Editorial introduction for the Neuroscience & Biobehavioral Reviews special issue "Social stress: Psychological and psychosomatic implications"

de Boer, Sietse F; Sgoifo, Andrea

Published in:
Neuroscience and Biobehavioral Reviews

DOI:
10.1016/j.neubiorev.2020.12.006

Publication date:
2021

Neuroscience and Biobehavioral Reviews 121 (2021) 156–159

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

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

Editorial introduction for the neuroscience & biobehavioral reviews special issue "*Social Stress: Psychological and Psychosomatic implications*"

Sietse F. de Boer [a,*], Andrea Sgoifo [b]

[a] Department of Behavioral Neuroscience, Groningen Institute for Evolutionary Life Sciences, University of Groningen, Groningen, The Netherlands
[b] Stress Physiology Lab, Department of Chemistry, Life Sciences and Environmental Sustainability, University of Parma, Parma, Italy

ARTICLE INFO

Keywords
Social stress
Social withdrawal
Cardiovascular disease
Depression
Anxiety

Although a longstanding scientific topic, during the last decade there is a renewed biomedical interest in the powerful influences social environmental factors have on disease risk and lifespan in both humans and animals. Obviously, this is fueled by the staggeringly strong statistic that gradients in socioeconomic status and associated experiences of social adversity predicts morbidity and mortality in humans (Marmot, 2015; Adler et al., 1993; Sapolsky, 2018). Like humans, most other animals live in complex social systems that are maintained by interactions between conspecifics. Even though evolution has shaped these social structures for optimal survival by favoring affiliative and cooperative exchanges, social interactions are often the main source of serious conflicts and resulting insidious stress that negatively impact physical and mental health of certain (susceptible) individuals but not others (resilient). Social stressors ranging from social isolation/withdrawal to social instability and social defeat/subordination recruit a highly conserved (neuro)biological machinery principally positioned to effectively cope with these adverse social life situations. Yet, disruptions in the fine-tuned molecular regulation of these neural and neuroendocrine systems may lead to breakdown of adaptation eventually resulting in serious physical illnesses (atherosclerosis, diabetes, malignancies, etc), mental problems (Alzheimer's, depression, etc) and accelerated senescence (telomere shortening, premature DNA damage) thereby negatively affecting healthy aging. What goes awry in the body and brain when the response to social stress stops being a healthy reaction to social life's inevitable challenges and starts to become pathological? Why do seemingly similar social stressors and adverse social life histories make one individual sick but leave others unaffected? How do early life experiences change adaptational capacities and their underlying brain mechanisms? And how can we leverage an ever-increasing understanding of the brain and behavior to design new ways to alleviate the suffering of people afflicted by stress-related diseases and, ultimately, prevent them altogether? These (and other) are the questions addressed – at multiple analytical levels, and from a wide variety of disciplinary perspectives - in the collection of papers contained in this special issue of NBR. Papers that have formed the collective product of a workshop held in the Erice Ettora Majorana Centre for Scientific Culture, Sicily, Italy from May 6–11, 2019. The present collection of 13 review papers in this special issue reflects the current research efforts across rodents and humans on social stress-related disorders.

While the majority of social stress studies in animals, most commonly laboratory mice and rats, focus on dyadic encounters in the so-called resident-intruder paradigm, *Annaliese Beery, Melissa Holmes and James Curley* (Beery et al., 2020) review findings from their studies in diverse non-traditional rodent species (prairie and meadow voles and mole-rats) and group-housing paradigms (visible burrow systems). Obviously, social hierarchy is a common organizational structure of most animal groups, and an individual's social status exerts a far-reaching influence on brain and behavior. They validly argue that the use of methods informed by the natural ecology of these rodent species provides novel insights into the relationship between social stress, behavior and physiology. The current advances in computer vision technology will soon

* Address for correspondence: Dept. of Behavioral Neuroscience, Groningen institute for Evolutionary Life Sciences (GELIFES), University of Groningen, P.O. Box 11103, 9700 CC, Groningen, The Netherlands.
E-mail address: s.f.de.boer@rug.nl (S.F. de Boer).

https://doi.org/10.1016/j.neubiorev.2020.12.006
Received 7 December 2020; Accepted 9 December 2020
Available online 17 December 2020

enable fully automated, high-throughput, unbiased behavioral analysis. Tracking behavior continuously and reliably in social settings will open the door to the development of new animal models of neuropsychiatric disorders like anxiety and depression, for which current models are overly simplistic.

