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# Consequences of pandemic-associated social restrictions: Role of social support and the oxytocin system

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## ABSTRACT

During pandemics, governments take drastic actions to prevent the spreading of the disease, as seen during the present COVID-19 crisis. Sanctions of lockdown, social distancing and quarantine urge people to exclusively work and teach at home and to restrict social contacts to a minimum; lonely people get into further isolation, while families' nerves are strained to the extreme. Overall, this results in a dramatic and chronic increase in the level of psychosocial stress over several months mainly caused by i) social isolation and ii) psychosocial stress associated with overcrowding, social tension in families, and domestic violence. Moreover, pandemic-associated social restrictions are accompanied by loss of an essential stress buffer and important parameter for general mental and physical health: social support. Chronic psychosocial stress and, in particular, social isolation and lack of social support affect not only mental health, but also the brain oxytocin system and the immune system. Hence, pandemic-associated social restrictions are expected to increase the risk of developing psychopathologies, such as depression, anxiety-related and posttraumatic stress disorders, on the one hand, but also to induce a general inflammatory state and to impair the course of infectious disorders on the other. Due to its pro-social and stress-buffering effects, resulting in an anti-inflammatory state in case of disease, the role of the neuropeptide oxytocin will be discussed and critically considered as an emerging treatment option in cases of pandemic-induced psychosocial stress, viral infection and during recovery. In this review, we aim to critically focus on possible short- and long-term consequences of social restrictions on mental health and the immune system, while discussing oxytocin as a possible treatment option.

## 1. Times of pandemics

During human history, multiple severe pandemics have been reported including plagues (the "Black Death"), tuberculosis or smallpox. After World War I, the 1918 "Spanish" flu was the first of two pandemics caused by H1N1 influenza A virus, and in 2009, the swine flu pandemic appeared as the second one. In the 21st century coronaviruses (CoVs) emerged with the spreading of the "severe acute respiratory syndrome coronavirus" (SARS-CoV)-1 from the south of China in November 2002. Although a limited number of people was infected (around 8100 people) and less than 1000 died worldwide, the World Health Organization (WHO) characterized it as a pandemic due to new definitions (Kelly, 2011). In 2012, the "Middle East respiratory syndrome coronavirus" (MERS-CoV) spread from Saudi Arabia and was defined as epidemic. In December 2019, a novel CoV termed SARS-CoV-2 started to spread and cause coronavirus disease 2019 (COVID-19) which has been characterized as a pandemic in March 2020 (WHO, 2020b). Until November

2021, almost 250 million cases of COVID-19 infections and more than 5 million deaths (WHO, 2021) have been confirmed worldwide; thus, the global death rate was estimated to be about 2% of infected people. Factors that promote spreading of viruses like SARS-CoV-1 and -2 are i) increased density of the population, ii) domestication of animals or closer contact to wild animals (zoonosis), iii) global traveling, iv) long incubation times of 1–2 weeks, v) lack of specific treatment options and vi) lack of herd immunity (Madhav et al., 2017). However, as seen during the COVID-19 crisis, mostly elderly people and people with pre-existing conditions are reported with the most severe course of disease (CDC COVID-19 Response Team, 2020; Zhonghua et al., 2020), whereas many people show only mild symptoms or are even asymptomatic (overall proportion 17%; Byambasuren et al., 2020; CEBM, 2020).

