology with the aim of "integration of the constructs, data and explanations" is possible ((100), p. 129). However, this will require "coordinated pluralism" (100) with regard to constructs, methods, and findings and awareness of differences in perspectives, for example between a focus on acute and chronic sickness behavior.

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JPK conceived of, wrote, and edited this work.

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REVIEW
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What Does CATS Have to Do With Cancer? The Cognitive Activation Theory of Stress (CATS) Forms the SURGE Model of Chronic Post-surgical Pain in Women With Breast Cancer

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Chronic post-surgical pain (CPSP) represents a highly prevalent and significant clinical problem. Both major and minor surgeries entail risks of developing CPSP, and cancer-related surgery is no exception. As an example, more than 40% of women undergoing breast cancer surgery struggle with CPSP years after surgery. While we do not fully understand the pathophysiology of CPSP, we know it is multifaceted with biological, social, and psychological factors contributing. The aim of this review is to advocate for the role of response outcome expectancies in the development of CPSP following breast cancer surgery. We propose the Cognitive Activation Theory of Stress (CATS) as an applicable theoretical framework detailing the potential role of cortisol regulation, inflammation, and inflammatory-induced sickness behavior in CPSP. Drawing on learning theory and activation theory, CATS offers psychobiological explanations for the relationship between stress and health, where acquired expectancies are crucial in determining the stress response and health outcomes. Based on existing knowledge about risk factors for CPSP, and in line with the CATS position, we propose the SURGEry outcome expectancy (SURGE) model of CPSP. According to SURGE, expectancies impact stress physiology, inflammation, and fear-based learning influencing the development and persistence of CPSP. SURGE further proposes that generalized response outcome expectancies drive adaptive or maladaptive stress responses in the time around surgery, where coping dampens the stress response, while helplessness and hopelessness sustains it. A sustained stress response may contribute to central sensitization, alterations in functional brain networks and excessive fear-based learning. This sets the stage for a prolonged state of inflammatory-induced sickness behavior – potentially driving and maintaining CPSP. Finally, as psychological factors are modifiable, robust and potent predictors of CPSP, we suggest hypnosis as an effective intervention strategy targeting response outcome expectancies. We here argue that presurgical clinical hypnosis has the potential of preventing CPSP in women with breast cancer.

Keywords: breast cancer, chronic postsurgical pain, cognitive activation theory of stress, expectancies, sickness behavior, stress, predictive coding, hypnosis

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INTRODUCTION

Chronic post-surgical pain (CPSP) affects a substantial amount of patients undergoing either major or minor surgeries (Shug and Pogatzki-Zahn, 2011). CPSP can be defined as pain that develops after surgical intervention and persists minimum 3–6 months after healed tissue damage (Cohen and Raja, 2020).

An example of debilitating CPSP is documented in women undergoing breast cancer surgery. More than 1 million women are diagnosed with breast cancer every year, and approximately 25–60% of them will struggle with CPSP, regardless of surgical procedure (Andersen and Kehlet, 2011; Wang et al., 2018b). The prevalence of severe CPSP following breast cancer surgery is estimated to be 5–10%, where CPSP causes patients to experience a significant reduction in daily functioning, work capability, and quality of life (Andersen and Kehlet, 2011).

As with any chronic pain condition, the pathophysiology of CPSP in breast cancer is multifactorial, and knowledge of the underlying mechanisms is still unclear. As an example of this complexity, only some of the women with CPSP following breast cancer surgery have peripheral pain drivers as a result of intra-surgical nerve damage (Gärtner et al., 2009; Schou Bredal et al., 2014). It is therefore acknowledged that CPSP is best understood through a bio-psycho-social model, with multivariate factors contributing to its development (Weinrib et al., 2017).

Some of the more established risk factors of CPSP includes pre-surgical stress-level, depression, anxiety, pain catastrophizing, and low optimism (Jackson et al., 2016; Weinrib et al., 2017; Jensen and Johannesen, 2019; la Cour, 2019; Giusti et al., 2021). Also, pre-surgical- or intense acute post-surgical pain can significantly increase the risk of CPSP in women with breast cancer (Gärtner et al., 2009; Schou Bredal et al., 2014).

When evaluating modifiable and well-documented risk factors for CPSP following breast cancer surgery, we argue for the potential impact of expectancies on psychoneuroimmunological responses to a stressful situation. Conceptualized by an expectancy model (SURGE), we propose that CPSP can be understood, delineated, and possibly prevented. Our suggested model incorporates the cognitive activation theory of stress (CATS), predictive coding principles, cortisol function, and inflammatory-induced sickness behavior.

SETTING THE SCENE FOR CPSP: LIFE LEADING UP TO A SURGERY

Throughout our lives, our learning history shapes expectancies, higher order beliefs about how we will respond to stressful challenges such as an impending surgery. Surgery in the context of cancer represents a highly stressful experience for most, if not all. It gives rise to multitude of expectancies of how the surgery and disease will unfold and how one is going to deal with the consequences. Dealing with such a challenge evokes past learning in the form of acquired expectancies and prior conditioning, here seen as complementary and overlapping constructs (Stewart-Williams and Podd, 2004).

Expectancies are commonly defined as "beliefs that something will happen or is likely to happen" (Schwarz et al., 2016) and can be acquired by direct experience, verbal instruction, or observation of others (Kube et al., 2017; Laferton et al., 2017; Rief and Joormann, 2019). In other words, any direct or indirect experience with surgery will contribute to the formation of expectancies. The subsequent expectancies can be colored by hope, trust, and optimism, but also by fear, worry, and catastrophic thoughts. As an example, if a loved one previously has undergone surgery and experienced CPSP, we might fear an approaching surgery.

This fear quickly becomes important as expectancies can be the powerful modulators of health outcomes (Benedetti, 2008; Kirsch, 2018; Lasselin et al., 2018). Some of the strongest effects from expectancies are seen in the placebo/nocebo literature. Positive expectancies about a given treatment can lead to increased pain relief, even if the given treatment is perceived as inactive, e.g., a calcium tablet or sham acupuncture (Benedetti, 2008; Atlas and Wager, 2012; Forsberg et al., 2017). Also, it is well-established that positive expectancies about the response of a given treatment may enhance the analgesic effects of active surgical (Gandhi et al., 2009), pharmacological (Bingel et al., 2011), and non-pharmacological treatments (Peerdeman et al., 2016). These processes are coined placebo analgesia. A related phenomenon is nocebo hyperalgesia. Here, negative response outcome expectancies are found to increase the intensity of pain in experimental and clinical studies (Colloca and Miller, 2011; Petersen et al., 2014). Negative expectancies about a treatment can block the analgesic effects of active treatments or exaggerate negative side effects (Petersen et al., 2014; Smith et al., 2020). While most of this research primarily focuses on experimental and acute pain, other lines of research have shown how negative expectancies can have debilitating effects on the development and maintenance of chronic pain (Atlas and Wager, 2012).

COGNITIVE ACTIVATION THEORY OF STRESS

From the moment an individual receives word about an upcoming surgery, particularly, a potential life-threatening cancer requiring surgery, a stress response usually follows. This response can be understood using the cognitive activation theory of stress (CATS), a psychobiological theoretical framework offering clear and formal definitions of the stress response and how this affects health (Ursin and Eriksen, 2004).

In CATS, "stress" is defined and operationalized as a psychobiological concept with four stages (**Figure 1**). The first stage is the orientation. Here, we orient toward what could be a *stress stimulus*, representing objective internal or external stimuli automatically processed by the brain, ultimately leading to appraisal.

The second stage is the appraisal or subjective anticipation of stress, where the stimuli have been filtered by the brain in terms of individual learning history. In CATS, learning history includes stimuli expectancies driven by classical conditioning, and response outcome expectancies driven by operant conditioning.

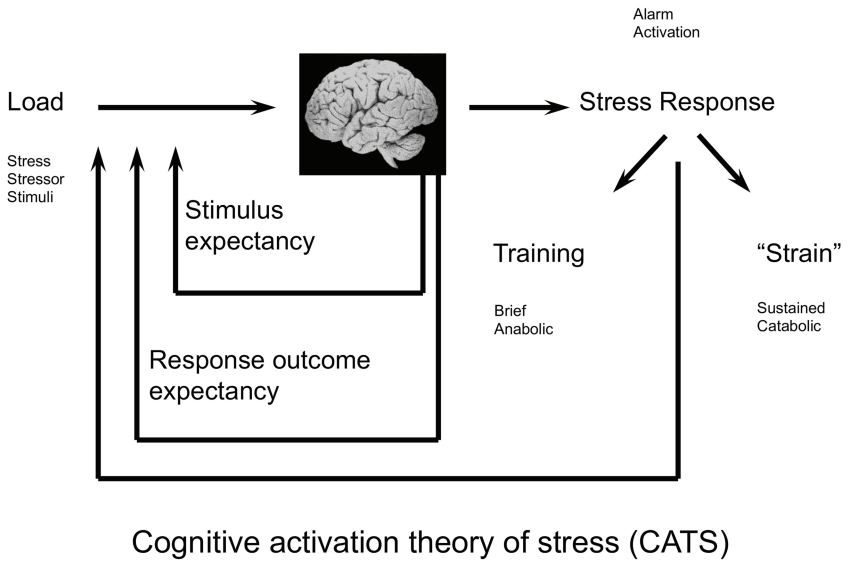

FIGURE 1 | The cognitive activation theory of stress (CATS; Ursin and Eriksen, 2010). The stress stimulus (load) is registered. Stimulus- and response- outcome expectancies influence whether the load is appraised as stressful. If so, a general physiological stress response is activated. Feedback from the physiological stress response is being fed back to the brain. A short activation of the stress response is healthy and adaptive, while a sustained stress response may lead to illness or disease. Reprinted from Ursin and Eriksen (2010), Copyright (2021) with permission from Elsevier.

These expectancies determine to a large degree intensity and duration of the third stage, the physiological stress response.

The physiological stress response is an alarm system representing a general, non-specific arousal response in the somatic and autonomic nervous system as well as in several endocrine axes (Ursin and Eriksen, 2010). The alarm goes off when an imbalance is expected in the homeostatic system, e.g., when experiencing novel or threatening stimuli or a discrepancy between what is expected and what actually is (Subjective set Value − Actual Value ≠ 0; Ursin and Eriksen, 2010).

The fourth and final stage of the definition represents the individual experience of the stress response, consisting of information from the arousal response being fed back to the brain, ultimately maintaining, adding to, or resolving the unpleasant feeling of stress.

According to CATS, stress is a beneficial reaction, meaning that an activation of a stress response in challenging situations is healthy and adaptive. The goal of a short activation of the physiological stress response is to restore homeostasis (Ursin and Eriksen, 2004), and the arousal response is gradually turned off when the individual expects to handle the challenge successfully. If not, the arousal may be sustained, leading to illness and disease. Whether the stress response is eliminated, dampened, or sustained relies on expectancy filters (Ursin and Eriksen, 2004). These filters are described as stimulus expectancies and response outcome expectancies.

Stimulus Expectancies

Our brain is designed to store information about the relationships between sets of stimuli and our available responses (Ursin and Eriksen, 2004). This information is stored as expectancies and is how we come to expect that one specific stimulus typically precedes another specific stimulus. In CATS, this is called as stimulus expectancies, and it represents classical conditioning within traditional learning theory (Ursin and Eriksen, 2004). A classic example of associative learning and stimulus expectancies is the work of Ivan Pavlov and his dogs. His now famous experiment showed how dogs that were continuously presented with food paired with a sound of the bell later would salivate when they heard the bell ring, regardless of food were offered or not (Pavlov and Thompson, 1902). A particular feature of Pavlovian conditioning is that stimuli sharing characteristics with the original conditioning stimuli may become capable of eliciting conditioned responses, depending on the perceptual or functional proximity between the two. This was exemplified in his studies showing that the dogs eventually started to salivate just as they heard the footsteps of the experimenters. Thus, during stimulus generalization, individuals extrapolate knowledge from one aspect of the situation to other aspects and situations – making more and more stimuli capable to elicit the conditioned response.

Response Outcome Expectancies

Response outcome expectancies are within CATS regarded as acquired information about available responses to a stimulus and how these responses affect subsequent outcomes. This type of learning follows principles of operant or instrumental conditioning, where the individual learns from positive and negative reinforcements of behavior (Ursin and Eriksen, 2004, 2010).

Through response outcome expectancies, you anticipate successful or unsuccessful handling of future threats without yet having experienced them, an essential prerequisite for avoiding or anticipating harm.

A physiological stress response experienced by a woman who is about to undergo surgery could thus be interpreted in different ways according to her expectancies; it could either be interpreted as a sign of anxiety implicating uncontrollable danger and harm, or as a normal response to a challenging situation. While the first interpretation has the potential to increase and sustain the stress activation, the second interpretation has the potential to dampen the stress response.

The power of beliefs and expectancy in regulating physiology is a hallmark of another important learning theory, the predictive coding framework of information processing. This theory suggests that the brain uses Bayesian prediction principles to constantly match bottom-up sensory information with top-down predictions created by prior experiences (Gilbert and Sigman, 2007; Petrovic et al., 2010; Büchel et al., 2014). These predictions are organized hierarchically in the brain, from lower-level momentary hypotheses about the causes of current sensory inputs (e.g., feeling pain from a gentle touch) to increasingly more overarching beliefs the nature of the world and yourself (e.g., "I cannot cope with this pain anymore"). These higher order beliefs are in many ways analog to the concepts of stimulus expectancies and response outcome expectancy in CATS.

One can envision generalized response outcome expectancies forming enduring overarching hypotheses (e.g., "I am not a person that handles pain"). When a person experiences a discrepancy between experience and expectancy, these higher order beliefs can overturn lower-level sensory input, motivating behavior and cognition in order to uphold an expectancy, regardless of lower level input and prediction errors. This has been described as cognitive immunization and is particularly evident in patients with depression (Kube et al., 2020). Numerous studies show how patients suffering from depression are prone to maintain their negative expectancies despite of positive, contradictory evidence (Korn et al., 2014; Liknaitzky et al., 2017; Everaert et al., 2018). This immunization contrasts that of a healthy population who show an overall optimism bias, i.e., a tendency mainly to update expectancies if new information are positive, while maintaining one's prior belief if the presented evidence is negative (Sharot, 2011).

The notion of a hierarchical organization of processing is also described in CATS through the feedback loop in the model, where lower level peripheral changes – i.e., the stress response – is being fed back to the brain, but can be prolonged or dampened according to higher order expectancies or predictions (Ursin and Eriksen, 2004). Principles from the predictive coding framework thus align with the expectancy principles outlined in CATS. In effect, generalized expectancies based on prior experiences can then override lower-level changes and new learning, potentially maintaining a stress response in the weeks leading up to breast cancer surgery. The CATS model has further specified three forms of generalized response outcome expectancies, namely coping, helplessness and hopelessness.

Coping

A significant contribution from CATS is its clarification of the coping term and its assumed correlates. Coping in CATS terminology is the acquired expectancy that most or all responses to a situation will lead to a positive outcome. Thus, it represents an anticipatory cognitive construct rather than objective abilities or strategies that could be applied in challenging situations. Coping in form of generalized response outcome expectancy may be associated with a proactive appraisal of the stressful situation, reflecting improved anticipatory stress regulation, ultimately resulting in a shortened physiological stress response (Ursin and Eriksen, 2004).

In the case of a woman undergoing breast cancer surgery, coping may refer to the expectancy of being able to handle the stressful aspects of the surgery, i.e., the post-surgical pain and potential side effects in a successful way. This taps into the established CPSP resilience factors of dispositional optimism (Powell et al., 2012) and self-efficacy (Weinrib et al., 2017).

According to CATS, it is when coping is defined as a generalized response outcome expectancy it may hold the strongest predictive power for health outcomes, mediated by its presumed reducing effects on the strength and the duration of the physiological stress response (Ursin and Eriksen, 2004, 2010). The authors of CATS argue that since *coping defined as coping strategies* can be carried out under various levels and lengths of arousal, it is not a robust predictor of stress-related illness or disease (Ursin and Eriksen, 2004).

Both human and animal studies suggest that positive expectancy attenuates the cortisol response to stress. Rats exposed to shocks will initially show high behavioral and endocrine arousal. However, in late stages of avoidance learning tasks when they have established that they will be able to escape the shocks, the arousal diminishes to a minimum (Coover et al., 1973). Ursin and Eriksen (2004) suggest that this happens so rapidly and efficient that it is not just a result of the avoidance behavior, but due to an expectancy that the behavior will lead to a successful outcome.

Ursin et al. (1978) also tested this position in humans. A group of novel parachutist trainees showed the high levels of endocrine and subjective reported arousal before their first jump. Already after their first training session, before there had been any real improvement of their performance, the arousal reduced significantly. This could indicate that it was not the actual performance, but the acquired expectancy of being able to handle the situation with a positive result, that explained the diminished stress response.