Although it is well-recognized that social support may potently buffer an individual's behavioral and physiological sequalae after stressful experiences, witnessing a conspecific being socially defeated (vicarious stress model) or interacting with a socially-stressed conspecific (stress contagion model) may actually also trigger a similar stressful state. In their article "the contagion of social defeat stress: Insights from rodent studies", *Luca Carnevali, Nicola Montano, Eleonora Tobaldini, Julian Thayer and Andrea Sgoifo* (Carnevali et al., 2020) review the existing literature on this interesting phenomenon and newly emerging area of social defeat contagion in rodents. Clearly, combining these animal models of social defeat stress contagion with the current novel imaging and manipulation technologies of specified neurons in the brain allows for testing the intensely debated hypotheses of mirroring mechanisms of emotional states and their neuronal encoding.

Another social factor that has frequently been associated with health and disease is the subjective quality and objective quantity of social relationships (Eisenberger and Cole, 2012; Cacioppo et al., 2015). There is mounting evidence that retraction of social engagement and interactions, resulting in social withdrawal, isolation and loneliness, is a strong predictor of poor health and emotional state in humans. Similarly, throughout the animal kingdom, social isolation can threaten individual's survival and fitness, and it is believed that evolutionary conserved mechanisms underlie the maintenance of social interactions. In their review "social withdrawal: An initially adaptive behavior that becomes maladaptive when expressed excessively" *Kevin Ike, Sietse de Boer, Bauke Buwalda and Martien Kas* (Ike et al., 2020) first present social withdrawal as a frequently occurring behavioral symptom across neuropsychiatric disorders and in numerous animal species under various conditions. After reviewing the various experimental paradigms to reliably assess social avoidance/approach behavior, they outline the key neural circuitry and molecular mechanisms underlying social behaviors and summarize how various environmental triggers and biological determinants affect these neurobiological mechanisms to withdraw from social interactions as an adaptive reaction. Yet, excessive expression of social withdrawal is a frequently occurring symptom in patients suffering from neuropsychiatric disorders. Often, it occurs prodromal to the disease suggesting that it is either an early behavioral biomarker or central to the etiology of these mental disorders. The authors make a strong case that this pathological social behavior likely originates from a faulty regulation of specific microcircuits of the so-called social brain neuronal network. As there is a considerable heritability in social disorders, the genetic building blocks of this social brain network is one of the relevant molecular targets for further investigation. In addition, *Lisa Quadt, Giulia Esposito, Hugo Critchley and Sarah Garfinkel* (Quadt et al., 2020) in their narrative review "Brain--body interactions underlying the association of loneliness with mental and physical health", provide an overview of published research and related literature describing the manifold interactions between loneliness, affective symptomatology, neural and embodied processing relevant to physical health, mental health, and neurodiversity. They propose a framework that can inform the identification of psychophysiological mechanisms underlying the link between loneliness and affective symptomatology that may represent interventional targets to mitigate the associated cycle of biopsychosocial morbidity.

An evolutionary perspective can substantially increase and broaden our understanding of why exposure to different types of social stress triggers the onset of psychiatric disorders. The application of evolutionary concepts not only clarifies and contextualizes how certain social experiences or events are implicated in the etiology of psychiatric disorders, it can also steer researchers toward novel hypotheses not anticipated by traditional models of the causal, proximal mechanistic link between social stress and psychopathology. As a matter of fact, already more than 50 years ago, John Price (1967) drew on observations in baboons and macaques and noted the striking similarities between patients with depression/anxiety and animals that lost in competitive encounters and were pressed into a subordinate social role. Basically, he and others (Nesse, 2000) initiated an evolutionary approach to mood disorders by suggesting that several mental illnesses should be regarded as an evolutionary adaptation to situations that arise as a result of human social network organization. In "Social stress and psychiatric disorders: Evolutionary reflections on debated questions", *Alfonso Troisi* (Troisi, 2020) comprehensively analyzes several debated questions in the field of social stress-induced mental disorders from the perspective of Darwinian Psychiatry. This emerging Evolutionary Medicine field is asking not only how, but also *why* exposure to different types of social stress triggers the onset of psychiatric illnesses. Taking the long-term processes of evolution into account in the analyses of short-term mechanistic adaptive processes and *vice versa* is important for understanding the diversity of stress responses, the prevalence and treatment of diseases resulting from a breakdown in adaption.