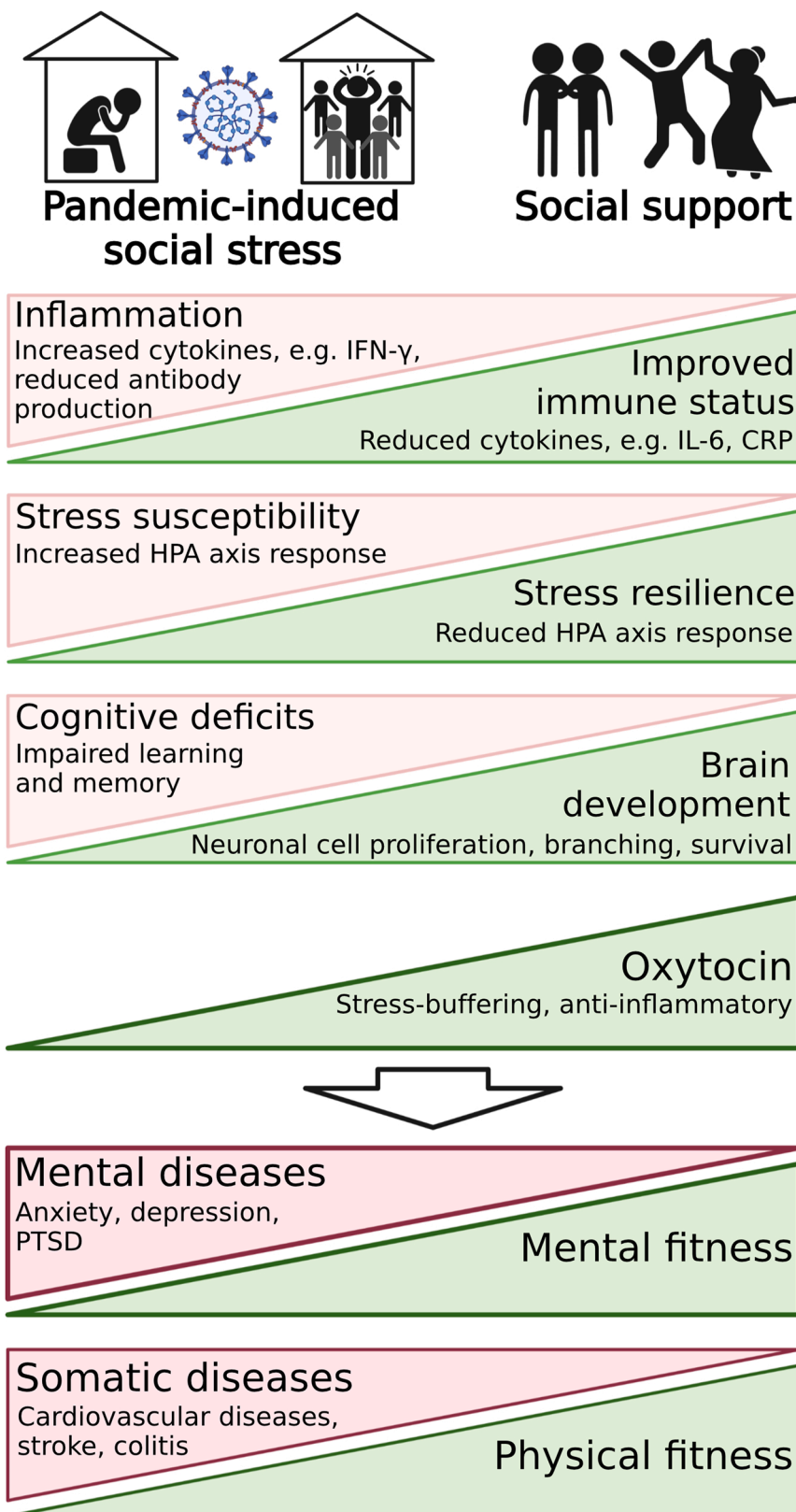
The COVID-19 crisis has affected and is still affecting our society at multiple levels. In order to avoid overloading of the medical system, hospitals and staff combat the spreading of SARS-CoV-2 and the

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emerging mutations has been the most important challenge of political decision makers. Repeated and long-lasting social restrictions have been announced since early spring 2020, and included nationwide lockdowns and home-confinement strategies with strict quarantine implemented in the majority of the COVID-19-hit countries. Although these actions seem

to be efficient, social restrictions have continuously developed into a large burden for the society - economically and psychologically. The exposure to home office, home schooling and home teaching, as well as the complete closure of, for example, restaurants, concert halls, theaters, cinemas, shopping centers and fitness clubs resulted in the loss of daily



**Fig. 1.** Schematic illustration of the negative effects of pandemic-induced social stress and the importance of social support. Social stress, either by social isolation or social tension due to overcrowding, increases inflammation and stress susceptibility, and impairs cognitive functions. In contrast, social support has protective effects and improves the immune status, stress resilience and brain development. Oxytocin, a nonapeptide with pro-social, stress-buffering and anti-inflammatory properties is activated by social interactions. Thus, pandemic-induced social stress increases the risk for mental and somatic diseases, while social support improves mental and physical fitness possibly mediated by oxytocin. CRP: C-reactive protein, HPA: hypothalamus-pituitary-adrenal, IFN: interferon, IL: interleukin, PTSD: post-traumatic stress disorder. Created with BioRender.com.

routines, financial restraints, social tension in families, social isolation and generally increased levels of psychosocial stress.