Recent studies of how we react to psychosocial stress confirm and expand upon these early reports of positive physiological effects from cognitive re-framing and coping. Jamieson et al. (2012) showed that during a psychosocial stress test, participants instructed to reappraise their arousal in a positive way had increased cardiac efficiency, lower vascular resistance, and decreased attentional bias. Similarly, Nasso et al. (2019) showed that when anticipating a stressful

task (i.e., giving a speech), individuals using an adaptive cognitive emotion regulation strategy showed better anticipatory stress regulation than individuals prone to worry or catastrophizing. Overall, these results suggest that positive response outcome expectancies can affect the long-term consequences of our physiological stress responses in a beneficial fashion.

Helplessness and Hopelessness

Helplessness refers to the acquired expectancy of one's actions having no impact on the outcome of an aversive event. This can be exemplified by a woman going into breast cancer surgery with the expectancy that there is nothing she can do to control the outcome of the surgery or potential negative side effects. A qualitative study by Lie et al. (2018) highlighted how young adult cancer patients, aged 18–35 years at time of diagnosis, describe that not being able to predict or control their situation was the most stressful aspect of all stages of their disease and treatment. This study focuses on patients in a particular vulnerable transitional life period. However, other studies find similar results on helplessness, i.e., the factors of uncertainty and lack of perceived control are common characteristics of stress and chronic disease, with negative effects on pain outcomes and quality of life (Johnson et al., 2006; Müller, 2011; Caruso et al., 2014; Engevold and Heggdal, 2016).

Hopelessness, on the other hand, is an expectancy of most or all responses leading to negative outcomes. In women with breast cancer going into surgery, this could be the expectancy that all attempts to handle or change the stressful situation evolving around the surgery, will only make it worse. Hopelessness implies that there is control, responses have effects, but they are all negative. These failed attempts combined with the assumed control could evoke feelings of guilt and self-blame in those who acquire expectancies of hopelessness. Thus, these expectancies are proposed by the authors of CATS as a cognitive model for depression (Ursin and Eriksen, 2004), a condition that increases the risk of developing CPSP (Weinrib et al., 2017).

The expectancies of helplessness and hopelessness are also conceptually close to another established risk factor of CPSP namely pain catastrophizing. When measured with the Pain Catastrophizing Scale (PCS; Sullivan et al., 1996), this is a strong and consistent predictor of CPSP (Hannibal and Bishop, 2014; Johannsen et al., 2018, 2020). In PCS, patients report about helplessness and hopelessness in response to pain (e.g., "It's terrible and I think it's never going to get any better" and "there's nothing I can do to reduce the intensity of the pain"; Sullivan et al., 1996). Moreover, the elements of hopelessness are captured within measures of injustice experiences (The Injustice Experience Questionnaire; Sullivan et al., 2008), which also is a significant psychological risk factor for developing CPSP (Yakobov et al., 2014).

In summary, CATS states that coping may reduce or eliminate the physiological stress response, and helplessness and hopelessness may sustain it. If sustained, the stress response affects specific psychological and neurobiological mechanisms that can reinforce and perpetuate pain relating to the surgery, increasing the risk for developing CPSP.

Stress and Sensitization

A line of experimental studies have demonstrated the link between a sustained stress response and the process of sensitization, which is suggested as a psychobiological mechanism in the transition from acute to chronic pain (Ursin, 2014). On the cellular level, sensitization is defined as an increased efficiency in a neural circuit, due to a change in synapses from repeated use (Collingridge et al., 2004). Sensitization of pain pathways in the central nervous system is widely accepted as a theory of neural mechanisms enhancing pain transmission (Ikeda et al., 2009). This central sensitization progressively amplifies the responses to pain stimuli. It manifests as pain hypersensitivity both as a reduction in pain threshold and an increase in pain responsiveness as well prolonged after sensations and an expansion of the receptive field (Woolf, 2011).

A large body of evidence showing central sensitization in chronic pain syndromes originates from research on patients with fibromyalgia, a condition with widespread pain in the body. Research has demonstrated widespread reductions in pain thresholds as well as an increased temporal summation and a spatial area of pain in this patient group (Gibson et al., 1994; Lorenz et al., 1996; Graven-Nielsen et al., 2000). Patients with CPSP also show the signs of central sensitization (Woolf, 2011; Johannsen et al., 2020). The role of central sensitization in CPSP is further supported by an indication of pain reducing effects due to centrally acting agents such as ketamine (Remérand et al., 2009), pregabalin (Mathiesen et al., 2009; Burke and Shorten, 2010), gabapentin (Sen et al., 2009; Verret et al., 2020), and duloxetine (Ho et al., 2010). However, more studies are needed to establish the effectiveness of pharmacological treatments.

Pre-surgical pain in the surgical area as well as other sites of the body is the strong predictors of CPSP (Poleshuck et al., 2006; Kudel et al., 2007; Gärtner et al., 2009; Nikolajsen and Aasvang, 2019). Patients who experience pre-surgical pain conditions, such as fibromyalgia, migraine, or chronic low back pain, have a significant increased risk of CPSP following breast cancer surgery (Bruce et al., 2012; Schou Bredal et al., 2014). The association between pre- and post-surgical pain could be due to an unknown common underlying factor (e.g., genetic and/or psychological), making a group of patients more vulnerable to persistent pain. Still, it could suggest that a central sensitization plays a role in CPSP through repeated pain stimuli increasing the efficiency and excitability of central pain pathways or stated another way; pain produces pain.

Different lines of research thus present the hypothesis that sensitized stress responses could interact with sensitized pain responses, and ultimately increase the risk of CPSP. However, it has proven difficult to establish direct causal delineation of sustained stress in chronic pain, but psychological and physiological stress is associated frequently with the development and persistence of chronic disease such as chronic pain conditions (McEwen and Kalia, 2010; Timmers et al., 2019). In a CATS perspective, sustained activation is the motor that accelerates

sensitization and prevents its reversibility, thus sustained stress activation will affect almost all bodily systems through the actions of cortisol. As principles of central sensitization likely contribute to the chronification of pain (Woolf, 2011), the potential maladaptive effects of stress hormones on pain transmission could mediate the relationship between chronic stress and chronic pain.

Cortisol Function and Chronic Pain

Cortisol is a catabolic hormone produced in the adrenal cortex, which plays a crucial part in the physiological stress response (Hannibal and Bishop, 2014). In stressful situations, cortisol levels rise to provide energy to deal with the situation or escape danger (fight or flight; Blackburn-Munro and Blackburn-Munro, 2003). Prolonged cortisol secretion, on the other hand, could have damaging effects and increase the risk of chronic pain.

During the stress response, unbound cortisol binds on glucocorticoid receptors (GRs) resulting in anti-inflammatory and pain inhibiting mechanisms (Fries et al., 2005; Sorrells et al., 2009). However, an exaggerated or sustained cortisol secretion may cause GR to downregulate, or block cortisol binding, ultimately creating cortisol dysfunction (Norman and Hearing, 2002). Further, an impaired binding to GR might disrupt the negative feedback loop, which under normal circumstances enables cortisol to regulate the release of corticotrophin-releasing hormone (CRH) (Fries et al., 2005). CRH upregulates glutamate and N-methyl-D-aspartate (NMDA) in the amygdala, which might set prime for a conditioned fear-based stress response (Tsigos and Chrousos, 2002; Shekhar et al., 2005; McEwen and Kalia, 2010). Additionally, it is indicated that the activation of CRH receptors in the amygdala may trigger pain in the absence of tissue damage and that hyperpolarized postsynaptic potentials might be able to make amygdala resistant to inhibitory signals from prefrontal cortex (Shekhar et al., 2005; Ji et al., 2013). Such reduced prefrontal modulation is associated with pain catastrophizing in chronic pain patients experiencing intense pain (Seminowicz and Davis, 2006).

Several studies have associated the actions of cortisol with increased activation in the amygdala during anxiety and fear (Shekhar et al., 2005; Ji et al., 2013; Vachon-Presseau et al., 2013). Using an animal model of neuropathic pain in rats, Li et al. (2013) found that lesions of the basolateral amygdala inhibit the transition from acute to chronic pain in the early stages of nerve damage. Due to the well-established role of the amygdala in the fear learning system, the authors suggest that a possible explanation of this involves interruptions of negative emotions and consolidation of fear-based pain memories. Such learning processes may possibly relate to the acquisition of negative response outcome expectancies, potentially leading to sustained activation, sensitization and chronic pain.

Pain catastrophizing, i.e., a sense of helplessness and hopelessness, elevates the cortisol secretion and sustains the activation of the stress response (Johansson et al., 2008; Quartana et al., 2010; Müller, 2011). Sustained activation of a sensitized stress response exhausts the HPA-axis, and chronic stress-induced hypocortisolism has been linked to chronic pain conditions (Tsigos and Chrousos, 2002; Tak and Rosmalen, 2010; Hannibal and Bishop, 2014). Paradoxically, hypercortisolism is also reported as a contributor to chronic pain (Blackburn-Munro and Blackburn-Munro, 2003; Dedovic et al., 2009), i.e., potentially mediated by the blunted feedback mechanisms discussed earlier in this section. The relationship between stress, chronic pain, and hypo- and hyper-cortisolism thus depend on temporal aspects of measurement, the individualized stress response, the different mechanisms of cortisol dysfunction described earlier and numerous situation-specific factors (Hannibal and Bishop, 2014). These inconsistencies call for more research on the relationship between cortisol and chronic pain, but available data suggest that stress-induced cortisol dysfunction could contribute to the development and persistence of chronic pain.

Cortisol dysfunction through the mechanisms discussed above represents potential harmful effects of sustained activation on a neurochemical level. In addition, prolonged secretion of stress hormones may alter both the functional and physical properties of the corticolimbic system with considerable consequences for the development and perpetuation of chronic pain following breast cancer surgery.

Corticolimbic Plasticity

The corticolimbic circuit of the brain consists of neural loops between structures such as the prefrontal cortex (PFC), the amygdala, the hippocampus, and hypothalamus in strong connections to the HPA-axis (Vachon-Presseau, 2018). The corticolimbic circuit is involved in a variation of cognitive-emotional processes and plays a crucial role in motivation and learning, i.e., in relation to pain and the anticipation of pain (Ploghaus et al., 2001; Apkarian et al., 2009). It has been suggested that the corticolimbic circuit may represent the primary system through which nociception accesses consciousness and is experienced as pain (Baliki and Apkarian, 2015). The corticolimbic structures show high affinity to stress hormones, which enable them to regulate the stress response through feedback loops to the HPA axis, and at the same time making them sensitive to the effects of long-term exposure to cortisol (Radley and Sawchenko, 2011; Vachon-Presseau, 2018).

The PFC is particular sensitive to the effects of stress hormones. Sustained exposure to cortisol has shown to generate extensive dendritic spine loss (Arnsten, 2009; McEwen and Morrison, 2013) similar to that observed in medial prefrontal cortex (mPFC) in animal models of neuropathic pain (Metz et al., 2009). Moreover, the mPFC has been associated with individual differences in subjective pain intensity in chronic pain patients. For example, an fMRI study by Baliki et al. (2012) indicated that the strength of the functional connectivity between mPFC and nucleus accumbens (NAc) is a dominating predictor of pain chronification in humans with subacute back pain (stronger mPFC-NAc connectivity was associated with pain persistence). The activity of the PFC regulates, and is regulated by, the amygdala. In animal models of chronic pain, the excitability of neurons in the amygdala rapidly increases in response to repeated pain stimuli (Ursin, 2014). This increased excitability compliments animal models showing hypertrophy

and increased spinogenesis in basolateral regions of the amygdala when animals are exposed to sustained stress (Roozendaal et al., 2009). Studies of post-traumatic stress disorder in humans expand upon this indicating that both pain and fear-based learning can drive hypertrophy in these regions of the amygdala (Morey et al., 2020). The increased activity and hypertrophy of the amygdala divergently affects plasticity in other brain regions such as the PFC and hippocampus (Patel et al., 2018). The amygdala then influences the corticolimbic circuit by modulating excitability of the inhibitory neurons in the mPFC, as well as neurons in the spinal cord (Neugebauer et al., 2004; Neugebauer, 2015), which may result in pain hypersensitivity. Thus, the connectivity between the amygdala and the PFC may be distorted by long-term exposure to cortisol, mediated by CRH as well as GR signaling (Galatzer-Levy et al., 2017), which have implications for the regulation of anxiety and pain (Shekhar et al., 2005; Ji et al., 2013).

Finally, several studies have implicated that alterations in the physical and functional features of the hippocampus are associated with chronic pain conditions. Using an animal model of neuropathic pain, Mutso et al. (2012) found decreased hippocampal neurogenesis and altered hippocampal short-term synaptic plasticity in mice with spared nerve-injury neuropathic pain compared with sham animals. In addition, this study found lower hippocampal volume in patients suffering from low back pain and complex regional pain syndrome. The authors propose that the functional hippocampal abnormalities found in their animal model of neuropathic pain potentially relate to the decreased hippocampal volume observed in chronic pain conditions, and that this ultimately contributes to emotional and learning deficits associated with chronic pain. The deteriorating effects of stress hormones on hippocampal volume and neurogenesis are indicated in both aging (Lupien et al., 1998) and psychiatric populations (Sapolsky, 2000; Videbech and Ravnkilde, 2004).

In summary, the corticolimbic system may be sensitive to maladaptive effects of long-term exposure to stress hormones, both in terms of its physical and functional properties. These stress-induced changes in the corticolimbic circuit may negatively affect the regulation of the stress response by impairing the inhibitory feedback loops from the HPA axis (Vachon-Presseau, 2018). This could contribute to a vicious cycle sustaining the activation of the stress response and presents direct and indirect implications for the chronification and experience of pain in a woman entering surgery for breast cancer.

PERI- AND POSTOPERATIVE STRESS – THE CRUCIAL TIME JUST BEFORE, DURING, AND AFTER SURGERY

In the perioperative phase, breast cancer patients often experience high levels of distress and expect a variety of post-surgery symptoms (Deane and Degner, 1998; Spencer et al., 1999). Such distress may include everything from concerns about diagnosis and prognosis (Schnur et al., 2008), to concerns about anesthesia (Shevde and Panagopoulos, 1991), and surgical procedures (e.g., pain during procedure and postoperative side effects; Klafta and Roizen, 1996). Pre-surgery distress and patient expectancies about the severity of postoperative side effects have both been found to predict pain severity, nausea, and fatigue 1 week after surgery in breast cancer patients (Montgomery et al., 2010). In addition, patients' presurgical expectancies of pain, fatigue, and nausea have been shown to partially mediate the effects of distress on pain severity 1 week after surgery, where expectancies and psychological distress together explained 28% of the variance in 1 week post-surgery pain (Montgomery et al., 2010). In CATS terminology, this would entail background arousal (high distress), stimulus expectancies (severe pain from surgery), and response outcome expectancies ("I have no power over what's to come"), resulting in a tonic (sustained) arousal with increased risk of negative health consequences (e.g., pain and other side effects 1 week after surgery).

A breast cancer surgery usually involves either total removal of the breast (mastectomy) or breast-conserving surgery (lumpectomy) with or without sentinel node biopsy. Breast conserving surgery is a less invasive yet a safe and effective option (Fisher et al., 1989) and is the most commonly performed surgery (Lazovich et al., 1999). While breast conserving surgery has fewer early post-operative complications (Chatterjee et al., 2015) and has been associated with better quality of life (Sun et al., 2014), incidence rates of CPSP appear to be less influenced by type of surgery (Wang et al., 2016). Instead, CPSP is heavily influenced by emotional distress, which has led to a general call for ways to target the emotional distress, since this is a modifiable risk factor that could be intervened on (Jackson et al., 2016). In a recent study, those women with the highest level of distress after surgery were those who benefited the most from a psychological treatment (Wang et al., 2018a,b). We therefore argue that from a prevention perspective, timing of the intervention is crucial. The time window immediately before surgery, on the day of surgery, is critical. If distress is reduced and coping increased already prior to surgery, an important risk factor for CPSP and other negative health outcomes could be eliminated, ultimately affecting the prognosis and risk for CPSP.

Inflammation, Sickness Behavior, and Post-surgical Pain

Stress, inflammation, and pain are inherently interlinked systems, whether you look at it from an acute or chronic perspective. Both pro- and anti-inflammatory processes kick in, in response to stressors such as pain, perceived or anticipated danger, injury, and infection (Slavich and Cole, 2013). A short-term pro-inflammatory response increases the chance of survival by accelerating wound healing and limit potential spread of an infection. In addition, pro-inflammatory cytokine activity, involving tumor necrosis factor-α (TNF-α) and interleukins 1β and 6 (IL-1β and IL-6), promote a distinct motivational state called as sickness behavior, observed in both human and animals (Hart, 1988; Dantzer, 2001; Shattuck and Muehlenbein, 2016).

The cluster of behavioral symptoms that constitutes sickness behavior includes fatigue, pain hypersensitivity, psychomotor retardation, social withdrawal, and decreased interest in hedonic

behaviors (Dantzer, 2001; Lasselin et al., 2020). Sickness behavior also involves an emotional component, i.e., heightened emotional distress, which are evident in humans exposed to experimentally induced inflammation (Lasselin et al., 2018). This motivational state lowers (social) activities in order to facilitate recovery and decrease the risk of spreading an infection to conspecifics. In addition, hypervigilance involving pain hypersensitivity and emotional distress would motivate the vulnerable organism to tend to one's wounds and stay away from potential danger while recovering.