While Major Depression (MDD) is a well characterized stress-related mental disorder, Burnout, a syndrome defined by emotional and physical exhaustion, is not listed as an independent mental disorder in the DSM-5. This is surprising given its frequent occurrence and high prevalence in our restless 24/7 western society with demanding work schedules. Both mental conditions have been associated with a dysregulation of the hypothalamus-pituitary-adrenal-axis and it has been debated as to whether major depression and burnout represent different aspects of the same syndrome or whether they reflect separate entities. In "Examination of peripheral basal and reactive cortisol levels in major depressive disorder and the burnout syndrome: similarities and differences between individuals with MDD or the burnout syndrome. A systematic review", *N. Rothe, J. Steffen, M. Penz, C. Kirschbaum, A. Walther* (Rothe et al., 2020) present a literature search including MDD and the burnout syndrome and peripheral cortisol measures that resulted in 190 studies for inclusion in their qualitative synthesis. After meticulously describing and discussing the differences and similarities in HPA-related measures between these two debilitating conditions, they tentatively conclude that the burnout syndrome, due to a large overlap in symptom presentation and some HPA measures, may be considered an additional MDD subtype but showing similarities with atypical depression. However, future large prospective cohort studies examining both conditions in parallel rigorously controlling for confounders are required to further elucidate the differences and similarities of the HPA axis in MDD and the burnout syndrome.

Depression and cardiovascular disease currently represent two of the most common stress-precipitated diseases and causes of disability and mortality in our human societies. Among the putative mechanisms that link depression disorders with cardiovascular diseases are dysfunctions of the autonomic nervous system. Heart rate variability (HRV) analysis is a widely-used non-invasive method that can simultaneously quantify the activity of the two branches of cardiac autonomic neural control and provide insights about their pathophysiological alterations. Generally, lowered HRV is a widely recognized prognostic risk factor for adverse cardiovascular events (e.g., myocardial infarction and arrhythmias) as well as cardiac mortality. Alterations of autonomic nervous system that promote vagal withdrawal are reflected in reductions of HRV. Hence, it is not surprising that a considerable body of research reports reduced HRV in patients with depression in comparison to healthy controls. In "Depression and cardiovascular autonomic control: a matter of vagus and sex paradox", *Eleonora Tobaldini, Angelica Carandina, Edgar Toschi-Dias, Luca Erba, Ludovico Furlan, Andrea Sgoifo and Nicola Montano* (Tobaldini et al., 2020) present an interesting issue: even though women seem to experience depressive disorders with a double incidence than men, depressed women, despite a higher vagally-mediated heart rate variability, still experience a higher risk of adverse cardiovascular events than depressed men. Unfortunately, this sex paradox is still

unresolved due to the lack of studies in sex-balanced populations and randomized clinical studies including a larger number of women. Obviously, the authors suggest that future longitudinal studies are required to assess the adaptation of the cardiovascular autonomic control in depressed patients and that sex differences should be more carefully considered as they can add new insights into the etiopathogenesis of both these pathologies and lead to more effective therapeutic approaches. In addition to vagal withdrawal, *Brittany Pope and Susan Wood* (Pope and Wood, 2020) in their review "Advances in understanding mechanisms and therapeutic targets to treat comorbid depression and cardiovascular disease", explore also the important contribution of inflammation and mitochondrial dysfunction in the stress-induced depression and cardiovascular disease comorbidity. Importantly, therapeutics targeted at immune mechanisms, mitochondria/ROS or parasympatic vagal tone all produce beneficial effects on behavioral endpoints and cardiovascular health in humans. In particular, accumulating evidence from clinical and preclinical studies demonstrate that physical exercise may protect against the deleterious effects of stress on the immune system, rescues mitochondrial function, and enhances vagal tone to promote resilience to stress-induced depression and cardiovascular disease. In "The compassionate vagus: A meta-analysis on the connection between compassion and heart rate variability", *Maria Di Bello Luca Carnevali, Nicola Petrocchi, Julian F. Thayer, Paul Gilbert, Cristina Ottaviani* (Di Bello et al., 2020) present the results of a meta-analysis study on the putative association between HRV and the soothing emotion compassion. Compassion is defined as "the sensitivity to suffering in self and others, with a commitment to try to alleviate and prevent it", that may have evolved from parental caring behavior. Recently, a growing body of evidence has started to link compassion with the function of the vagus nerve (Porges, 2017). There is now very good evidence that vagal tone plays a salient role in the ability for people to both be caring and respond to being cared for (Petrocchi and Cheli, 2019). The current analysis performed on 16 studies yielded a significant positive association with a medium effect size. Hence, this study suggests that cardiac vagal indices might represent a biomarker of the degree to which people feel a sense of safeness in and connectedness to the social environments. In "Parsing inter- and intra-individual variability in key nervous system mechanisms of stress responsivity and across functional domains", *Sharona L. Rab, Roee Admon* (Rab and Admon, 2020) focus on biological, environmental, social, habitual, and psychological factors that may influence the inter-individual variation in social stress-induced responsivity patterns of HRV, cortisol secretion and large-scale cortical network activity. They conclude that understanding the inter-and intra-individual variability of the brain mechanisms of stress responsivity across functional domains is imperative for proper translation of neuroscientific findings in clinical practice.