## 2. Aim of the review

Here, we will discuss - based on the immunological background of COVID-19 infections – the psychosocial consequences of pandemic-induced social restrictions, including social isolation on the one side and elevated level of psychosocial stress due to overcrowding, social tension and domestic violence on the other, on mental well-being and, consequently, on the resilience of the immune system. In this context, we will also discuss the importance of social support for physical and mental health as well as, in the contrary, the consequences of isolation and psychosocial stress on the oxytocin (OXT) system as revealed in human and animal studies (see Fig. 1). The neuropeptide OXT was shown to exert not only pro-social and stress-reducing, but also anti-inflammatory effects (Jankowski et al., 2010; Jurek and Neumann, 2018; Neumann and Landgraf, 2012; Oliveira-Pelegrin et al., 2013; Wang et al., 2015). Specifically, OXT mediates the stress-buffering and anti-inflammatory effects of social support (Heinrichs et al., 2003; Riem et al., 2020; Tsai et al., 2019). We will discuss options to increase OXT signaling in the brain and body including either activation of the endogenous OXT system or treatment with synthetic OXT to reduce the symptoms of pandemic-induced psychosocial stress and, consequently, to enhance the defensive power of the immune system.

## 3. The corona virus

CoVs are large RNA viruses that are widely distributed among mammals and birds, and cause respiratory and enteric diseases after invading the body via droplet infection either by being inhaled or by touching contaminated surfaces before touching mucosa membranes (WHO, 2020a). Along with new human respiratory pathogens, CoVs were taxonomically separated into an own family (Almeida and Tyrrell, 1967; Masters, 2006). SARS-CoV-1 and -2 are named due to their genetic similarity based on a positive-sense single-stranded RNA (reviewed in Groß et al., 2020) and contain envelop proteins, membrane proteins and spike proteins, with the latter promoting attachment to the host cell and membrane fusion during infection (Wu et al., 2020). SARS-CoV spikes have a strong binding affinity to the human angiotensin-converting-enzyme 2 (ACE2), which increases the likelihood that ACE2 represents the respective receptor during infections in humans (Ou et al., 2020; Zhang et al., 2020). ACE2 is highly expressed on the cell surface of the renal and pulmonary epithelium as well as of cells of the cardiac and gastrointestinal system. Thus, both SARS-CoV-1 and -2 specifically affect the pulmonary tract and induce symptoms like coughing, sneezing, sore throat and shortness of breath, but also fever and gastrointestinal disorders (Chen et al., 2020; Groß et al., 2020). However, recent studies could show that the expression level of ACE2 is even higher in the brain, i.e. in neurons and endothelial cells (Li et al., 2020b). In line, epileptic seizures and encephalitis have been reported in CoV-infected people. Since SARS-CoV-2 has even a higher binding affinity to ACE2 than SARS-CoV-1, SARS-CoV-2 might efficiently invade the brain and affect central nervous structures more severely than previous CoVs (Natoli et al., 2020). Consistently, symptoms of confusion and headache have been reported following SARS-CoV-2 infection (Chen et al., 2020). Interestingly, even though the expression pattern of ACE2 is equal in men and women as well as in young and old people, Li and colleagues showed that the correlation between ACE2 expression and the immune response of the lung following SARS-CoV-2 infection was negative in women and young, but positive in men and elderly people. Thus, women and young people with a high expression of ACE2 in the lung show a weaker immune response to SARS-CoV-2 infection compared to men and elderly with similarly high expression of ACE2. This might explain that pneumonia is more severe in men compared to women, and in elderly compared to young people (Li et al., 2020b).

The mechanisms of SARS-CoV effects on the immune system include binding of SARS-CoV spikes to ACE2, uptake into the cell by endocytosis, release of viral RNA into the cytosol, and replication and translation of viral RNA into novel viral proteins making use of host enzymes (Groß et al., 2020). During SARS-CoV infection, the Toll-like-receptor-7 expressed in the lung and spleen supports the recognition of the viral RNA as well as the activation of the immune system by an increasing production of pro-inflammatory cytokines including interleukin (IL)-1 $\beta$  and IL-6 (reviewed in Ahmadpoor and Rostaing, 2020). As the main communicators between immune cells cytokines initially activate the innate and subsequently the adaptive immune response. This includes the proliferation of CD8<sup>+</sup>-specific cytotoxic and CD4<sup>+</sup> helper T cells, antigen-specific B cells producing antibodies as well as regulatory T cells, preventing an exaggerated immune response (Delves and Roitt, 2000; Duffy et al., 2018). In cell culture studies, SARS-CoV-2 has been shown to upregulate pro-inflammatory cytokines, including interferon- $\gamma$  (IFN- $\gamma$ ), leading to a so called “cytokine storm” (Groß et al., 2020; Mehta et al., 2020). In support, in SARS-CoV-1 patients, several pro-inflammatory cytokines and chemokines including IFN- $\gamma$  are elevated, similarly contributing to the “cytokine storm” (Huang et al., 2005), which is likely to contribute to increased organic cell death, e.g., within the lung, and the general pathogenicity of the viruses (Channappanavar and Perlman, 2017). These mechanisms may explain the observation of an exacerbated disease progression in elderly patients and patients with pre-existing conditions due to a shrinking population of naïve T-cells. In contrast, a significantly lower mortality rate has been observed in children, which have a naturally high level of naïve T cells, thus, preventing an exaggerated immune response and “cytokine storm” (Ahmadpoor and Rostaing, 2020). However, not only the “cytokine storm” represents an immunological challenge, also different aspects of pandemic-associated psychosocial stress challenge the individual mental and physical health.