As with the stress response, a short increased inflammation and subsequent sickness behavior is adaptive and desirable. However, the inflammation and sickness behavior need to subside for health and healing to take place. Unfortunately, fear-based learning, threat monitoring (i.e., searching for pain in the area of surgery), and sustained stress can maintain inflammation processes through stress-driven alterations in the nucleuses of the amygdala. Recent imaging studies in humans have shown how a hyperactive amygdala activates leukopoietic tissue in the bone marrow, increasing arterial inflammation (Tawakol et al., 2019) and C-reactive protein (CRP) (Osborne et al., 2020). Elevated levels of CRP are strongly associated with reduced pain tolerance and increased pain sensitivity (Schistad et al., 2017), and increased pain sensitivity would increase acute post-operative pain, furthering the risk of developing CPSP (Wilder-Smith, 2011).

Increased inflammation in persistent pain also has a behavioral analog. Using a cross-sectional design, Jonsjö et al. (2020) concluded that chronic pain patients report high levels of sickness behavior (assessed with a validated questionnaire for subjective sickness behavior, Sickness Q; Andreasson et al., 2018). The level of sickness behavior in chronic pain patients was similar to the levels reported by healthy volunteers following injection with a lipopolysaccharide (LPS), a method used to induce a strong inflammatory response in human or animals (Jonsjö et al., 2020; Lasselin et al., 2020). LPS-injected individuals report higher pain sensitivity compared to controls, and the increase in pain sensitivity correlates with lower activation in the ventrolateral prefrontal cortex and the rostral anterior cingulate cortex – areas associated with top-down pain modulation (Karshikoff et al., 2016). Moreover, when compared to others, the levels of self-reported sickness behavior in chronic pain patients and LPS-injected individuals are significantly higher than general care patients and healthy subjects (Jonsjö et al., 2020).

In sum, when undergoing breast cancer surgery, the surgery naturally and adaptively elicits stress-, immune-, and pain-responses. Inflammatory-induced sickness behavior serves adaptive and protective functions in the acute post-surgical phase. However, if the women undergoing surgery enter and exit the surgery with brain alterations and increased inflammation driven by a sustained stress response, this could result in pain hypersensitivity and hypervigilance toward pain following in the weeks after surgery. This fits with persistent sickness behavior mirroring these alterations. While neural and humoral pathways that restore homeostasis may terminate sickness behavior, the same sickness behavior processes can be maintained without an ongoing infection (Jonsjö et al., 2020), possibly through inflammation driven by a sustained stress response.

Significantly elevated levels of the pro-inflammatory cytokine interleukin 6 (IL-6) are found in chronic pain patients compared to healthy controls (Koch et al., 2007). In addition, increased plasma concentrations of TNF-α and IL-1β, other common markers of low-grade systemic inflammation, were detected in chronic pain patients with severe pain, though not in patients with light or moderate pain, suggesting a potential role of low-grade inflammation in chronic pain at least when pain intensity exceeds a certain threshold (Koch et al., 2007). Overall, higher plasma concentrations of inflammatory markers correlate with higher self-reported pain intensity (Koch et al., 2007). As cytokines are thought to be the main mediators in this stress-induced pro-inflammatory effect, this has led to low grade pro-inflammatory processes being proposed as a biological mechanism directly contributing to the pathophysiology of stress-related diseases (Rohleder, 2014).

The previous sections have discussed various mechanisms through which sustained stress activation may contribute to CPSP following breast cancer surgery. Sickness behavior, cortisol dysfunction, and alterations in the corticolimbic circuit due to prolonged secretion of cortisol are essential. They combine to drive the physical and functional irregularities characteristic for chronic pain states, as evident in human and animal studies. Moreover, disrupted corticolimbic connectivity has negative consequences for the regulation of the HPA-axis through its inhibitory feedback loops. The potential maladaptive effects of long-term exposure to stress hormones are important aspects of the vicious cycle of chronic stress and chronic pain, preventing the "alarm" to be turned off, and enabling the stress and pain to persist many years after surgery.

Common to the proposed pathophysiological mechanisms of a stress-induced transition from acute to chronic pain is the involvement of various forms of learning. The corticolimbic circuit, in particular, the amygdala and the hippocampus, is essential in learning and consolidation of fear-based memories, i.e., in response to pain (Hannibal and Bishop, 2014; Vachon-Presseau, 2018). This contributes to the conditioning of a sensitized stress response, readily activated in response to pain (Hannibal and Bishop, 2014). It seems reasonable to hypothesize, that the corticolimbic pathways play a role in the conditioning of response outcome expectancies. Helplessness and hopelessness in response to pain relate to outcomes with strong affective value during high arousal, which make it likely to involve activation of limbic pathways. Furthermore, the relationship is likely bidirectional, in such that hopelessness and helplessness sustain the stress response and contribute to the long-term exposure and maladaptive effects of stress hormones on the corticolimbic circuit.

THE SURGE MODEL

According to SURGE, generalized response outcome expectancies in form of helplessness and hopelessness sustain a physiological stress response before and after surgery. This sets the stage

for fear-based learning, pain sensitization, and maladaptive effects from stress hormones. Moreover, the sustained stress response may contribute to increased pro-inflammatory activity in the peri- and post-operative phase. An increased and prolonged inflammatory state may lead to chronic sickness behavior with its characteristic cluster of hyperalgesia, emotional distress, and other debilitating behaviors.

We here propose that the SURGE model of CPSP (**Figure 2**) offers a possible explanation on how acute pain following breast cancer surgery may develop into CPSP depending on generalized response outcome expectancies. The model further proposes which psychobiological mechanisms drive this transition in form of a sustained activation of the stress response and inflammatory processes. Moreover, the model suggests targets for interventions that could prevent the development of CPSP in women with breast cancer.

HOW TO ADDRESS THE PROBLEM: MANAGING EXPECTANCIES

If response outcome expectancies are an important driver in the development of CPSP, mediated by sustained stress activation, a change in these expectancies should be followed by reduced stress activation and a correspondingly reduced risk of acute as well as CPSP. Challenging and changing negative expectations are fundamental to several psychological interventions. In cognitive behavioral therapy (CBT), unhelpful cognitions are targeted and challenged with a goal of reversing thoughts of helplessness and hopelessness (Beck and Dozois, 2011). The efficacy of CBT has been demonstrated in several populations and settings, including women with breast cancer (Antoni, 2013), with evidence from self-reported outcomes as well as cancer-relevant biological outcomes (McGregor and Antoni, 2009). A more recent approach from the third generation CBT is Acceptance and Commitment Therapy, which also holds promise as a valuable adjunct to surgical interventions (Weinrib et al., 2017).

Nevertheless, in the myriad of psychological interventions and techniques, one particular intervention stands out as notably potent in the context of surgery namely clinical hypnosis. Verbal suggestions appear to be a particularly powerful way of changing expectancies, and this very element is refined and perfected in hypnosis. The seminal study by Montgomery et al. (2007) demonstrates the effects of a hypnosis in women undergoing breast cancer surgery, where a brief session of hypnosis focusing on increasing coping expectancies right before surgery, produced large reductions in pain, distress, and discomfort immediately after surgery.

Hypnosis has been defined in various ways, but is most often described as a state of highly focused attention and increased suggestibility (Lynn et al., 2010). It is often compared to the everyday state of becoming so immersed in a good book

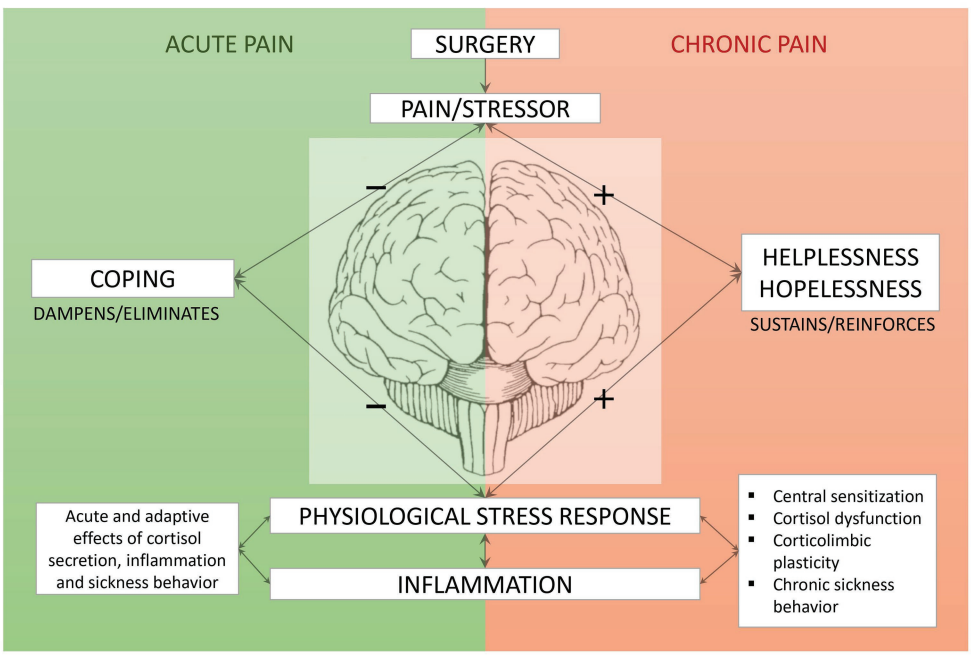

FIGURE 2 | The SURGE Model of chronic post-surgical pain in women with breast cancer: surgery activates the central nervous system and creates acute pain. In line with CATS- and predictive-coding framework principles, the pain is appraised based on previous experiences in form of response outcome expectancies. An expectancy of being able to handle the pain with a positive outcome (coping) dampens or eliminates the physiological stress response. An expectancy of not being able to control or influence the pain (helplessness) or only making the pain worse (hopelessness) sustain the activation of the stress response. The sustained activation creates a vicious cycle of chronic stress, chronic inflammation, and chronic pain mediated by pathophysiological mechanisms such as central sensitization, cortisol dysfunction, impairment of corticolimbic connectivity, and inflammatory-induced sickness behavior.

or a movie that you enter the imagined world and loose contact with the real world (Lang et al., 2000; Montgomery et al., 2002).

The evidence-base for clinical hypnosis as an effective adjunctive non-pharmacological analgesia is strong, as demonstrated in several articles and meta-analyses in top-tier journals (Lang et al., 2000; Montgomery et al., 2002; Tefikow et al., 2013; Kekecs et al., 2014). Of particular relevance here are effects that involve pain reduction, reduced need for medication, and shorter duration of surgery, with effect sizes indicating better clinical outcomes in patients receiving hypnosis than 89% of patients in control groups (Montgomery et al., 2002). Hypnosis has further been shown to be superior to other psychological techniques (e.g., therapeutic suggestions; Kekecs et al., 2014) and might also provide benefits when delivered *during* general anesthesia (Berlière et al., 2018; Lacroix et al., 2019; Nowak et al., 2020). While studies of long-term effects of hypnosis are scarce, one recent study indicates the potential for preventing CPSP with peri-operative hypnosis (Berlière et al., 2018) in line with the SURGE model of CPSP.

Mechanisms of Hypnotic Analgesia

Exactly how hypnotic analgesia works is heavily debated and not agreed upon. While some insists that hypnosis involves an altered state of consciousness (Lynn et al., 2010) others refer to hypnosis as a cognitive behavioral technique (Montgomery et al., 2007), implying that it works through the same system as placebo analgesia works through. Our approach is mostly in line with the latter position. Consistent with the SURGE model, we propose that hypnotic analgesia might work through hypnotic suggestions inducing positive coping expectancies in response to surgery and pain, leading to a dampening of the physiological stress response and ultimately a decrease in pain intensity and a lower risk of developing CPSP.

Nevertheless, earlier studies have demonstrated that hypnotic analgesia could occur through other systems than through the endogenous pain inhibitory mechanisms within the central nervous system that placebo works through (Barber and Mayer, 1977). Injections of naloxone, which is an opioid antagonist, have for instance not been able to change the elevated pain threshold induced by hypnosis in acute (Barber and Mayer, 1977) or in chronic pain (Spiegel and Albert, 1983).

Rather than a placebo effect "in disguise," or an altered state of consciousness, we argue that hypnotic analgesia instead involves an altered perception. This has been suggested by leading experts in the field (Spiegel, 2007) and aligns well with the SURGE model. Through a mobilization of attention pathways in the brain brought about by hypnosis, specific instructions are given that alters the experience of pain and associated anxiety.

The recent predictive coding approaches have also shown relevance to hypnosis. By suggesting that hypnosis causes a shift in the default mode network (DMN; Carhart-Harris and Friston, 2019), an opportunity is created for the psychotherapeutic context surrounding the administration to establish longer-term changes in predictive coding activity. By increasing their sensitivity toward prediction errors, otherwise stable beliefs become more easily updated (Carhart-Harris and Friston, 2019). Furthermore, bottom-up information that is normally inhibited by compressive beliefs becomes liberated and is allowed to "travel up the (brain-body) hierarchy with greater latitude and compass" (Carhart-Harris and Friston, 2019). A central characteristic of this state is increased context sensitivity, i.e., a heightened susceptibility toward ongoing processes in the internal and external context. The hypnosis session then becomes a catalyst creating a unique opportunity to modulate behavioral activation in order to promote a functional homeostasis (Greenway et al., 2020). We propose that all the mentioned findings on mechanisms involved in hypnotic analgesia are in fact not contradictory, but instead pointing toward a common ground – the role of stress and expectancies.

CONCLUSION

Acute pain after breast cancer surgery is expected and adaptive, while the development from acute to CPSP represents a highly prevalent and significant clinical problem. Overall, CPSP is a multifaceted syndrome involving physiological, cognitive, and emotional factors (in addition to important socioeconomic aspects, which have not been discussed here). Expectancy effects are well-established in pain research, showing how expectancies strongly modulate acute and experimental pain. By applying CATS and principles from predictive coding framework, this review has argued how expectancies might contribute to chronic pain, in the specific case of CPSP following breast cancer surgery – mediated by sustained activation, inflammatory-induced sickness behavior, sensitization, and the neurotoxic effects of stress hormones. Clinical hypnosis is suggested as an effective intervention strategy targeting response outcome expectancies, with the potential of preventing CPSP in women with breast cancer.

AUTHOR CONTRIBUTIONS

HJ conceived the idea to the manuscript. AM and SR provided critical intellectual input to the disposition and conceptual framework. AM performed the literature review and wrote the first draft of the manuscript. All authors contributed to the conceptualization, writing, and approval of the final manuscript.

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A Translational Perspective of Maternal Immune Activation by SARS-CoV-2 on the Potential Prenatal Origin of Neurodevelopmental Disorders: The Role of the Cholinergic Anti-inflammatory Pathway

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The emergent Coronavirus Disease 2019 (COVID-19) caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) could produce a maternal immune activation (MIA) via the inflammatory response during gestation that may impair fetal neurodevelopment and lead to postnatal and adulthood mental illness and behavioral dysfunctions. However, so far, limited evidence exists regarding long-term physiological, immunological, and neurodevelopmental modifications produced by the SARS-CoV-2 in the human maternal-fetal binomial and, particularly, in the offspring. Relevant findings derived from epidemiological and preclinical models show that a MIA is indeed linked to an increased risk of neurodevelopmental disorders in the offspring. We hypothesize that a gestational infection triggered by SARS-CoV-2 increases the risks leading to neurodevelopmental disorders of the newborn, which can affect childhood and the long-term quality of life. In particular, disruption of either the maternal or the fetal cholinergic anti-inflammatory pathway (CAP) could cause or exacerbate the severity of COVID-19 in the maternal-fetal binomial. From a translational perspective, in this paper, we discuss the possible manifestation of a MIA by SARS-CoV-2 and the subsequent neurodevelopmental disorders considering the role of the fetal-maternal cytokine cross-talk and the CAP. Specifically, we highlight the urgent need of preclinical studies as well as multicenter and international databanks of maternal-fetal psychophysiological data obtained pre-, during, and post-infection by SARS-CoV-2 from pregnant women and their offspring.

Keywords: cholinergic anti-inflammatory pathway, quality of life, COVID-19, neurodevelopmental disorders, human development, heart rate variability, SARS-CoV-2, maternal immune activation

INTRODUCTION

During pregnancy, there is an increased risk of infection by viruses and bacteria (Silasi et al., 2015; Barinov et al., 2020). Throughout this unique physiological condition, pregnant women are susceptible to gestational infections owing to immunomodulatory changes that naturally occur in their bodies, allowing the implantation and growth of the fetal allograft (Hedge, 1991). Pregnancy was early considered as a high-risk condition for contracting the COVID-19 disease (Phoswa and Khaliq, 2020); approximately 200 million pregnant women were estimated as having a potential risk of SARS-CoV-2 infection worldwide (Vogel, 2020). It could be presumed that the gestational period makes difficult the clinical course of COVID-19 and thus become related with an increased mortality rate.