Normal aging is associated with a number of biological changes, including cognitive dysfunction, reduced motor skills, metabolic and chronobiological abnormalities and so on. For several neurodegenerative diseases, and most notably Alzheimer's disease (AD), age is the main risk factor. Stress has been associated with accelerated senescence (i.e., telomere shortening, premature DNA damage) thereby increasing the onset and progression of this devastating neurodegenerative disease. *Carey E. Lyons and Alessandro Bartolomucci* (Lyons and Bartolomucci, 2020) in "Stress and Alzheimer's disease: A senescence link?" comprehensively review human and animal literature studying the impact of (social) stress on AD and discuss the putative mechanisms implicated in this interaction. One emerging mechanism they consider crucial is the impact of stress on the aging and senescence process per se. Senescent cells can secrete pro-inflammatory factors, which have been shown to exacerbate pathological features of AD. These cells may be an important mediator of stress-induced neuroinflammation, which appears to be an active driver of AD pathology.

The involvement of innate immune system (over)activation has also been implicated in various other stress-associated pathologies. In "The role of physical trauma in social stress-induced immune activation", *Sandra Foertsch and Stefan Reber* (Foertsch and Reber, 2020) lucidly outline how social stress-induced bone marrow myelopoiesis, priming, emigration, and activation of myeloid cells and accumulation of these cells in the spleen, gut and brain promote septic shock, colitis and anxiety. They further make the important case that the combination of chronic psychosocial stress and either planned (i.e., surgery) or unplanned (i.e., bite wounds, injury) physical trauma drives splenic activation and subsequent activation of myeloid cells. Another important topic in the field of social stress where both the immune system as well as the vagus nerve play an important mediating role is the microbiota-gut-brain axis. Increasingly, it is recognized that microbes resident in the gastrointestinal tract can potently influence brain physiology and behavior. Research has shown that gut microbiota can signal to the brain via a diverse set of pathways, including immune activation, production of microbial neurotransmitters and neuromodulators and activation of the vagus nerve that was comprehensively presented during the Erice meeting by *Eoin Sherwin and John Cryan,* and that they recently published as a review in the journal Science (Sherwin et al., 2019).

The final topic in this issue revolves around the extracellular space of the brain that is occupied by a complex network of proteins, macromolecules and cell-surface receptors, which combined, create a mesh-like assembly known as the extracellular matrix (ECM). Emerging evidence suggests that ECM alterations occur with stress and are implicated in the pathophysiology of psychiatric disorders. Specifically, increases in perineuronal net (PNN) deposition have been observed in rodents exposed to persistent social defeat stress. The PNN is a specific form of ECM that is predominantly enveloping parvalbumin-expressing inhibitory interneurons where it modulates neuronal excitability. In their contribution "Incubation of depression: ECM assembly and parvalbumin interneurons after stress", *Sabine Spijker, Maija-Kreetta Koskinen and Danai Riga* (Spijker et al., 2020; Beery et al., 2020) give an interesting and elaborate review of the social stress-induced changes in ECM/PNNs focusing on preclinical models for depression. They validly argue that by advancing our understanding of ECM remodeling in stress responses, new therapeutic avenues against stress-related pathologies may likely emerge.

Overall, the present collection of review papers in this special issue broadly reflect the current research advances across rodents and humans on social stress-precipitated disorders. Obviously, the rapidly emerging understanding of how social stress influence brain's neural and molecular mechanisms that are underlying the behavioral and physiological alterations that eventually lead to disease will generate new effective therapeutic strategies for the various crippling stress-related disorders.