## 4. Consequences of pandemic-induced social restrictions on mental health

To prevent further spreading of SARS-CoV-2, governments were globally forced to take drastic sanctions, which included nationwide lockdown programs over several weeks and months, forced mass quarantine, and overall social distancing (Sohrabi et al., 2020). These actions developed into a rising social, psychological and economic burden. People lost their daily routines and were urged to work and teach from home (home office), school children and university students had to learn at home (home schooling), and toddlers were not allowed to go to child care centers. Grandparents, especially those living in retirement homes, were restricted from their children, grandchildren and friends, thus losing an important life motivator. All of them, independent of age, experienced the lack of otherwise daily face-to-face interactions with colleagues, fellow students, friends or more distant family members. Although social restrictions should mainly affect older people as well as singles and lonely people, the feeling of loneliness due to physical separation from friends and others has been reported across age span and also in people living in families (Clair et al., 2021; Liu et al., 2020; Shah et al., 2020; British Red Cross, 2020).

Moreover, in young families, the lockdown-associated closure of daycare centers and schools over several months in combination with home office has challenged parents to simultaneously work at home, do the household and supervise, e.g., the children’s school duties. The lack of stress-buffering sportive or cultural events, or of manifold other social interactions outside the family unit further contributed to a general increase in the level of social tension. The level of psychosocial stress in families, but also of singles, has been amplified by socio-economic restrictions due to short-time work or missing income in self-employed persons working, e.g., in cultural, service or other branches (Neelsen and Stratmann, 2012; Patel et al., 2020). Moreover, factors like boredom, poor sleep quality as well as lack of proper information or

uncertainty regarding the progression of the disease have further increased the level of stress and mental illness (Brooks et al., 2020).

Further manifesting the condition of chronic psychosocial stress, several alarming reports have already been published regarding increased domestic violence towards women and children in the UK and other countries with an early onset after the lockdown in the COVID-19 crisis (Boserup et al., 2020; Bradbury-Jones and Isham, 2020; Campbell, 2020; Guerra Lund et al., 2020; Tang et al., 2020a; Taub, 2020; Usher et al., 2020), which may even go unnoticed, as children do not regularly go to daycare or school.

Together, the pandemic-associated social restrictions resulted in increased levels of psychosocial stress, and the loss of an essential stress buffer and important parameter for general mental and physical health - social support. This in combination with the fear of the disease, the COVID-19 pandemic has substantial impact on the world's mental health (Cusinato et al., 2020; Dubey et al., 2020; Kola et al., 2021; Lima et al., 2020; Mednick et al., 1988; O'Callaghan et al., 1991; Shigemura et al., 2020; Zandifar and Badrfam, 2020). Indeed, the incidence of acute panic, anxiety, obsessive behaviors, hoarding, paranoia, depression and post-traumatic stress disorder (PTSD) increased (Dubey et al., 2020; Guessoum et al., 2020; Liu et al., 2021; Ravens-Sieberer et al., 2021; Vahratian et al., 2021). Many of these psychopathologies are highly comorbid, and many of them correlate with suicidal attempts (Angst et al., 1999; Ginzburg et al., 2010; Khan et al., 2002; Pfeiffer et al., 2009). In line, a rise in suicides among elderly, young adults and adolescents has been reported during the COVID-19 pandemic (Caballero-Domínguez et al., 2020; Manzar et al., 2020; Nomura et al., 2021; Tanaka and Okamoto, 2021).