Cardinal clinical manifestations of patients with COVID-19 disease include fever, cough, and dyspnea (Harapan et al., 2020; Knight et al., 2020; Rodriguez-Morales et al., 2020). Among these patients, the most significant comorbidities are hypertension, cardiovascular disease, and diabetes (Rodriguez-Morales et al., 2020). In pregnant women, recent evidence has shown that the occurrence of COVID-19 during gestation is mainly associated with higher preterm birth rates (Allotey et al., 2020). Yet, an increased number of intrauterine fetal and neonatal deaths, premature rupture of membranes, and miscarriages as well as a reduction of fetal movements have also been documented in a systematic review (Amaral et al., 2020).

The COVID-19 pandemic has forced to establish priority in the short-term mitigating health systems mechanisms. However, owing to the pandemic recent upsurge, no evidence has been reported concerning the middle- and long-term neuroimmune perinatal alterations. Specifically, the effects caused by this disease in vulnerable groups, such as pregnant women and their offspring. Some authors have already proposed that this disease could alter fetal neurodevelopment and even postnatal life (Liu H. et al., 2020). With this perspective article, we first describe the principle of a potential maternal immune activation (MIA) by SARS-CoV-2, as well as the maternal response and inflammation occurred in response to this severe infection. Next, we consider the possibility of neurodevelopmental disorders of the offspring in response to a COVID-19 disease. Additionally, we introduce a possible relationship between the cholinergic anti-inflammatory pathway (CAP), a complex neuroimmune mechanism (Huston and Tracey, 2011), and COVID-19 in pregnancy. Finally, we discuss some autonomic measures, such as those derived from the analysis of maternal and fetal heart rate variability (HRV), which may contribute to our current understanding of COVID-19 in a perinatal translational research. The hypothesized associations among SARS-CoV-2, MIA, the CAP, and neurodevelopmental disorders are shown in **Figure 1**.

Some specific examples and evidence concerning MIA, CAP, and neurodevelopmental disorders are presented in the following subsections, whereas our final hypothesis and opinions linking these topics are mainly addressed in the perspective section.

MIA AND SARS-CoV-2

Infections during pregnancy can cause disturbances in fetal neurodevelopment by the elevation of pro-inflammatory cytokines in the maternal host. Interleukin 6 (IL-6) has been described as a key molecular mediator for the early pathophysiological mechanisms that predispose to neuropsychiatric disorders such as schizophrenia and autism (Smith et al., 2007). Actually, a link between influenza outbreaks and increased risks for schizophrenia in the offspring has been already reported (Tochigi et al., 2004). In a mouse model of influenza infection in pregnancy, an upregulation of the serotonin 5-HT_{2A} receptor in the offspring cortex is observed, which is similarly reported in the postmortem prefrontal cortex from schizophrenic patients (Saunders et al., 2020). In other preclinical models of MIA, the activation of the innate immunity of a pregnant female mouse is mediated by the Toll-like receptor 3 (TLR-3) pathway through the use of a synthetic immunogen, poly-inosinic acid: poly-cytidylic (Poly I:C), which is a mimetic molecule of the replicating genome of single-stranded RNA viruses. This molecular pattern of a double strand of RNA is recognized by the TLR-3 of host innate immune cells, inducing the activation of the transcriptional factor NF-κB that promotes the expression of inflammatory cytokines and the production of type 1 interferons (Alexopoulou et al., 2001). Similarly, several infections of other single-stranded RNA genome viruses such as SARS-CoV and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) have also been found to activate TLR pathways, specifically that of the TLR-3, generating aberrant signaling through inflammatory cytokines, chemokines, and interferons (Totura et al., 2015).

It has been consistently documented that the infection by SARS-CoV-2 generates a complex production of molecules of the inflammatory response. For example, increased levels of cytokines (IL-6, IL-10, and TNF-α), lymphopenia in T cells (CD4 + and CD8 +), and a decreased expression of IFN-γ in CD4 + T cells have all been reported (Pedersen and Ho, 2020). These immunological changes are even associated with the severity of COVID-19 disease (Pedersen and Ho, 2020). Similarly, some patients with SARS-CoV-2 have shown a TH17 cytokine profile, contributing to the cytokine storm syndrome (CSS) (Ur and Verma, 2020; Ye et al., 2020). Notwithstanding that several cytokines are involved in such TH17 cell response, the most relevant is the surge of IL-17 that is responsible for granulopoiesis and neutrophil recruitment (Wu and Yang, 2020). This evidence suggests that patients with severe COVID-19 manifest an uncontrolled excessive inflammatory response, characterized by a hyperinflammatory response to SARS-CoV-2 that is facilitated by a possible unregulated immune system of the host. At present, few clinical studies have been carried out to explore the manifestation and the effects of CSS by COVID-19 during human pregnancy. Nonetheless, some case studies showing respiratory diseases, abnormal Apgar indexes, and pneumonia have already been reported in neonates born from SARS-CoV-2-infected women (Nayak et al., 2020; Wu et al., 2020).

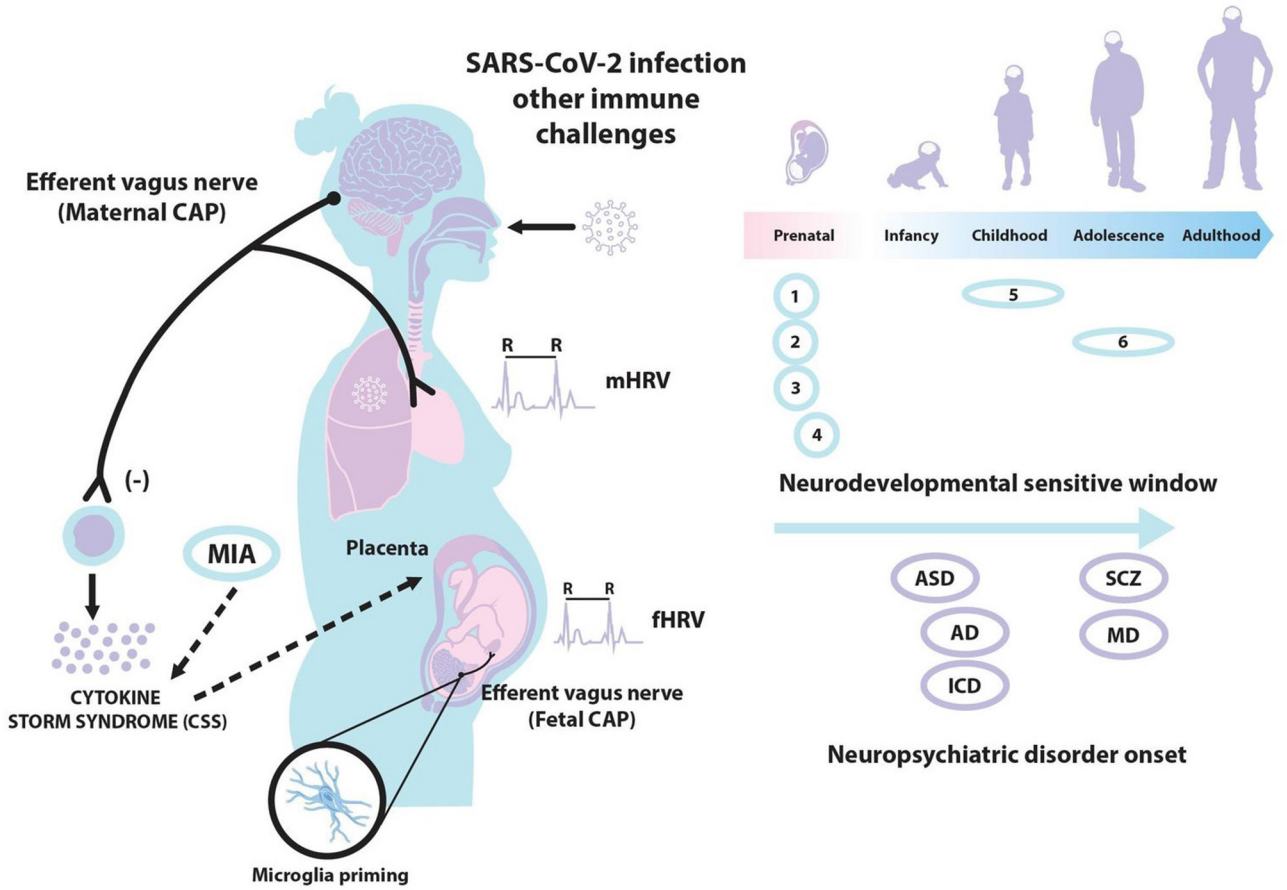

FIGURE 1 | A gestational infection triggered by SARS-CoV-2 may produce a maternal immune activation (MIA) and cytokine storm syndrome (CSS). The activation of the maternal and/or fetal cholinergic anti-inflammatory pathway (CAP) via the efferent vagus nerve and transplacental interactions could downregulate such CSS. The analysis of maternal and fetal heart rate variability (mHRV and fHRV) might be considered for assessing maternal and fetal CAP activation. Also, a gestational infection by SARS-CoV-2 may produce fetal neuroinflammation and microglial activation, increasing the risks of several neurodevelopmental disorders in the offspring and even an altered long-term cognitive function in adulthood: (1) neuronal migration; (2) axonal and dendritic growth; (3) programmed cell death; (4) synaptogenesis; (5) myelination; and (6) process modeling/synaptic refinement. ASD, autism spectrum disorder; SCZ, schizophrenia; AD, anxiety disorders; MD, mood disorders; ICD, impulse-control disorders.

Furthermore, relevant evidence documented that the transplacental transmission of SARS-CoV-2 infection is possible during the last weeks of pregnancy (Vivanti et al., 2020). Recent pathology findings in placentas of SARS-CoV-2-infected cases show mononuclear cell inflammation of the intervillous space, which is accompanied by a syncytiotrophoblast necrosis (Schwartz and Morotti, 2020). In addition to placental inflammation and neonatal viremia, the transfer of pro-inflammatory cytokines across the placenta could lead to fetal brain cortical malformations, and changes in macrophages function that may be even sustained up to adulthood in accordance with the so-called "*Barker hypothesis of the fetal origin of adult disease*" (Barker, 2001). Novel preclinical findings indicate that MIA alters fetal brain development, with implications for long-term cognitive function and behavioral phenotype (Baines et al., 2020; Easterlin et al., 2020).

NEURODEVELOPMENTAL DISORDERS AND COVID-19

Findings derived from epidemiological and preclinical models also show that MIA caused by a viral infection might be linked to an increased risk of neurodevelopmental disorders in the offspring, such as the autism spectrum disorder, schizophrenia, and depression (Pacheco-López et al., 2013; Meyer, 2014; Al-Haddad et al., 2019). Recent studies have even postulated that the dietary intake of anti-inflammatory nutrition in pregnant women with COVID-19 infection and their children could help reduce the risk of neuropsychiatric disorders (Hashimoto, 2020). Other evidence indicates that a severe crisis or traumatic situation in childhood may lead to difficulties in psychological regulation (Thabrew et al., 2012) and increase the risk of diseases during adult life (Vargas, 2012). In the antenatal and early childhood stages, these episodes can cause adverse effects to the subjects,

who are supposed to live in a stable and protective environment (López Soler, 2008). Therefore, an irruption of the life cycle at any of such stages may generate long-term repercussions in different areas of human development, its capacities, and corresponding quality of life (United Nations Development Programme, 2014).

Some studies show that critical or stressful situations during pregnancy generate posterior difficulties in childhood. For example, external environmental factors such as domestic violence, other crises, and psychological trauma affect pregnancy outcomes (López Soler, 2008; Vargas, 2012). COVID-19 should thus act as a complex insult for pregnant women. In fact, knowing a positive diagnostic test result of COVID-19 may generate important physical and emotional implications in pregnant women who may become anxious in identifying themselves as sick people at risk (Bermejo-Sánchez et al., 2020; Lorenzo Ruiz et al., 2020). Different studies have shown that the presence of a variety of psychiatric disorders in adulthood has been associated with early traumatic experiences (Ordóñez-Camblor et al., 2016). Events in early life and childhood alter the neurodevelopment, the dynamic gene-environment interplay, and the programming of the body's neurological, immune, and endocrine systems (National Research Council (US) Institute of Medicine (US) Committee on Integrating the Science of Early Childhood Development, 2000). We consider that this neuro-immune-endocrine insult, as COVID-19, has long-lasting implications for subsequent trajectories of human development (United Nations Development Programme, 2014).

Pregnant women with confirmed COVID-19 infection should be closely supervised and monitored to be able to early recognize any clinical deterioration of the mother and fetus. In this context, we propose, as one possible approach to facilitate this follow-up, to monitor both maternal and fetal neuro-immune interactions by assessing the CAP (Gallowitsch-Puerta and Pavlov, 2007).

THE CAP AND COVID-19

Our knowledge about the neuroimmune changes that exists in the maternal-fetal binomial owing to a COVID-19 infection is minimal; however, some homeostatic mechanisms such the maternal or fetal CAP could be crucial or become altered during pregnancy. The CAP is a complex neuroimmune homeostatic mechanism that suppresses pro-inflammatory cytokine release via the vagus nerve (Huston and Tracey, 2011; Ur and Verma, 2020). The nucleus tractus solitarii integrates the CAP with other immunomodulatory responses because it spreads afferent vagal nerve neuroimmunomodulation signals to the brain (Pavlov et al., 2003). Specifically, an inflammation of the nucleus tractus solitarii can cause a disruption of the CAP and the hypothalamic–pituitary–adrenal axis resulting in a CSS (Ur and Verma, 2020).

In pregnant women, we hypothesize that the activation of the maternal and fetal CAP and the placental interactions might modulate the neuroimmune mechanisms employed to mitigate the CSS, possibly reducing tissue and cell damages, and potentially minimizing the effects of a SARS-CoV-2 infection (Kreis et al., 2020). Interestingly, recent studies have proposed that some severe COVID-19 manifestations could be linked to an impairment of the CAP (Farsalinos et al., 2020). Some authors even consider that the administration of a cholinergic agonist (e.g., pyridostigmine) could inhibit the inflammatory response and lower the mortality of COVID-19 patients (Ahmed, 2020). A disruption of the CAP may thus cause or exacerbate the severity of the maternal and fetal CSS. Interestingly, some preclinical evidence shows that a decreased fetal neuroinflammation is correlated with higher vagus nerve activity fluctuations in near-term ovine fetuses (Frasch et al., 2016).

The CAP may be more relevant in a SARS-2-CoV infection compared with other physiological mechanisms because further evidence indicates that the vagus nerve plays a relevant role in pulmonary inflammation (dos Santos et al., 2011). A detailed description of the neuroimmune mechanisms related to a possible CAP and its impairment in the case of this infection can be found elsewhere (Leitzke et al., 2020; Liu W. et al., 2020). In SARS-CoV-2 infections, young patients generally experience mild symptoms, while fatal interstitial pneumonia is more frequently reported in older patients. It is known that vagal activity declines with normal aging (De Meersman and Stein, 2007), and some authors have already suggested that a deregulated CAP can be associated with the severe manifestations of COVID-19 disease (Farsalinos et al., 2020). Thus, we speculate that an attenuated maternal CAP could also lead to a worse prognosis of COVID-19 in pregnant women and their offspring.

In pregnancy, preclinical studies support a presumed link between cholinergic signaling in fetal brain microglia and the inflammatory state, suggesting the possibility that early disruptions in microglial iron metabolism may impair fetal neurodevelopment (Cortes et al., 2017). Owing to the changing nature of human development from childhood to adulthood, and the participation of peripheral macrophages in the synaptogenesis of brain's microglia as well as innate immune responses, other authors consider that the effects of a permanent peripheral cholinergic activation can have an effect on the programming of the brain wiring and immune function (Frasch et al., 2018).

Additionally, other findings suggest that fetal CAP activity via vagal nerve stimulation using agonists of the α7 subunit of the nicotinic acetylcholine receptor (α7nAChR) abrogates the activation of brain astrocytes and microglia, thereby restoring their physiological immunometabolic phenotype and thus preventing a sustained switch to a reactive phenotype with decreasing glial priming (Frasch et al., 2019). We speculate that a disrupted fetal or maternal CAP during COVID-19 disease may thus contribute to fetal neuroinflammation, prenatal stress, and even preterm labor.

A non-invasive psychophysiological approach to indirectly evaluate the activity of the autonomic nervous system is the analysis of HRV, which has been considered as an important "window" for understanding the neuroimmune interactions involving the vagus nerve (Huston and Tracey, 2011) and also the response to inflammatory processes (Williams et al., 2019). Thus, we propose the analysis of maternal and fetal HRV as a non-invasive, economic, and quantitative approach to reliably assess the maternal and fetal CAP and the potential MIA produced by COVID-19 disease during human pregnancy.

PERSPECTIVE

Given the possible effects on neurodevelopment that can affect human development and the quality of life, the understanding of the maternal and fetal vagal–immune pathway during a gestational infection by SARS-CoV-2, and exploring the short- and long-term psychophysiological condition of the offspring, warrant special attention. This knowledge demands the use of non-invasive and economic physiological measures to assess fetal and maternal cardiac vagal activity, such as the maternal and fetal HRV. In this context, the use of a vagal nerve stimulation (VNS) for treating COVID-19 has also been proposed (Bonaz et al., 2020; Fudim et al., 2020). By activating the vagus nerve, it has been demonstrated positive therapeutic effects on COVID-19 symptoms via anti-inflammatory mechanisms (Mazloom, 2020). Further preliminary observations suggest that VNS provides clinical benefits in patients with this disease (Staats et al., 2020). Our main perspective is that the continuous monitoring of maternal and fetal vagal activity by HRV would also be an innovative application for managing COVID-19 patients.