References

Adler, N.E., Boyce, W.T., Chesney, M.A., Folkman, S., Syme, S.L., 1993. Socioeconomic inequalities in health. No easy solution. JAMA 269 (24), 3140–3145.

Beery, A.K., Holmes, M.M., Lee, W., Curley, J.P., 2020. Stress in groups: lessons from non-traditional rodent species and housing models. Neurosci. Biobehav. Rev. 113, 354–372.

Cacioppo, J.T., Cacioppo, S., Capitanio, J.P., Cole, S.W., 2015. The neuroendocrinology of social isolation. Annu. Rev. Psychol. 66, 733–767.

Carnevali, L., Montano, N., Tobaldini, E., Thayer, J.F., Sgoifo, A., 2020. The contagion of social defeat stress: insights from rodent studies. Neurosci. Biobehav. Rev. 111, 12–18.

Di Bello, M., Carnevali, L., Petrocchi, N., Thayer, J.F., Gilbert, P., Ottaviani, C., 2020. The compassionate vagus: a meta-analysis on the connection between compassion and heart rate variability. Neurosci. Biobehav. Rev. 116, 21–30.

Eisenberger, N.I., Cole, S.W., 2012. Social neuroscience and health: neurophysiological mechanisms linking social ties with physical health. Nat. Neurosci. 15 (5), 669–674.

Foertsch, S., Reber, S.O., 2020. The role of physical trauma in social stress-induced immune activation. Neurosci. Biobehav. Rev. 169–178.

Ike, K.G.O., de Boer, S.F., Buwalda, B., Kas, M.J.H., 2020. Social withdrawal: an initially adaptive behavior that becomes maladaptive when expressed excessively. Neurosci. Biobehav. Rev. 116, 251–267.

Lyons, C.E., Bartolomucci, A., 2020. Stress and Alzheimer's disease: a senescence link? Neurosci. Biobehav. Rev. 115, 285–298.

Marmot, M., 2015. The health gap: the challenge of an unequal world. Lancet 386 (10011), 2442–2444.

Nesse, R.M., 2000. Is depression an adaptation? Arch. Gen. Psychiatry 57, 14–20.

Petrocchi, N., Cheli, S., 2019. The social brain and heart rate variability: implications for psychotherapy. Psychol. Psychother. 92, 208–223.
Pope, B., Wood, S.K., 2020. Advances in understanding mechanisms and therapeutic targets to treat comorbid depression and cardiovascular disease. Neurosci. Biobehav. Rev. 116, 337–349.
Porges, S.W., 2017. Vagal pathways to compassion. In: Seppälä, E.M., Simon-Thomas, E., Brown, S.L., Worline, M.C. (Eds.), The Oxford Handbook of Compassion Science. Oxford University Press, New York, pp. 189–202.
Price, J., 1967. The dominance hierarchy and the evolution of mental illness. Lancet 290, 243–246.
Quadt, L., Esposito, G., Critchley, H.D., Garfinkel, S.N., 2020. Brain-body interactions underlying the association of loneliness with mental and physical health. Neurosci. Biobehav. Rev. 116, 283–300.
Rab, S.L., Admon, R., 2020. Parsing inter- and intra-individual variability in key nervous system mechanisms of stress responsivity and across functional domains. Neurosci. Biobehav. Rev.
Rothe, N., Steffen, J., Penz, M., Kirschbaum, C., Walther, A., 2020. Examination of peripheral basal and reactive cortisol levels in major depressive disorder and the burnout syndrome: a systematic review. Neurosci. Biobehav. Rev. 114, 232–270.
Sapolsky, R.M., 2018. The health-wealth gap. Sci. Am. 319 (5), 62–67.
Sherwin, E., Bordenstein, S.R., Quinn, J.L., Dinan, T.G., Cryan, J.F., 2019. Microbiota and the social brain. Science 366 (6465). November 1.
Spijker, S., Koskinen, M.K., Riga, D., 2020. Incubation of depression: ECM assembly and parvalbumin interneurons after stress. Neurosci. Biobehav. Rev. 118, 65–79.
Tobaldini, E., Carandina, A., Toschi-Dias, E., Erba, L., Furlan, L., Sgoifo, A., Montano, N., 2020. Depression and cardiovascular autonomic control: a matter of vagus and sex paradox. Neurosci. Biobehav. Rev. 116, 154–161.
Troisi, A., 2020. Social stress and psychiatric disorders: evolutionary reflections on debated questions. Neurosci. Biobehav. Rev. 116, 461–469.