The dramatic consequences of pandemic-associated social restrictions on mental health are not surprising, since both social isolation or loneliness as well as chronic psychosocial stress have long been acknowledged as a risk factor for the majority of these psychopathologies (Davidson and Baum, 1986; Hwang et al., 2020; Lee et al., 2007; Liu et al., 2020; Lopez-Duran et al., 2015; Maes et al., 1998; Steinhart et al., 2011; Vindegaard and Benros, 2020; Wu et al., 2005). Recent studies suggested that the COVID-19 pandemic itself and the associated social restrictions can be considered as a traumatic event for the population due to the significant increase in the number of people suffering from PTSD (Forte et al., 2020).

In summary, two main aspects of social restrictions have to be considered: (i) social isolation and loneliness on the one side, and (ii) lockdown-associated psychosocial stress due to family tension or domestic violence on the other.

#### 4.1. Social isolation affects mental health in humans

Social distancing and lockdowns, and the associated significant loss of social support result in emotional responses of "loneliness" and feelings of social exclusion, irritability, hostility, dysphoria and mistrust, while lowering the feelings of self-worth (Ernst and Cacioppo, 1999; reviewed in Matthews and Tye, 2019; Xia and Li, 2018). Thus, social isolation disrupts the individual social homeostasis (Matthews and Tye, 2019) resulting in increased levels of psychosocial stress associated with hyper-activity of the two physiological stress systems - the hypothalamus-pituitary-adrenal (HPA) axis and the sympathetic nervous system (Adam et al., 2006; Doane and Adam, 2010; Hawkey et al., 2006; Kiecolt-Glaser et al., 1984; Xia and Li, 2018). Also, lonely individuals show enhanced sensitivity to social cues and increased socially affiliative motivation (DeWall and Baumeister, 2006; Maner et al., 2007; Pickett et al., 2004). Social isolation-induced lack of social support and loneliness have been linked with the etiology of schizophrenia (Morgan and Fisher, 2007; van Os et al., 2010), major depression (Cacioppo et al., 2006; Oxman et al., 1992), anxiety, social withdrawal (Cacioppo et al., 2010; Ernst and Cacioppo, 1999; Meltzer et al., 2013), PTSD (Liu et al., 2020), and learning deficits (Koike et al., 2009). Also in children, social distancing generally affects mental and physical development, increases

the risk of experiencing two or more psychotic experiences (Bennett et al., 2020) and may facilitate the development of cardiovascular diseases, stroke, high body mass index, and high blood pressure and cholesterol levels (Caspi et al., 2006). Long-term social isolation has also been associated with compromised longevity (Holt-Lunstad et al., 2010) and a higher risk of morbidity and mortality (Brummett et al., 2001).

#### 4.2. Social isolation affects socio-emotional behavior in animals

In support of human studies, in laboratory animals including rats, mice and prairie voles, prolonged periods of social isolation (2–9 weeks in rodents) were found to increase emotional reactivity to stress, depressive-and anxiety-like behavior (Donovan et al., 2020; Grippo et al., 2011) and aggression (Donovan et al., 2020; Haller et al., 2014; Matsumoto et al., 2005; Oliveira et al., 2019; Ross et al., 2019), to impair social affiliation, and to induce cognitive deficits (Fone and Porkess, 2008; Ieraci et al., 2016; Pereda-Pérez et al., 2013; Pohl et al., 2019). Social isolation for several days or weeks also led to a dysregulation of the HPA axis, including an increased sensitivity of the pituitary corticotrophic cells to corticotropin-releasing factor (CRF), increased adrenal response to acute stressors and impaired negative feedback in a sex-dependent manner resulting in a higher circulating corticosterone levels and increased susceptibility to subsequent acute stressors (Bosch et al., 2009; Donovan et al., 2020; Gądek-Michalska et al., 2019; Mumtaz et al., 2018; Ohline and Abraham, 2019; Serra et al., 2005; Takatsu-Coleman et al., 2013; Weintraub et al., 2010; Weiss et al., 2004).