Currently, there is insufficient evidence of the relationship among MIA, SARS-CoV-2, the CAP, and neurodevelopmental disorders. Our manuscript aims to offer a brief perspective and hypothesizes about a potential MIA by SARS-CoV-2, which could lead to neurodevelopmental disorders. We have also considered a cytokine cross-talk between the mother and the fetus as well as the role of the CAP (**Figure 1**). We highlight the urgent necessity of creating multicenter and international databanks of maternal-fetal psychophysiological signals, obtained pre-, during, and post-infection by SARS-CoV-2 from pregnant women. Preclinical studies over long enough periods should also be conducted, allowing these disorders to appear. Other authors support the consideration that health indicators of maternal, neonatal, and subsequent development should be also monitored after *in-utero* exposure to SARS-CoV-2 (Easterlin et al., 2020). Furthermore, longitudinal recordings and offspring neurodevelopmental assessments including immunological markers are desirable to appraise long-term effects. We anticipate that the collection of such multivariate data will help to understand the neuroimmune mechanisms activated by the SARS-CoV-2 infection from a translational perspective in both pregnant women and offspring.

AUTHOR CONTRIBUTIONS

JR-L: conceived and designed the document and writing—review and editing. EA-C, JE, HM-Z, and AV-C: writing—review and editing. GP-L: conceived and designed the document, writing—review and editing, and supervision. All authors contributed to the article and approved the submitted version.

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Relationship Between Blood Cytokine Levels, Psychological Comorbidity, and Widespreadness of Pain in Chronic Pelvic Pain

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Background: Low-grade inflammation has been implicated in the etiology of depression, long-term fatigue and chronic pain. TNFα and IL-6 are perhaps the most studied pro-inflammatory cytokines in the field of psychoneuroimmunology. The purpose of our study was to further investigate these relationships in patients with chronic pelvic pain specifically. Using plasma samples from a large, well-described cohort of patients with pelvic pain and healthy controls via the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network, we examined the relationship between TNFα and IL-6 and comorbid psychological symptoms. We also investigated the relationship between IL-8 and GM-CSF, and widespreadness of pain.

Methods: We included baseline blood samples in the analyses, 261 patients (148 women) and 110 healthy controls (74 women). Fourteen pro- and anti-inflammatory or regulatory cytokines were analyzed in a Luminex® xMAP® high-sensitivity assay. We used regression models that accounted for known factors associated with the outcome variables to determine the relationship between cytokine levels and clinical measures.

Results: There were no statistical differences in cytokine levels between patients and healthy controls when controlling for age. In patients, TNFα was significantly associated with levels of fatigue ($p = 0.026$), but not with pain intensity or depression. IL-6 was not significantly related to any of the outcome variables. Women with pelvic pain showed a negative relationship between IL-8 and widespreadness of pain, while men did not ($p = 0.003$). For both sexes, GM-CSF was positively related to widespreadness of pain ($p = 0.039$).

Conclusion: Our results do not suggest low-grade systemic inflammation in chronic pelvic pain. Higher TNFα blood levels were related to higher fatigue ratings, while higher systemic GM-CSF levels predicted more widespread pain. Our study further suggests a potentially protective role of IL-8 with regard to with regard to the widepreadness of pain in the body, at least for women.

Keywords: chronic pain, pelvic pain, cytokine-immunological terms, inflammation, comorbidity

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INTRODUCTION

An estimated 50–100 million United States (US) adults suffer from chronic pain (CP) with an annual cost of over $500 billion per year, representing one of the most prevalent, costly, and disabling health conditions (1, 2). The highest-need and most impacted patients are those with high-impact chronic pain (affecting ∼20 million Americans), or pain associated with substantially restricted work, social, and self-care activities for six or more months (1, 3). Current pharmacological, interventional, behavioral, and surgical therapies for chronic pain are limited in their effectiveness (2, 3). Indeed, chronic pain—and high-impact chronic pain in particular—is often treated with prescription opioids, and is linked to opioid-use disorder. A target for future safe and effective pain treatments may in fact be the immune system and its interaction with the nervous system (4). Experimental and epidemiological studies suggest that the immune system communicates with the central nervous system. It is well-known, for example, that inflammation affects peripheral nerves by sensitizing nerve endings and increasing sensitivity to nociceptive stimuli (5, 6). Psychoneuroimmunological and immunopsychiatric research has expanded the knowledge of neuroimmune interactions, showing that inflammatory components of the immune system also interact with neurons and glial cells in the spinal cord (7, 8), and in the brain (9, 10). Some neuroimmune effects are intrinsically pathological, such as misdirected antibody attacks in rheumatoid arthritis (11) and multiple sclerosis (12). Similar pathological effects potentially trigger schizophrenic episodes over time (13). In contrast, some neuroimmune interactions are adaptive in healthy states (7, 8).

The term "sickness behavior" is often used to describe the behavioral, emotional and physiological adaptations of an organism to the invasion of pathogens (4, 14, 15). These physiological adaptations are driven by inflammatory components secreted by the immune system, and promote recovery during short-term infections. However, some of these adaptations, when dysregulated, appear to lead to complex and persistent illness, such as depressive states (16) and long-term fatigue (17, 18). The role of dysregulated neuroimmune functions in the development and maintenance of chronic pain states is well-documented on a peripheral and spinal level (5, 6, 19, 20). Chronic pain has been associated with elevated blood cytokine levels repeatedly (21), but studies are contradictory. Some cytokines are implicated in several pain disorders, while others seem more specific for a certain syndrome. We and others have suggested that the immune-driven changes, in brain function and affective states, fit mechanistically into the broader understanding of chronic pain (4). Chronic pain is particularly complex, with both physiological and psychological components. To understand how neuroimmune interactions contribute to chronic pain, it is essential to study not only how these contribute to pain intensity, but to the broader experience of pain among patients.

In chronic pain, the brain's generation of the experience of pain may, or may not be, rooted in actual physiological damage. It is believed that as acute pain transitions to chronic states, the nervous system transitions to a state in which the nervous system itself maintains the pain independently from any acute injury. In this chronic state, the pain is very challenging to effectively treat. Several mechanisms that lead to and maintain chronic pain have been suggested, of neurological, psychological and inflammatory nature (4, 22). Neurologically, peripheral and central neurons become hypersensitized, so that the neurons produce greater responses to external stimuli. Neuroimmune mechanisms are involved in this process, linking the immune system to the pain system (5). Researchers have identified sex differences in neuroimmune interactions (19, 20, 23). For example, male rodents require spinal microglial activation, while female rodents appear to use T-cell mediated activity for pain progression. For a review of peripheral and central neuroimmune mechanisms, please see (5, 6, 19, 20). Imaging studies have revealed that the brain processes pain differently once pain has become chronic. Both functional and structural spinal cord and brain changes have been identified in individuals with chronic pain vs. healthy individuals (24–28). Further, these differences in brain structure and function suggest that the brain processes chronic pain differently than acute pain [for an overview see (22, 29–31)]. Some of the areas of identified changes in chronic pain include brain regions involved in emotional process, linking pain to other psychological process, such as anxiety, catastrophizing and depression (26, 32). This indicates that the pain experience, from a subjective and emotional point of view, changes as the pain becomes inescapable and persistent for the afflicted individuals. Conversely, the presence of chronic pain itself increases risk of developing, or worsening, psychiatric problems, creating a vicious circle once the chronic pain state takes hold. Similarly, from a neuroimmune perspective, overlapping neuroimmune influences on the relationship between pain and depression have also been suggested (33, 34). Further, epidemiological and clinical studies show that prior anxious and depressed tendencies, and stress, are risk factors for developing chronic pain (35–39). Few pain syndromes can be explained, or treated, targeting a single mechanism. Peripheral low-grade inflammatory activity may be one of the mechanisms involved in the complexity of chronic pain mechanisms (21). Large-scale peptide analyses suggest ongoing inflammatory activity both centrally and peripherally (40–42) in chronic pain populations. In some studies, the levels correlate with clinical assessments, but not in all, and the focus is often on pain intensity, as this is what one primarily would like to decrease and control. Adding to the challenges, reported cytokines vary between different types of chronic pain and are sometimes even inconsistent across research studies of the same chronic pain condition.

Interestingly, inflammation affects many brain areas that are also involved in pain processing and chronic pain states (9, 10, 43, 44). For example, the insula, the anterior cingulate cortex, amygdala and prefrontal cortices are involved in pain processing and are activated during inflammation. Inflammation has also been shown to directly affect mood, and pain sensitivity in acute inflammatory models. In these models, increased anxiety, depressed mood, and fatigue occur during immune activation (45–47). During immune activation the inflammatory effects are of peripheral origin, but the inflammatory signals

are transmitted to the central nervous system (7). These inflammatory signals are transmitted to the brain in a controlled manner via a few dedicated pathways (8). These pathways include the passive transfer of cytokines via brain regions that lack the blood-brain-barrier (BBB), active transport and signaling across the BBB, as well as direct neural signaling, such as via the vagus nerve (14). To improve our understanding of the role of inflammation in chronic pain, we explored the relationship between low-grade inflammation, pain intensity, and psychological measures in patients with chronic pelvic pain. We based our study on hypotheses generated from research on experimental inflammatory models and epidemiological research on populations with inflammatory disease. We had access to a unique sample of blood plasma from chronic pelvic pain patients via the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network and the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) (48, 49). Standardized sampling procedures ensured high quality plasma samples from a large and well-characterized population of patients with pelvic pain and healthy controls (49). The exact mechanisms that contribute to chronic pelvic pain are still poorly understood, and the MAPP Research Network plays an integral part in advancing understanding of chronic pelvic pain. Historically, chronic pelvic pain has not been largely considered an inflammatory pain disorder. Overall, the population is characterized by a large variation in comorbid pain diagnoses, how widespread the pain is, and psychological comorbidity, as is generally seen in chronic pain populations (28, 50, 51). Prior studies from the MAPP Research Network point to similar levels of pain intensity and psychological comorbidity between men and women with chronic pelvic pain, but more widespread distribution of pain across the body and more comorbid pain diagnoses amongst women (52). Disease severity has been associated with urine markers, such as matrix metalloproteinase (MMP)-2, MMP-9, Lipocalin 2 and vascular endothelial growth factor (VEGF) (53). Regarding blood measures, one prior study showed higher IL-6 levels, but no association with clinical measures, in a subsample of 58 women with chronic pelvic pain (54). However, levels of immunoreactivity, that is, the levels of pro-inflammatory cytokines expressed by immunologically provoked white blood cells, predicted worse outcomes and more pain (54, 55) in women with chronic pelvic pain.

Our primary goal in this cross-sectional study was to assess a broad range of peripheral inflammatory cytokines and characterize cytokine patterns in chronic pelvic pain. Our secondary goal was to characterize the relationship of blood levels of cytokines with pain intensity, widespreadness of pain, and psychological measures in chronic pelvic pain. We hypothesized that inflammatory effects would be more subtle than the well-established variables important for pain, such as stress or anxiety. Yet, inflammatory activity may contribute to biological and psychological aspects of chronic pain, not only affecting the neurons directly, but also impacting psychological well-being in a broader sense. We hypothesized that the pelvic pain group would have higher inflammatory levels in the blood compared to healthy controls (54), and that women in the pain group would have higher inflammatory cytokine levels than men. Furthermore, we hypothesized that TNFα and IL-6 levels would correlate with depressive mood (47, 56, 57) and fatigue (17, 45, 58), when controlling for other psychological factors that are well-established covariates for pain, but not with pain intensity (54, 55). We further hypothesized that higher IL-8 levels would predict more widespread pain, because higher IL-8 levels, both centrally and peripherally, are implicated in several studies of the prototypical widespread pain disorder, fibromyalgia (59–61). As previous MAPP research found that TLR-4 inflammatory response was associated with widespread pain (55), we also performed exploratory analyses on the relationship of the other cytokines in our panel and the widespreadness of pain.

METHODS

Study Design

The MAPP Research Network is a unique project studying chronic pelvic pain using both subjective (e.g., self-reported survey data) and objective, or quantitative, measures (e.g., neuroimaging scans, blood biomarkers) (49). The project has collected data from 424 (233 women, 191 men) individuals with chronic pelvic pain, 415 healthy controls and 200 patient controls (e.g., irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome). Blood samples, surveys and neuroimaging data were collected at up to four timepoints. For study and sampling details, please see (49, 62).

Participants

From the whole MAPP sample, participants were primarily included for plasma analysis based on the presence of neuroimaging data and timing of blood draw with neuroimaging data (used for other analyses). In total, 304 (166 f, 138 m) samples from patients with chronic pelvic pain and 110 (74 f, 36 m) healthy control samples were analyzed for plasma cytokines (**Table 1**). All of these individuals are included in the analyses that compare the chronic pelvic pain group with the healthy controls. However, all surveys were not included at all scanning time points, which is why the number of responses vary for the surveys in **Table 2**. For the regression analyses exploring the relationship between cytokine levels and subjective ratings, only patients that sampled blood at baseline are included (261 total, 148 f, 113 m), as this is when the pain intensity and stress ratings were matched with the blood sample, to ensure timely matching between ratings and blood markers.

Subjective Ratings

Differences in subjective ratings between groups have been reported and discussed thoroughly before (50–52, 63, 64) and are thus not discussed in this study. Survey measures include The Brief Pain Inventory (BPI) Pain Severity Scores (65, 66), the Hospital Anxiety and Depression Scale (HADS) (67), NIH Patient Reported Outcomes Measurement Information System (PROMIS) Fatigue (7-items) Score (68), the 10-item Perceived Stress Scale (PSS) (69), and the adapted BPI body map for numbers of pain sites (70) [for further details see (49)].

TABLE 1 | Median cytokine levels of the pain group vs. the control group.

Variable	Pelvic pain group median (IQR)	Healthy controls median (IQR)	*P*	*P* adjusted for age
GM-CSF	34.38 (20.94–58.06)	36.72 (24.34–69.88)	0.064	0.314
IFNγ	7.06 (4.13–10.87)	7.80 (4.29–10.66)	0.562	0.464
IL-1β	2.06 (1.41–3.36)	2.16 (1.36–3.60)	0.568	0.550
IL-2	2.4 (1.44–3.82)	2.35 (1.59–4.56)	0.244	0.314
IL-4	11.39 (8.28–15.20)	12.34 (8.58–16.71)	0.075	0.149
IL-5	1.13 (0.77–1.43)	1.23 (0.88–1.63)	0.028	0.089
IL-6	0.87 (0.61–1.25)	0.83 (0.63–1.19)	0.860	0.834
IL-8	3.98 (3.17–5.13)	3.98 (3.04–4.99)	0.380	0.959
IL-10	3.14 (2.06–4.55)	3.25 (2.31–4.39)	0.313	0.743
IL-12 (p70)	1.58 (1.05–2.42)	1.74 (1.07–2.54)	0.455	0.702
IL-13	2.50 (1.57–3.54)	2.63 (1.63–3.87)	0.592	0.806
IL-17A	9.88 (5.74–13.92)	10.25 (6.1–14.69)	0.325	0.331
IL-23	137.83 (87.02–289.14)	184.35 (99.56–325.58)	0.095	0.272
TNFα	4.14 (3.35–5.25)	3.81 (3.26–4.58)	0.024	0.216

Interquartile range and p-value for Mann-Whitney U-test presented.
IL, interleukin; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; TNF, tumor necrosis factor.

TABLE 2 | Overview of the covariates of interest in the two groups (mean and standard deviation), and proportion of patients with comorbid pain diagnoses (%).

Variable	Pelvic pain group Mean (SD)	Healthy controls Mean (SD)
Age	43.47 (14.89)	36.64 (11.45)
BMI	26.33 (5.55)	25.2 (5.02)
Anxiety	7.44 (4.52)	3.52 (2.85)
Depression	5.13 (4.10)	1.47 (2.24)
Fatigue	18.63 (5.42)	12.58 (3.68)
Stress	15.98 (8.03)	9.59 (5.96)
Pain intensity	3.82 (1.9)	0.17 (0.39)
Number of pain sites	5.54 (6.36)	0.69 (1.3)
Comorbid pain diagnoses[a]	55.1 %	

[a]*Collected in the MAPP study: Fibromyalgia, irritable bowel syndrome, migraine, chronic fatigue, vulvodynia, temporomandibular joint dysfunction. Please see references (49) for more information and deeper analysis.*

Cytokine Analysis

All samples were collected at the same time in the morning at nine different study sites, and handled and shipped in a standardized manner (49, 62, 71). The samples were not fasting samples. The Human High Sensitivity T-Cell Discovery Array 14-plex Luminex® xMAP® assay (Millipore MILLIPLEX, Eve Technologies Corp, Calgary, AB, Canada) was used for cytokine analysis (single samples). The cytokines included in the assay were granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon gamma, Interleukin (IL)-1beta, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-13, IL-17A, IL-23 and tumor necrosis factor (TNF) α. For sensitivity and accuracy measures, see **Supplementary Table 1**.