At brain level, impaired neurogenesis (Dunphy-Doherty et al., 2018) and alterations in neuronal activity, microgliosis and BDNF expression in distinct regions of the social network, such as the hippocampus, Nucleus accumbens (NAc), amygdala, hypothalamus and prefrontal cortex (PFC) were found in rats, mice and prairie voles after social isolation (Donovan et al., 2020; Ieraci et al., 2016; O'Keefe et al., 2014). Given their substantial role in modulating social and emotional behaviors it is not surprising that neuropeptide systems, such as arginine vasopressin (AVP), OXT, CRF, angiotensin II and tachykinin 2 systems, were found to be profoundly affected by social isolation in a sex-dependent manner with respect to peptide or peptide receptor expression (Armando et al., 2001; Harvey et al., 2019; Ieraci et al., 2016; Oliveira et al., 2019; Pan et al., 2009; Pournajafi-Nazarloo et al., 2011; Senst et al., 2016; Zelikowsky et al., 2018; Matthews and Tye, 2019). For example, social isolation of adolescent rats or adult voles resulted in elevated OXT expression in the PVN, but reduced OXT receptor binding, e.g., in the NAc, which has been linked to elevated intermale aggression (Oliveira et al., 2019), increased anxiety and impaired social behavior (Grippo et al., 2008). Similar effects were found in Syrian hamsters (Ross et al., 2019). In male prairie voles, 3 days of isolation from the bonded female partner increased depression-like behavior accompanied by decreased hypothalamic OXT expression and OXT receptor binding in the NAc shell (Bosch et al., 2016). A lower density of neuronal branching within distinct brain regions following social isolation (Grinevich and Neumann, 2020) together with the lack of socially stimulated intracerebral OXT release (Heck et al., 2020; Zoicas et al., 2014) were hypothesized to contribute to isolation-induced stress- and anxiety-related behaviors (Donovan et al., 2020).

Social isolation also significantly alters the activity of other brain systems within days, including the noradrenergic system, which is important for stress-related arousal and vigilance (Berridge and Waterhouse, 2003), the midbrain dopamine system essentially for social reward and affiliative social behavior (Gunaydin and Deisseroth, 2014; Ikemoto, 2007), and the GABA system of the PFC along with reduced benzodiazepine binding (Saavedra et al., 2006; Matthews and Tye, 2019). Although the brain opioid system has been mainly associated with regulating pain, analgesia (Basbaum and Fields, 1984) and reward processing (Le Merrer et al., 2009), it also plays an important role in social bonding (Machin and Dunbar, 2011). Social isolation affects the

endogenous opioid system of juvenile rats at multiple levels, and an increased number of opioid receptors and affinity was found in the PFC (Vanderschuren et al., 1995b). Both  $\mu$ -opioid and  $\kappa$ -opioid receptors were revealed to mediate the isolation-induced alterations in social play (Vanderschuren et al., 1995a). Isolation-induced alterations in the dopaminergic, oxytocinergic and opioid systems were found to interfere with reward-related behavior and to increase the preference for addictive drugs such as ethanol and opioid in rats (Heyne, 1996; Wolffgramm, 1990). Dysregulation of these systems are also likely to underlie reduced pain sensitivity found in male mice and juvenile rats after several days of social isolation (Konecka and Sroczyńska, 1990; Naranjo and Fuentes, 1985; Matthews and Tye, 2019).

Social isolation is also likely to affect the communication between the brain, immune system and gut microbiome, called gut-immune-brain axis. Thus, post-weaning social isolation in rats and adult social isolation in prairie voles were found to alter the diversity and abundance of gut microbiota (Dunphy-Doherty et al., 2018), and the expression of the gut barrier protein claudin controlled by mineralocorticoids receptors (Karailiev et al., 2021). These effects were accompanied by increased anxiety-like behavior (Donovan et al., 2020; Karailiev et al., 2021), reduced neurogenesis and impaired associative learning and memory (Donovan et al., 2020; Dunphy-Doherty et al., 2018).

In sum, in rodents, social isolation induces substantial alterations in the well-balanced activity of brain neuropeptides including CRF and OXT, and in dopamine, opioid and other brain neurotransmitter systems, and the gut-brain axis. These mechanisms are likely to underlie the isolation-induced increase in stress perception, emotional dysfunctions, altered reward processing especially in a social context, and pain sensitivity.