Statistical Analysis

Mean values for cytokines, age and BMI were calculated. A Mann-Whitney significance test was performed for the cytokines due to non-normal distribution (IBM SPSS Statistics version 25). When controlling for age and BMI, regression analysis and the log-transformed cytokine values (see below) were used.

In order to determine the relationship between cytokine levels and clinical measures, we used regression models that accounted for known factors associated with the outcome variables: age, sex, BMI, pain intensity, stress, anxiety, depression, and fatigue (adapted for the respective outcome variable). For all cytokines, the log-transformed values are used to normalize the distribution. A generalized linear mixed model with log gamma models was chosen to account for clustering of chronic pelvic pain patients within sites, skewed distribution, and heteroscedastic errors. Dependent variables were pain intensity, depression, and fatigue. In these analyses, extreme values were not excluded, but the regression models were performed with and without extremes. The results from the regression models were visually inspected to ensure that the relationships were not driven by one or a few participants.

RESULTS

The mean values of TNF-a and IL-5 differed between groups, but these differences were not statistically significant when adjusting for age, which differed between the patients with chronic pelvic pain and the healthy controls (**Table 1**). Adjusting for BMI and sex, which also differed between groups, had no effect on the outcome. Mean values of the variables of interest are presented in **Table 2**. Spearman correlation for the cytokines are presented in **Supplementary Table 2**.

In the patient group, TNFα was significantly associated with levels of fatigue (0.22 [0.03 0.41] $p = 0.026$), but not with

TABLE 3 | Relationship between TNFα and IL-6, respectively, to fatigue, depression and pain intensity.

Fatigue	B (CI)	*P*	Depression	B (CI)	*P*	Pain intensity	B (CI)	*P*
TNFα			**TNFα**			**TNFα**		
(Intercept)	2.17 (1.97 2.38)	<0.001	(Intercept)	−0.33 (−0.77 0.70)	0.929	(Intercept)	0.78 (0.28 1.28)	0.002
Sex	0.12 (0.07 0.18)	<0.001	Sex	−0.39 (−0.58 −0.19)	<0.001	Sex	0.08 (−0.06 0.21)	0.240
Age	0 (0)	0.351	Age	0.01 (0 0.01)	0.082	Age	0 (−0.01 0)	0.192
BMI	0 (0)	0.160	BMI	−0.01 (−0.02 0)	0.285	BMI	0.01 (−0.01 0.02)	0.314
Anxiety	0 (0)	0.396	Anxiety	0.02 (0.01 0.05)	0.208	Anxiety	−0.01 (−0.03 0.02)	0.501
Depression	0.02 (0.01 0.03)	<0.001	Fatigue	0.05 (0.03 0.08)	<0.001	Depression	0.05 (0.02 0.07)	0.000
Stress	0.01 (0.01 0.02)	<0.001	Stress	0.04 (0.02 0.06)	<0.001	Fatigue	0.02 (0 0.03)	0.034
Pain intensity	0.02 (0.00 0.04)	0.018	Pain intensity	0.07 (0.02 0.12)	0.008	Stress	0 (−0.02 0.01)	0.661
TNFα	0.22 (0.03 0.41)	0.026	TNFα	−0.02 (−0.74 0.70)	0.960	TNFα	−0.09 (−0.57 0.40)	0.722
IL-6			**IL-6**			**IL-6**		
(Intercept)	2.32 (2.13 2.52)	<0.001	(Intercept)	−0.19 (−0.86 0.48)	0.578	(Intercept)	0.75 (0.32 1.18)	0.001
Sex	0.12 (0.07 0.18)	<0.001	Sex	−0.40 (−0.59 −0.20)	<0.001	Sex	0.08 (−0.05 0.21)	0.225
Age	0 (0)	0.473	Age	0.01 (0 0.01)	0.060	Age	0 (−0.01 0)	0.188
BMI	0 (0)	0.082	BMI	−0.01 (−0.03 0.01)	0.250	BMI	0.01 (−0.01 0.02)	0.333
Anxiety	0 (0)	0.401	Anxiety	0.02 (−0.01 0.05)	0.201	Anxiety	−0.01 (−0.32 0.14)	0.455
Depression	0.02 (0.01 0.03)	<0.001	Fatigue	0.05 (0.03 0.08)	<0.001	Depression	0.05 (0.02 0.07)	0.000
Stress	0.01 (0.01 0.02)	<0.001	Stress	0.04 (0.02 0.06)	<0.001	Fatigue	0.02 (0 0.03)	0.050
Pain intensity	0.02 (0.00 0.03)	0.038	Pain intensity	0.08 (0.02 0.13)	0.005	Stress	0 (−0.02 0.01)	0.730
IL-6	−0.03 (−0.08 0.02)	0.250	IL-6	0.12 (−0.04 0.28)	0.146	IL-6	−0.14 (−0.42 0.14)	0.327

Means, 95% confidence intervals and p-values for the models including TNFα and IL-6 presented.
The estimates represent the change in relation to log transformed values of the cytokine analysis.

pain intensity, depression, or widespreadness of pain in the full regression model (**Table 3**). Sex was significantly associated with fatigue, however, the added interaction term sex × TNFα was not significant. Thus, sex differences were not implicated in the relationship between TNFα levels and fatigue (i.e., how fatigued the patient felt as the time of blood draw). IL-6 was not associated with any of the dependent variables.

IL-8 was showed a negative relationship with widespreadness of pain, that is, lower IL-8 levels were associated with more pain sites across the body (−0.44 [−0.87 −0.02] $p = 0.039$). This relationship was driven only by women with chronic pelvic pain (−1.30 [−2.14 −0.045] $p = 0.003$, **Table 4** and **Figure 1**).

In the explorative analyses, GM-CSF showed a positive relationship with the widespreadness of pain (i.e., number of pain sites across the body) (−0.36 [−0.70 −0,02] $p = 0.039$) (**Table 4**), suggesting that higher GM-CSF levels predicted more widespread pain. The association between GM-CSF and widespreadness of pain was not sex dependent.

Robustness of the Regression Models

Simple models with only sex, age, and BMI as covariates did not show an association between TNFα and fatigue, or between GM-CSF and number of pain sites, however the significant findings for IL-8 and widespreadness of pain remained (**Supplementary Table 3**). Models adding medicine usage at the time of the lab visit and duration of pain in years, variables that may in theory also be related to the investigated outcome variables, did not improve the model fit or change the results in any significant way. As these analyses were exploratory, we did not control for multiple comparisons.

DISCUSSION

Our aim was to characterize cytokine blood levels in patients with chronic pelvic pain and relate cytokine levels to clinical characteristics. We used a high-sensitivity cytokine panel, as it is known that cytokine levels in patients with chronic pain resemble the levels in healthy individuals, as compared to acutely inflamed patient groups, such as cancer patients. The 14 pro- and anti-inflammatory cytokines in the panel have been implicated previously in chronic pain research. We could not show a difference in any of the analyzed systemic cytokines between patient and healthy controls, when controlling for age and BMI. Prior findings from the Research Network reported higher IL-6 levels in chronic pelvic pain compared to healthy controls (54) in a subgroup of women with pelvic pain, which was not replicated in this larger group including both sexes. Overall, our results suggest that this patient population does not seem to suffer from an ongoing low-grade inflammation. However, in the patient group, we saw a positive relationship between TNFα levels in the blood and subjectively rated fatigue levels. Higher TNFα levels were associated with more fatigue in both men and women with chronic pelvic pain. TNFα-levels were not related to depression scores or pain intensity, nor was IL-6.

Low or normal blood levels may not be the crucial point when looking into relationships between immune markers and clinical

TABLE 4 | Relationship between IL-8 and GM-CSF and the widespreadedness of pain in the patient group.

No. of sites with pain	B (CI)	*P*
IL-8		
(Intercept)	−1.14 (−2.19 to 0.08)	0.036
Sex	1.06 (0.5 to 1.6)	< 0.001
Age	0 (−0.01 to 0)	0.399
BMI	0.01 (−0.0to 0.03)	0.177
Anxiety	0.02 (0.02 to 0.05)	0.432
Depression	0 (−0.03 to 0.04)	0.890
Fatigue	0.06 (0.03 to 0.08)	< 0.001
Stress	0 (−0.02 to 0.03)	0.909
Pain intensity	0.03 (−0.3 to 0.09)	0.355
IL-8	1.44 (0.09 to 2.78)	0.036
Sex * IL-8	−1.30 (−2.14 to 0.45)	0.003
GM-CSF		
(Intercept)	0.31 (−0.58 to 1.20)	0.493
Sex	0.34 (0.12 to 0.57)	0.004
Age	0 (−0.01 to 0)	0.283
BMI	0.01 (−0.01 to 0.03)	0.274
Anxiety	0 (−0.04 to 0.04)	0.961
Depression	0.01 (−0.03 to 0.05)	0.586
Fatigue	0.05 (0.02 to 0.08)	< 0.001
Stress	0.01 (−0.01 to 0.04)	0.610
Pain intensity	0.02 (−0.04 to 0.08)	0.460
GM-CSF	−0.36 (−0.70 to 0.02)	0.039

Means, 95% confidence intervals and p-values for the models including IL-8 and GM-CSF presented. The estimates represent the change in relation to log-transformed values of the cytokine analysis.

aspects in chronic pain. Theoretically, low levels of circulating signaling molecules could induce a stronger response in a primed immune system. Immunoreactivity can be assessed by provoking cytokine-producing immune cells in some way, for example, by inflammatory stimuli such as lipopolysaccharides, or stress stimuli such as glucocorticoids, or specific receptor ligands. The provoked response shows how reactive, or primed, the immune system is, despite low-grade systemic activity under normal circumstances. From the MAPP initiative, there is evidence that immunoreactivity is enhanced in individuals with chronic pelvic pain, at least in women (54, 55, 72), and that this exaggerated immunoreactivity is associated with comorbid symptoms and the lack of disease resolution over time. TNFα levels in chronic pelvic pain patients may be specifically important for the feeling of fatigue. For patients with chronic pain, the profound fatigue that many experience can be almost as debilitating at the pain itself (73). Patients describe the fatigue as different and more pronounced than normal fatigue, and with stronger cognitive effects than fatigue experienced under healthy circumstances (17, 74). In individuals with rheumatoid arthritis, anti-cytokine treatments are effective for fatigue, in addition to pain-relieving and anti-inflammatory benefits (75). However, over time, long-term fatigue often persists even when the rheumatoid arthritis swelling and pain are under control (76). Mechanistically, inflammation-driven fatigue is yet to be fully explained (17), but the phenomenon is increasingly being recognized, and several potential pathways have been suggested. These potential pathways of inflammation-driven fatigue include mechanisms of oxidative stress and mitochondrial dysfunction (77), as well as an imbalance in energy availability and expenditure driven by inflammation-induced insulin resistance (74). However, it is important to note that these mechanisms are rather distinct from potential pathways of inflammation-driven pain.

In contrast, for chronic pain and depression, several common neuroinflammatory pathways have been proposed (33, 34). One of the most interesting pathways with regard to both pain and depression, may be the kynurenine and tetrahydrobiopterin (BH4) pathways (78, 79). BH4 blockers show promising treatment abilities with few side effects for pain (80). These interacting pathways are readily affected by peripheral inflammation, and they limit the availability of several monoamines, including serotonin. In pain research, the main location of study of immune-to-CNS connections is the spinal cord, while in depression research, the study of immune-to-CNS connections is focused on the brain. It is not known how the crosstalk and regulation between spinal cord and brain areas occur for neuroimmune communication. However, for pain processing, the communication between spinal cord and brain is constant and bi-directional. Despite neuroimmune overlap between pain and depression, our findings did not suggest a relationship between pro-inflammatory blood levels and depressive states in chronic pelvic pain. It should be noted that none of the patients suffered from clinical depression. Only ten individuals had HADS scores of 11 or higher, which would be the cut-off for suspected clinical depression (67, 81). In experimental inflammatory models, depressed mood is readily induced by immune activation (14, 15). In these models however, the peak blood cytokine levels are higher than in the chronic pelvic pain population. With regard to clinical depression, the connection to inflammatory activity is undisputable (56, 57, 82, 83), but the relationship is complex and potentially only relevant for a subgroup of clinically depressed patients. For the studied patient group of non-inflammatory chronic pelvic pain and relative psychological health, immune-driven depressive mood may not be a major concern.

In individuals with chronic pain, an important clinical feature is where pain is felt across the body. In general, as the distribution of experienced pain is more widespread across the body of an individual, this can contribute to greater suffering and greater challenges in finding successful treatment options. Fibromyalgia is a chronic pain condition characterized by widespread pain across the body. Several studies of fibromyalgia implicate a role for IL-8, a pro-inflammatory cytokine (59–61). We therefore aimed at understanding the relationship of IL-8 and widespreadness of pain in our cohort of individuals with chronic pelvic pain. Among the women with chronic pain in our study cohort, we did see a relationship between IL-8 levels and number of painful body sites. However, the relationship was opposite to our hypotheses, with lower IL-8 levels peripherally related to greater widespreadness of pain. This suggests that IL-8 could have

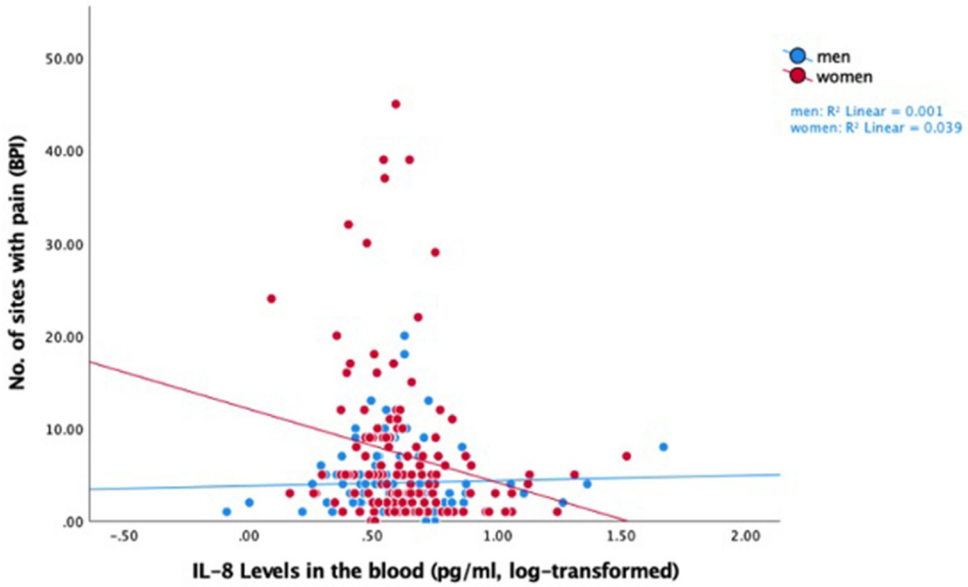

FIGURE 1 | Raw data scatter plot of the relationship between log-transformed IL-8 levels and widespreadness of pain, for men and women in the pelvic pain group.

a protective role in chronic pelvic pain, at least in women, and in pain conditions that are not characterized by high peripheral inflammatory activity. We are not aware of any studies that report such an inverted and sex-dependent relationship for blood IL-8 levels, but a previous study in osteoarthritis patients reported a negative relationship for CSF IL-8 levels with both physical function and quality of life measures (84). On the contrary, GM-CSF levels appeared to have a non-protective, pain exacerbating role, with lower GM-CSF predicting less widespreadness of pain in our chronic pelvic pain population. This correlation was not sex dependent. GM-CSF is an immunoregulatory cytokine that can tap into pro- and anti-inflammatory pathways in feedback loops and has a key role in homoeostasis and pathogen clearance. However, GM-CSF has been implicated in several inflammatory and autoimmune disorders. GM-CSF is believed to play a critical role in both the resolution of inflammatory responses, as in the development of chronic inflammation [for an overview see (85–87)]. With regard to pain, the actions of the GM-CSF cytokine appear somewhat contradictory. Anti GM-CSF treatment seems promising in inflammatory pain states, such as rheumatoid arthritis and osteoarthritis (88). For example, in an osteoarthritis model, GM-CSF deficient mice develop less inflammatory pain than wildtype mice (89). In contrast, lower amounts of GM-CSF expressing cells in the synovial lining are associated with greater knee pain intensity in patients with osteoarthritis (90). Additionally, lower blood levels of GM-CSF have been identified in chronic back patients compared to healthy controls (91). Teware et al. argue that while nociceptors themselves may have receptors for GM-CSF, GM-CSF may in fact modulate pain perception specifically *via* secondary, inflammatory pathways (92). Seemingly contradictory relationships between GM-CSF and depression have been identified as well. For example, one recent study found elevated GM-CSF levels in adolescent major depression (93), while a recent rodent study found that GM-CSF has anti-depressive effects (94). Ultimately, the roles of IL-8 and GM-CSF in chronic pain require further investigation.