#### 4.3. Psychosocial stress affects mental and general health in humans

In addition to - and in the other extreme to social isolation - pandemic-associated social restrictions require home schooling and home office, and force families to live in close full-day interactions. With high probability, this results in increased levels of social tensions due to overcrowding especially in families living with socio-economic restrictions and in rather small flats. Social tension and overcrowding contribute to an increased level of psychosocial stress and, consequently, the etiology of psychopathologies (Galea and Abdalla, 2020; Kamal and Othman, 2020). Overcrowding in the own home has been directly linked to poor mental and physical health, poor social relationship in and outside home, poor child care (Gove et al., 1979) as well as increased occurrence of aggression and domestic violence (Ireland and Power, 2004). The latter are known to generally rise in times of pandemics (Boserup et al., 2020; Bradbury-Jones and Isham, 2020; Campbell, 2020; Taub, 2020; Usher et al., 2020) and are further facilitated by an elevated consumption of alcohol (Campbell, 2020; Catalá-Miñana et al., 2017). Domestic violence may reach from verbal aggression to bullying among siblings or adults (Hollins Martin and Martin, 2010; Wolke et al., 2015), domestic abuse to physical violence especially towards children and women (Thackeray et al., 2010; Taub, 2020), and even murder of family members (reviewed in Bradbury-Jones and Isham, 2020). Domestic violence with high rates of repeated victimization (Howard et al., 2010) and the chronic threat of being maltreated are not only sources of broken bones and trauma, but have been associated with general distress, cardiovascular and gastrointestinal diseases, self-harm, depression, anxiety, PTSD, and increased suicidal risk (Bergman and Brismar, 1991; Campbell, 2002; Golding, 1999; Hollins Martin and Martin, 2010; Kaslow et al., 2002; Lucas et al., 2016; Sharhabani-Arzy et al., 2003; Wolke et al., 2015). The pandemic-induced lockdowns exacerbate the tense psychosocial situation for the victims without chances to escape the domestic conflict zone for other activities.

Very little is generally known regarding the biological mechanisms involved in social tension and psychosocial stress in humans (Heim et al., 2000; Penninx et al., 2007; Heim and Nemeroff, 2001; van Winkel

et al., 2008). However, multiple consequences of childhood abuse have been identified (for review see Heim et al., 2009), which include an impaired development of the stress system and the endogenous OXT system reflected by reduced OXT levels in saliva and cerebrospinal fluid (Seltzer et al., 2014; Suzuki et al., 2020).

#### 4.4. Psychosocial stress affects socio-emotional behavior in animals

The effects of psychosocial stress on socio-emotional behavior and related brain systems have been studied in detail in clinically relevant rodent models of chronic overcrowding, subordination, social defeat, social trauma and instability, which confirmed and extended the findings in humans (Berton et al., 2006; Langgartner et al., 2015; Reber et al., 2016a, 2007; Slattery et al., 2012; Toth et al., 2012; Nyuyki et al., 2012). General physiological and behavioral consequences of chronic psychosocial stress include reduced body weight gain, adrenal hypertrophy, HPA axis dysregulation, elevated levels of anxiety- and/or depressive-like behavior and abnormal social behavior, such as lack of social preference (Berton et al., 1997; Golden et al., 2011; Gruver and Sempowski, 2008; Heinrichs et al., 1992; Huhman et al., 1990; Keeney and Hogg, 1999; Reber et al., 2007; Saavedra-Rodríguez and Feig, 2013; Slattery et al., 2012; Nyuyki et al., 2012; for review see Masis-Calvo et al., 2018). For example, the mouse model of chronic subordinate colony housing (CSC; Reber et al., 2016a; Reber et al., 2007; reviewed in Langgartner et al., 2015) can be used to mimic the situation found during pandemic-induced lockdown, such as social tensions, bullying and violence. Three-weeks exposure to CSC, i.e., of 4 experimental mice to a slightly larger and dominant male, results in severe behavioral mal-adaptations, increased anxiety-like and impaired social preference behaviors (Slattery et al., 2012) accompanied by HPA axis dysregulations including diurnal hypocorticism, hyperactivity during subsequent heterotypic stressor exposure and reduced adrenal ACTH sensitivity (Foertsch et al., 2017; Füchsl et al., 2013; Reber et al., 2007).

Interestingly, there exist specific age windows with increased susceptibility to psychosocial stress, with profound consequences on the behavioral and endocrine development especially early in life (Bosch et al., 2006; Kaiser and Sachser, 2005, 1998; Saavedra-Rodríguez and Feig, 2013). For example, the effects of overcrowding on increased anxiety-like behavior was only seen in juvenile, but not adults rodents, whereas an increased vulnerability towards social tension was found in adults (Arakawa, 2005).