Limitations and Future Directions

Our study has several limitations. First, we studied a limited set of cytokines with single sample analyses in plasma, and these analyses were selected as a starting point in order to achieve an overall understanding of the peripheral inflammatory state of the MAPP chronic pelvic pain patient cohort. Second, our analyses include several covariates, therefore we acknowledge a risk of overfitting the model. Nonetheless, we believe that the sample is large enough to accommodate our statistical choices. Ethnicity and other demographics were not available in this substudy of MAPP and were not included in the analyses. Furthermore, the estimates are related to log-transformed plasma cytokine levels in pg/ml, which makes them hard to interpret in a practical sense, for example, to estimate the relevance for clinical treatment. The results of this study are thus to be interpreted as potential mechanistic relationships to be further explored.

Our findings exemplify the complexity of studying blood cytokines in patient groups, particularly in cross-sectional studies. In cross-sectional studies, we get a glimpse of the current biological and psychological status of a patient, but we cannot know which "developmental stage" of the chronicity of the disease the individuals are currently experiencing. The biological networks of an organism will adapt during the course of a disease as part of allostasis. Presumably, the feedback loops lose their normal regulatory function over time as the strain on the biological systems becomes long-term or chronic. This is exemplified by the flattening of the hypothalamic-pituitary-adrenal (HPA) axis in many chronic disorders, including pain (95). This means that a higher or lower level of a cytokine

may have a different impact on the biological system it governs in the beginning of a disease, than it may have 10 years later. Furthermore, it is important to question the common assumption that increases in pro-inflammatory cytokines, and conversely decreases in anti-inflammatory cytokines, are problematic in chronic disease. Importantly, organisms would not survive without inflammation. In fact, in some aspects of disease development, increases in inflammatory activity appear to be protective. For instance, IL-8 may play a protective role in women with chronic pelvic pain as suggested by our observed relationship between lower IL-8 and greater widespreadness of pain. Finally, different cytokine networks may be responsible for pain intensity and psychological distress, as suggested by a recent study in fibromyalgia (96). A comprehensive understanding of neuroimmune mechanisms in chronic pain will require human longitudinal studies, largescale peptide analyses, and consideration of a large variety of covariates.

CONCLUSIONS

Overall, the population with chronic pelvic pain does not show a pro-inflammatory cytokine profile in the blood, but cytokine levels resemble those of healthy individuals. Higher TNFα blood levels were related to higher fatigue ratings, while higher systemic GM-CSF levels predicted more widespread pain. Widespreadness of pain in women was, contrary to our hypotheses, negatively correlated with IL-8 blood levels, suggesting a potentially protective role of IL-8. None of the studied cytokines correlated with pain intensity. We conclude that when studying inflammatory mechanisms in chronic pain, psychological measures and the spread of pain need to be considered along with pain severity.

DATA AVAILABILITY STATEMENT

All data supporting the conclusions of this article can be obtained from The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) repository. Further enquiries should be directed to the authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Stanford University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

BK: statistical analyses and drafted manuscript. All authors conceptualization and design of the study, interpretation of results, read, modified, and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.651083/full#supplementary-material

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Perceived Risk of Infection Linked to Changes in Comfort in Social Situations From Before to During the COVID-19 Pandemic

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Background: Social lives have significantly changed since social distancing measures have been implemented to prevent the spread of the coronavirus disease 2019 (COVID-19). This study aimed to investigate how our appraisal of social situations changed during the pandemic.

Methods: In two online surveys, conducted in October 2019 and April 2020, 58 participants rated their personal level of comfort for sketches depicting social situations. Situations were separately categorized according to the risk of a possible COVID-19 infection and changes in ratings were analyzed by using a repeated measures ANOVA. Moreover, potential influencing factors on the change in ratings such as perceived infection risk and social factors like regular frequency and liking of social interactions were examined.

Results: There was a significant interaction ($p < 0.001$) between time of measurement and risk category. Comfort ratings of depicted situations with low and medium infection risk were higher during the second compared to the first survey period. Ratings of high-risk situations did not change significantly, although there was a tendency toward lower ratings during the pandemic. Multiple regression analyses showed that perceived probability of short-term infection could explain variance in the change of ratings of social situations with low- and medium risk, but not perceived probability of long-term infection or social factors.

Conclusion: The results suggest that the change of participant's appraisal of the social situations during the COVID-19 pandemic relates to perceived infection risk. Both, the risk associated with the specific scenario as well as the general belief of short-term infection risk were associated with change. This change predominantly manifested in greater thought of comfort during low and medium risk situations, which might give a sense of safety during the pandemic. The finding that high-risk social situations were not rated as uncomfortable as expected must be considered with regard to the young

sample and may not be generalizable to other individuals. Further research is necessary to evaluate long-term effects on social interactions caused by global pandemics such as the COVID-19 pandemic.

Keywords: COVID-19, pandemic, social distancing, risk perception, mental health, social interactions, disease avoidance

INTRODUCTION

Since the beginning of the Coronavirus disease (COVID-19) pandemic in early 2020, our social lives have significantly changed. In most countries, social distancing measures were set in place to prevent the virus from spreading (1)[1]. Common activities that were previously considered to be pleasant, like going to a party or concert, eating at a restaurant, or even hugging or standing close to someone, now pose a potential threat to one's own and the society's health and safety. While social distancing measures are a necessary and effective intervention to keep the transmission of SARS-CoV-2 under control (2, 3), they also come with negative side effects. Several studies investigated how stay-at-home orders and social distancing measures during the first wave of the pandemic in 2020 affected mental health: Most, but not all (4) studies found negative effects on mental health (5–7), including higher levels of depression, anxiety (8), stress and tension (9), greater health anxiety, financial worry, and loneliness (10). Dawel et al. (11) found in a representative Australian sample that COVID-19-related impairments in work, financials, and social functioning were associated with reduced psychological well-being, irrespective of potential or actual exposures to SARS-CoV-2.

Apart from these effects on mental health, little is known about the consequences of social distancing guidelines and rules for our perception and appraisal of social interactions. It can be assumed that the constant threat of a potential infection may have an effect on how people perceive situations in which they engage with other persons. Anecdotally, Koren [(12), April 17] wrote in The Atlantic[2]:

> "Sometime in the past few months, as social-distancing measures tightened across the country, many of us […] discovered new, pandemic-specific tics. […] The sight of two people shaking hands. Someone touching their uncovered face. A group of people hanging out less than six feet apart. Mundane behaviors [people] would not have thought twice about previously now trigger sudden, visceral reactions—of discomfort or disgust, fear or indignation—whether they're occurring on-screen or in real life. It almost seems as if the response to the pandemic has somehow, quietly and without warning, rewired our brains."

Koren proposed that the COVID-19 pandemic had "created a collective aversion to previously innocuous behaviors and settings."

Several studies found that the perceived risk of getting infected with SARS-CoV-2 increased with the implementation of protective measures and public health messages (13, 14) and is associated with experience with the virus as well as local occurrences of SARS-CoV-2-infections (15, 16). A higher risk perception is associated with more protective behavior such as social distancing and hand washing (13, 17) and might in turn lead to a devaluation of social situations with an increased risk of infection. To this date, research on change in the appraisal of social interaction in the course of the COVID-19 pandemic has been scarce. Casoria et al. (18) conducted an online experiment in France during the first wave of the COVID-19 pandemic (March–June 2020). Among other tasks, participants rated the appropriateness of the behavior of a hypothetical person inviting friends over for dinner (norm-elicitation task) and answered questions concerning their own compliance with social distancing measures (changes in behavior). They found that reported behavior and norm perception were closely related to current social distancing rules. In a review on the regulation of interpersonal distances, Welsch et al. (19) hypothesized that social distancing rules might lead to larger interpersonal distance preferences that could persist even after the end of the pandemic. However, as far as we know, there has been no research on the change in perception of social interaction during the COVID-19 pandemic so far.

To close this gap in previous research, the current study aimed at investigating how our appraisal of social situations changed during the ongoing pandemic. To this end, we used data of an online survey which was obtained in October 2019 before the pandemic started in the context of another research project and repeated data collection during the first wave of the pandemic in April 2020 with the same subjects. This stimulus material consisted of sketches depicting different social situations which were assessed by an independent group of raters for their risk regarding possible infection with COVID-19. Participants were asked to rate how comfortable they would feel in these situations. We hypothesized that change in comfort would depend on the risk of infection as implied in the social interaction. Specifically, the reported comfort in high-risk situations should reduce contrary to situations with lower risk of infection. Furthermore, we explored how interindividual differences regarding the fear of infection, frequency and liking of social interactions were associated with a possible change in people's appraisal of social situations during the pandemic. Lastly, we aimed to investigate whether there was a connection between the change in comfort ratings and changes in mental health of participants during the pandemic.

[1]https://www.who.int/publications/i/item/overview-of-public-health-and-social-measures-in-the-context-of-covid-19.

[2]https://www.theatlantic.com/science/archive/2020/04/coronavirus-pandemic-cringe/610180/.

METHODS

The study was approved by the ethics committee of the University of Lübeck (AZ 18-078) and all subjects gave informed consent before starting each survey.

Participants

Initially, $N = 171$ participants took part in a preliminary study to evaluate stimulus material for a planned neuroimaging project on eating behavior in October 2019. Participants were recruited via the University of Lübeck's student mailing list, via a Facebook group of psychology students at the University of Lübeck and via notice boards at the universities of Lübeck and Frankfurt. Since the planned neuroimaging project will only include female subjects, only women were asked to participate in the online survey. As compensation for their participation, they were able to choose between joining a lottery for winning 20 € or receiving course credits (only applicable for psychology students). All participants who had entered their e-mail address in the first survey ($N = 170$) were contacted again in April 2020 during the first wave of the COVID-19 pandemic in Germany and asked to fill out the same survey again. Seventy participants completed it a second time. As the original preliminary study was intended as a one-time measurement only, there was no clear assignment of participants to the data. Using the demographic information (age, height, weight, subject studied, and semester), we were able to successfully and distinctly match 63 cases. Of these, five cases were excluded for the analyses because of a potential bias in the ratings—one person because she reported she had been positively tested for COVID-19 and four participants because they claimed they had rated the sketches with regard to the current pandemic (see below for details on these decisions).

Thus, the final sample consisted of 58 participants (56 female, 1 male, 1 diverse) aged 19–37 years ($M = 23.3$; $SD = 3.81$). Most of them (91.4%) were University students, the others worked in the university/university hospital context (3 physicians, 1 medical technical assistant, 1 research assistant).

Most participants (77.2%) did not know anyone personally who had been infected with SARS-CoV-2. 17.5% knew one or two infected people personally, and 5.3% knew three or more persons (maximum: 7). All participants indicated that they were complying with the social distancing rules (37.9%: rather agree; 62.1%: agree strongly) and 77.6% of them stated that they considered COVID-19 more dangerous than the common flu.

Online Surveys

The first online survey, which aimed at evaluating stimulus material for a planned fMRI project on eating behavior, was accessible on www.soscisurvey.com between October 9 and October 30 2019, i.e., long before the first headlines about COVID-19 went public (see **Figure 1**).

In the survey, participants were asked to rate 45 hand-drawn sketches of situations related or unrelated to eating according to how pleasant they found the situations (the stimulus material can be found under https://osf.io/xec9v/files/). Each sketch showed a different social situation with several persons (e.g., in the supermarket, restaurant, park, or on the street). Participants were asked to put themselves into the place of the person marked with a red arrow (see **Figure 2**). Each sketch was accompanied by a two-sentence description of the current situation (e.g., "You are on the train. You are looking for a seat."). Participants were asked three questions about each sketch: (1) "How comfortable do you feel in this situation?", (2) "How much do you feel like you're being observed in this situation?", (3) "How ashamed does this situation make you feel?". Responses were assessed on

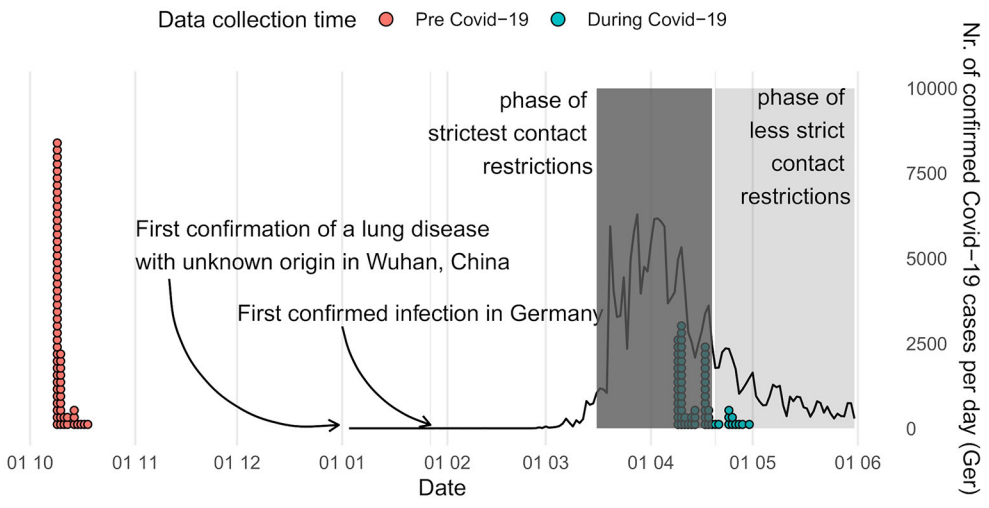

FIGURE 1 | Time of data collection and overview of the development of the COVID-19 pandemic in Germany [(20); https://covid19.who.int/table]. Contact restrictions included cancellation of mass events, ban on gatherings of more than two persons, instructions to maintain a distance of more than 1.5 m to others, school and day care center closures as well as closures of all public spaces (e.g., playgrounds) and non-essential stores. Face masks in stores and public transport became mandatory on April 27.

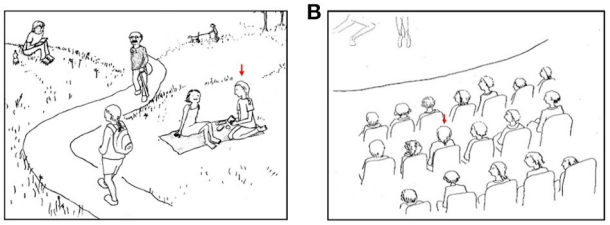

FIGURE 2 | Two examples of sketches of situations related **(A)** and unrelated **(B)** to eating. Participants were asked to imagine being the person marked with a red arrow. These sketches were accompanied by the following descriptions: **(A)** "You are at a picnic with a friend. You are eating a sandwich." **(B)** "You are at a performance. You are watching it intently".

TABLE 1 | Characteristics of the situations belonging to the three risk categories.

	Risk category		
	Low risk	**Medium risk**	**High risk**
Number of sketches	19	13	10
Compliance with social distancing rules (% Yes)	84.69	36.15	4.0
Ventilated area (% Yes)	89.47	27.69	11.0
Close physical contact (<1.5 m) for more than 15 min (number of persons), *M* (*SD*)	0.321 (0.242)	0.842 (0.299)	3.02 (3.42)
Risk of transmission by fomites (1 = low, 2 = medium, 3 = high), *M* (*SD*)	1.25 (0.244)	1.87 (0.138)	2.15 (0.178)

a scale ranging from one (e.g., "very uncomfortable") to seven ("very comfortable").

The second survey period extended from April 9 to April 30 during the first wave of COVID-19 infections and the period of the strictest social distancing measures in Germany up to that timepoint (see **Figure 1**). The goal of this second data collection was to examine changes in participants' evaluation of social situations after the beginning of the global pandemic. In order to avoid influencing the ratings and possibly creating a bias, the aim of the study was concealed from the participants before completing the survey. They were told that the purpose of the second survey was to examine the stability of the stimulus ratings over time. The first section of the survey was identical to the initial survey: Again, the same 45 sketches were presented. As described above, the sketches showed people in situations of varying social contexts and thus of varying risk of a possible COVID-19 infection. In order to stay consistent with the first survey, participants were asked the same three questions about each sketch, although only the first question ("How comfortable do you feel in this situation?") was of interest in the context of the current study. After completing the sketch ratings, participants were informed about the true purpose of the current study. Afterwards, they were asked to answer questions related to the pandemic: They were asked how much they had thought of the current situation of social distancing while rating the pictures and then, more importantly, whether they rated the sketches in regard to the current situation during the pandemic or in a general sense, i.e., unrelated to the current circumstances. This question was asked because the current study aimed to capture differences in the perceptions of social situations that are not directly tied to the global pandemic (e.g., whether the situations violated social distancing measures). Four participants reported they had rated the sketches with regard to the current pandemic and were thus excluded from further analyses. Next, participants were asked questions about how they were being affected by the virus (e.g., "How many people do you know personally, who are or have been infected with the virus?"), estimates of the likelihood they might contract or transmit the virus within the next 2 weeks/2 months/year/in their lifetime [based on (21)], attitude toward restrictions/the virus (e.g., "I am following the current social distancing rules"), usual social habits and the liking thereof (e.g., "How often do you usually have physical contact with family members/friends/work colleagues/strangers […]"), fear of infection (e.g., "Are you worried about getting COVID?"), and quality of life (e.g., "How much have the pandemic and social distancing rules and their consequences affected you quality of life?", for a full list of all questions see https://osf.io/xec9v/files/).

Categorization of Sketches

Initially, the 45 sketches had been categorized into situations related and unrelated to eating. However, for the current study a different categorization was needed regarding the contact to other persons in the situation and the associated risk for a COVID-19 infection. To classify the sketches into different risk categories, 10 lab members independently rated the potential risk of an infection for each sketch as low, medium, or high. Sketches were assigned to one of the three risk categories if at least 50% of the raters had classified them in this category. Three sketches were excluded, because there was no majority of ratings for one risk category. To further explore the reasons for the subjective feeling of risk, each sketch was additionally rated with respect to several aspects of the situation (for a full list of questions see https://osf.io/xec9v/files/), for example compliance with social distancing rules (yes/no), sufficient area ventilation (yes/no), close physical contact (<1.5 m) for more than 15 min (estimated number of people), and risk of transmission by fomites (low/medium/high). The number of sketches classified into the three categories and the corresponding mean ratings of risk-associated aspects of the situations can be found in **Table 1**.

Data Analysis

Factor analyses were performed in R (22), all other statistical analyses were performed in Jamovi (23).

To get an impression of the impact the pandemic had on the participants, we first analyzed changes in quality of life and mental health using one-sample *t*-tests against the value of the respective scale which indicated no change (see https://osf.io/xec9v/files/ for details on the questions). Furthermore, we tested whether participants worried more about getting infected

themselves or the infection of close other persons by using a paired-samples *t*-test.

Then, we tested our hypothesis about changes in the ratings of the social situations over time using a repeated measures ANOVA with the within-subject factors "time" (T1, T2) and "risk category" (low, medium, high). Mauchly's test indicated that the assumption of sphericity had been violated for the factor risk, therefore degrees of freedom were corrected using Huynh-Feldt estimates of sphericity ($\varepsilon = 0.86$). Correlations were used to evaluate the relationship between the above-mentioned mental health variables and changes in ratings over time.

Finally, we examined potential influences of the perceived probability of getting infected, the general frequency of social contacts, and the liking of social contacts on the change in the ratings of the situations of the different risk categories using multiple hierarchical regression. First, we reduced the number of covariates, because there had been several items to measure the perceived infection probability (within the next 2 weeks, 2 months, year, and in the participant's lifetime), the frequency of social contacts (with family members, friends, work colleagues, strangers at leisure activities, strangers while traveling, and strangers on commute to work or while doing essential shopping), and the liking of social contracts (with family members, friends, work colleagues, strangers at leisure activities, while traveling, and on commute to work or while doing essential shopping). Therefore, we first ran exploratory factor analyses (varimax rotation, factoring method maximum likelihood) using the "psych"-package for R (24) within the three aforementioned item blocks (infection probability, frequency of social contacts, and liking of social contacts). The number of factors were determined by parallel analysis, comparing the empirical eigenvalues to the 99th quantile of the simulated data. The four items about the perceived probability of getting infected yielded a two-factor solution. After varimax rotation (sum of squares loadings: 1.60, 1.41, proportion of variance explained: 0.40, 0.35), the items for perceived probability of getting infected within the next year and life-time loaded predominantly on one factor (loadings: 0.96, 0.70, respectively) and the infection probability for the next 2 weeks and 2 months on a second factor (loadings: 0.72, 0.90, respectively) with little cross-loadings between factors (<0.43). This suggests that people differ with respects to their perceived probability of getting acutely infected and the perceived probability of being infected in the long term. The six items about the frequency of social contacts yielded a one-factor solution (sum of squares loading: 1.98, 33% variance explained), regardless of the relationship to the other people. The factor structure of the six items about the liking of social contacts was more ambiguous but the parallel analysis favored a two factor solution, which we decided to use for further analyses. After varimax rotation (sum of squares loadings: 1.40, 1.16; proportion of variance explained: 0.23, 0.19), the two factors reflected individual differences in liking of meeting friends or people during leisure activities, and during traveling in one factor (loadings: 0.42, 0.99, 0.44; cross-loadings <0.29) and liking of meeting with family, work colleagues and commuting/shopping in another factor (loadings: 0.36, 0.86, 0.44; cross-loadings <0.14). Bartlett factor scores were extracted from all three factor analyses, resulting in five variables (two for perceived infection risk, one for frequency of social contacts, and two for liking of social contacts). These five variables were then used in the regression analyses to explain individual differences in change of comfort. Three individuals had to be excluded because they had not answered all questions regarding perceived infection risk, frequency or liking of social contacts, and factor scores could thus not be computed. Regression analyses were built for comfort ratings of each of the three risk categories separately using the following two-step procedure: The first model included confounding factors related to individual differences in social behavior ("social factors model"): (1) frequency of experiencing social interactions, (2) liking of work and family interaction, and (3) liking of social interactions during leisure time, holidays, and interactions with friends. The second model included the factors of interest related to perceived risk of infection ("infection risk factors model"): (4) perceived probability of short-term and (5) long-term infection risk. Model comparisons were conducted to compare the relative explanatory power between both sets of predictor variables.

RESULTS

Reported Impact of the Pandemic on Quality of Life and Mental Health

Since the beginning of the pandemic participants had felt a decrease in their quality of life, deterioration of their mood, as well as an increase in tension and stress, while there was no significant change in anxiety, sleep, or alcohol consumption (see **Table 2**). A paired-samples *t*-test showed that participants were significantly more worried that persons close to them might get infected with SARS-CoV-2 ($M = 3.245$, $SD = 0.96$) than they were about their own possible infection [$M = 2.26$, $SD = 0.93$; $t_{(57)} = -11.0$, $p < 0.001$].

Changes in Ratings From Before to During the Pandemic

There was a significant main effect of the factor time [$F_{(1,57)} = 5.82$, $p = 0.019$, $\eta_p^2 = 0.093$], but no significant main effect of risk

TABLE 2 | Reported changes in quality of life and mental health since the beginning of the pandemic.

	M (*SD*)	*t*	*df*	*p*
Quality of life	2.51 (0.69)	16.6	56	<0.001
Mood	3.51 (0.91)	4.23	56	<0.001
Tension and stress	3.46 (0.98)	3.50	56	<0.001
Anxiety	3.14 (0.61)	1.74	56	0.088
Sleep	3.14 (0.90)	1.18	56	0.242
Alcohol consumption	2.93 (0.78)	−0.64	56	0.498

Responses were given on a 4-point Likert scale for quality of life (1 = not affected; 4 = very strongly affected) and a 5-point Likert scale for all other items (For mood and sleep: 1 = significantly improved; 3 = unchanged; 5 = significantly worsened. For tension and stress, anxiety, and alcohol consumption: 1 = significantly less; 3 = unchanged; 5 = significantly more).

category [$F_{(1.72,98.25)} = 3.10$, $p = 0.057$, $\eta_p^2 = 0.052$]. However, there was a significant interaction between time and risk category [$F_{(2,114)} = 24.26$, $p < 0.001$, $\eta_p^2 = 0.299$]. *Post-hoc t*-tests showed that situations of low and medium risk were rated significantly more comfortable in the second survey [low risk: $t_{(57)} = -2.83$, $p = 0.006$; medium risk: $t_{(57)} = -4.91$, $p < 0.001$], while ratings for situations of high risk did not differ significantly between the two surveys, $t_{(57)} = 1.65$, $p = 0.105$ (see **Figure 3**).

To analyze whether changes in ratings of the sketches were associated with reported changes in mental health, correlations were calculated. None of the variables mentioned above (quality of life, mood, tension/stress, anxiety, sleep, and alcohol consumption) correlated with changes in ratings ($0.11 < p < 0.995$).

Influences of Individual Differences in Social Behavior and Perceived Probability of Infection on Change in Comfort

To assess the potential impact of individual differences on the change of the level of comfort in situations of the three different risk categories, we explored associations with individual frequency and liking of social interactions (social factors) as well as perceived probability of infection (infection risk factors) using model comparisons in multiple regressions. Results indicated that the social factors did not significantly explain variance in the change of comfort for neither risk category (see **Table 3**). However, the model which additionally included the infection risk factors had a significant increase in the explained variance for the low [$\Delta R^2 = 0.12$, $F_{(2,49)} = 3.70$, $p_{adj} = 0.048$] and medium risk situations [$\Delta R^2 = 0.19$, $F_{(2,49)} = 5.93$, $p_{adj} = 0.015$]. *Post-hoc* examinations of the individual predictors in the model showed that only the associations with the perceived short-term probability of infection were significant for both the low ($B = 0.23$, $SE = 0.08$, $t_{(49)} = 2.693$, $p_{adj} = 0.015$, $\beta = 0.35$, 95% CI: [0.09;0.62]) and medium-risk ($B = 0.27$, $SE = 0.09$, $t_{(49)} = 3.20$, $p_{adj} = 0.006$, $\beta = 0.42$, 95% CI: [0.16;0.68]) situations. For high-risk situations, the infection risk model did not explain variance in the change of comfort significantly (see **Table 3**). All *p*-values were corrected for multiple comparisons between the three models using the Benjamini-Hochberg-procedure (25), as implemented in the "stats"-package for R. For detailed model fit indices and estimates for individual predictors please see **Supplementary Tables 1–3**.

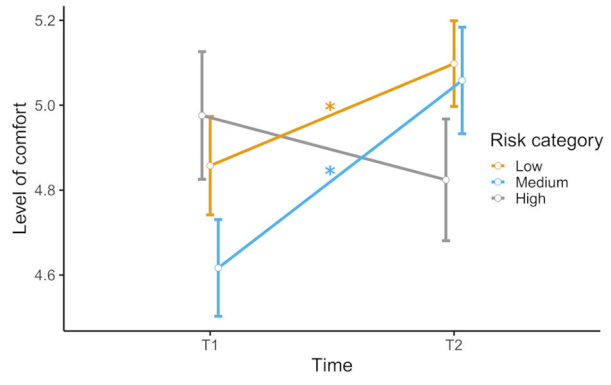

FIGURE 3 | Rated level of comfort in low-, medium-, and high-risk scenarios before (T1) and during (T2) the COVID-19 pandemic. Error bars indicate standard error (S.E.). Significant comparisons of T1 and T2 are indicated by asterisks.

DISCUSSION

The COVID-19 pandemic and its ramifications have had a substantial impact on people's lives all over the world. The effects on mental health have been the object of several studies. Most studies found negative effects on mental health (5–7), including higher levels of depression, anxiety (8), stress and tension (9), greater health anxiety, financial worry, and loneliness (10). Here we extend on these findings and show how the threat of a SARS-CoV-2 infection and social distancing measures have affected people's perception and appraisal of social interactions from before to during the COVID-19 pandemic.

Our main finding is that comfort ratings of social situations changed from before to during the first wave of the COVID-19 pandemic and this change depended on the risk of infection. Importantly, this change in comfort could be explained by the perceived short-term risk of infection.

The general pattern well-reflects the prior assumption that change in the appraisal of social situations varies according to the inherent risk of infection and depicted violations of social distancing rules, however, our findings also deviate from initial anecdotal observations. While the rated level of comfort increased for low and medium risk situations, there was no statistically significant change in the ratings of high-risk situations, although there was a tendency toward a lower level of comfort during the pandemic. The negative appraisal of high-risk situations could not be confirmed by our findings. One possible explanation for these results might be that participants were asked to rate rather abstract drawn sketches of social situations,

TABLE 3 | Outcomes of multiple regression analyses for all three risk categories with differences in ratings of the sketches as outcomes and factor scores from factor analyses (of variables on perceived probability of infection, frequency of social contacts, and linking of social contacts) as regressors.

	Social factors (M1)			Infection risk factors (M2)		
	F (*df*)	*p* (adj.)	Δ*R2*	*F* (*df*)	*p* (adj.)	Δ*R2*
Low risk	1.30 (3, 51)	0.283 (0.849)	0.07	3.70 (2, 49)	0.032 (0.048)	0.12
Medium risk	0.11 (3, 51)	0.953 (0.953)	0.01	5.93 (2, 49)	0.005 (0.015)	0.19
High risk	0.25 (3, 51)	0.863 (0.953)	0.01	0.55 (2, 49)	0.581 (0.581)	0.02

The "Social Factors" model served as baseline model and contained the three factor scores representing individual differences in the general frequency of social interactions, liking of interaction at work and with family, liking of interactions with friends, and liking of social interaction during leisure time. The "Infection Risk Factors" model additionally included two variables representing the perceived short-term or long-term probability of infection with SARS-CoV-2. Adj.: adjusted p-value after Benjamini-Hochberg-correction for comparison between the three models.

which might not be able to elicit as strong responses as real situations or seeing social interactions on TV. Furthermore, our sample consisted of young participants (all younger than 38 years) based in Northern Germany, an area in Germany that was not severely affected by the pandemic during the time of data acquisition. Even though they reported a negative effect of the pandemic or, more likely, the social distancing measures on their mental health, they were more worried about people close to them (presumably older relatives) getting infected than they were about themselves. Thus, imagining themselves in the portrayed situations may not have seemed too threatening as it might have been for people belonging to a high-risk group. Additionally, history effects could contribute to the observed differences. It is possible that the perceived comfort of social situations in such kind of thought experiment might increase in context of social deprivation. Such changes in the appraisal of social interactions should overlay the changes associated with infection risk and might generally attenuate ratings toward being more positive as they would fulfill their need for being socially integrated. Such confound would result in a similar response pattern as observed here with high-risk social situations not being evaluated as uncomfortable as initially hypothesized. The high-risk situations in our sketches consisted mainly of social gatherings such as parties and eating out at restaurants. Considering the fact that participants stated that they had rated the sketches in a general sense and not in regard to the current pandemic, the typical desirability of those kinds of situations might have outweighed the negative connotation during an ongoing pandemic.

The change in appraisal of social situations during the pandemic seems to be more apparent in low- to medium-risk social situations in our study. In this context it is important to note that we found the perceived probability of short-term infection, but not the frequency or liking of social contacts or the perceived probability of infection in the long term, to explain variance in the change of ratings of low- and medium risk social situations. The higher participants rated the probability of getting infected in the upcoming weeks the more comfortable low- and medium-risk situations were rated during the pandemic compared to before. These findings support the notion that pandemic-related cognitions affect the different appraisal of social scenarios. The increased motivation for and implementation of protective measures due to a heightened perceived risk of infection with SARS-CoV-2 (13, 17) possibly lead to a higher valence of lower risk social situations that are more in line with personal self-restraint intentions (14). It might thus be the case that lower risk situations were more appreciated during the first wave of the pandemic because they give a sense of safety. Policy makers should keep this mechanism in mind, as individual risk perception seems to play an important part in the adherence to social distancing measures. Thus, a clear communication by authorities which aspects of a situation are most important for viral transmission might increase compliance with preventive measures by influencing risk perception and (dis-)liking of situations with these characteristics.

Similar to previous findings (5–7, 9), participants reported a decrease in their quality of life and a deterioration of mood, as well as an increase in tension and stress and a tendency toward increased anxiety. There was no significant change in quality of sleep or alcohol consumption. None of these variables correlated with changes in ratings of the depicted social situations.

To our knowledge, this study is the first examining the change of people's appraisal of social situations during the COVID-19 pandemic. One of its strengths is that there was data available collected before the pandemic which could be compared to data collected from the same subjects during the first wave of the pandemic. However, this advantage also comes with the limitation that the sketch material was originally designed for another purpose. Thus, risk categories had to be defined retrospectively and comprised a varying number of sketches. Also, there was no data on participant's mental health in the first survey and participants were asked about changes in their mental health retrospectively with one item questions per category (i.e., depression, anxiety, etc.) in the second survey. This limits the reliability and validity of these measures. This study also has several other limitations. First, the sample consisted of relatively young, mostly female, and highly educated participants and is therefore not representative for the German population. Presumably, effects would have been significantly stronger in a high-risk sample. It should also be noted that the low number of responses in the second survey (70 compared to 170) could indicate a selection bias, for example those subjects most affected by the pandemic might not have responded to the request for the second survey. Second, data was only collected during the first wave of the pandemic from March until May 2020. It is thus unknown if or how effects change over the course of the pandemic and how long they may persist after the pandemic. The findings of Casoria et al. (18) suggest that the appraisal of social situations is closely related to current social distancing measures and may thus change back to normal once the pandemic is over. However, another possible development is that this pandemic will have long-lasting effects on how people will interact with each other in the future, possibly always keeping the threat of another infectious disease in mind, as proposed by Welsch et al. (19). Long-term studies will be needed to further evaluate possible lasting effects on social interactions caused by pandemic events.

DATA AVAILABILITY STATEMENT

The datasets of the two online surveys are not readily available because no consent had been obtained from the participants since the study was originally planned only as a pilot study of another project. Requests to access data should be directed to the corresponding author. Datasets of the ratings for the categorization of sketches into risk categories can be found under https://osf.io/xec9v/files/.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the University of Lübeck.

The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LR, SK, and JS conceived the research and designed the questionnaire. JS, LR, FL, and FP performed data analysis and wrote the manuscript. SK revised the manuscript. All authors discussed the results, contributed to the article, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.678072/full#supplementary-material

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