At brain level, alterations in neuronal activation patterns have consistently been observed in brain areas implicated in the regulation of fear, anxiety, stress and social behaviors including the amygdala, hippocampus, lateral septum, BNST, periaqueductal gray and the hypothalamic PVN following exposure to different modes of chronic psychosocial stress (Langgartner et al., 2015; Martinez et al., 1998; Singewald et al., 2009). Moreover, maladaptations in relevant brain systems including the CRF, AVP, OXT and dopamine systems (Keeney et al., 2006; Krishnan et al., 2007; Reber and Neumann, 2008) have been described. Again, dysbalance of these fine-tuned systems is likely to underlie the observed behavioral and physiological alterations. In line, CRH and AVP are known regulators of the HPA axis response, although AVP seems to become prominent during chronic or prolonged psychosocial stress (Keeney et al., 2006; Füchsl et al., 2013; Aguilera, 1994). Furthermore, social trauma induced by social fear conditioning results in abolished release of OXT within the septum both in male and female socially fearful mice (Menon et al., 2018; Zocas et al., 2014). At receptor level, social fear increased septal OXT receptor binding, whereas chronic psychosocial stress exposure reduced OXT receptor expression and binding in the medial raphe nucleus (Peters et al., 2014), a brain region where OXT mediates its anxiolytic effects (Yoshida et al., 2009).

## 5. Consequences of social restrictions on the immune system

In addition to the adverse consequences of pandemic-related social

restrictions on mental health, social isolation and chronic psychosocial stress also impact the immune system not only in aged, but also younger people (Balter et al., 2019; Hackett et al., 2012; Hawkey and Cacioppo, 2004; Jaremka et al., 2013b). Generally, the immune system is divided in the peripheral and the central immune system. Macrophages, natural killer cells and dendritic cells as parts of the innate immune response, as well as T- and B-cells as parts of the adaptive immune response constitute the peripheral immune system, whereas microglia make up the main components of the brain's immune system. In both systems, second messenger molecules, such as cytokines, are responsible for immune cell communication, regulation and proliferation (Janeway and Travers, 2005; Kofler and Wiley, 2011). Clinical and pre-clinical studies revealed that both the peripheral and the central immune systems are highly affected by (social) stress, and become dysregulated in mental disorders including PTSD and depression (Ambrée et al., 2018; Hodes et al., 2014; Maes et al., 1998; Marsland et al., 2002; Wang and Young, 2016).

### 5.1. Consequences of social isolation and psychosocial stress on the immune system in humans

Both social isolation and chronic psychosocial stress are well acknowledged to exert negative effects on the immune system, which has particularly dramatic consequences during a pandemic such as COVID-19. Thus, loneliness, for example, was found to increase the risk to develop pain, depression and fatigue in cancer survivors (Jaremka et al., 2013a). Thereby, loneliness has been associated with a higher inflammatory response to, e.g., a mild immune challenge, reflected by increased IL-6, IL-1R or TNF- $\alpha$  synthesis (Balter et al., 2019; Hackett et al., 2012; Jaremka et al., 2013b). Interestingly, vice versa, an inflammatory challenge has been shown to even induce feelings of loneliness and social disconnection (Eisenberger et al., 2010, 2009; Smith and Bilbo, 2021). Moreover, in men, loneliness-induced systemic inflammation was correlated with an increased risk to develop diseases (Vingeliene et al., 2019), while in women diagnosed with breast cancer, social isolation increased the risk of mortality (Kroenke et al., 2006; reviewed in Usta, 2012). In College students, loneliness or being part of only small compared to medium or large social network groups throughout the semester resulted in lower antibody titers after influenza vaccination (Pressman et al., 2005). This observation is highly relevant for the present Corona pandemic as forced social restrictions prior to Corona vaccination potentially lower its effectiveness. Moreover, social isolation and socio-economic stress have been shown to lower the activity of natural killer cells and the response of T-lymphocytes (Kiecolt-Glaser et al., 1984), to upregulate pro-inflammatory genes, and to downregulate antibody- and antiviral immunity-related genes (Powell et al., 2013; Xia and Li, 2018). Isolation-induced dysregulation of the immune system is further reflected by reduced expression of antigen-presenting cells including dendritic cells and monocytes, as well as antibody-producing B cells (Cole et al., 2011). Thus, social distancing generally weakens the immune system, which is highly disadvantageous during exposure to a pathogen like SARS-CoV-2 with the simultaneous lack of treatment options and innate immunity. Especially elderly people with a generally weaker immune system (Ahmadpoor and Rostaing, 2020), and a higher susceptibility to bacterial (e.g. pneumonia) and viral (e.g. influenza) infections (reviewed in Castle, 2000; Hawkey et al., 2007) are at higher risk in social isolation.

Not only social isolation, but especially chronic psychosocial stress induced by social tension and social trauma discussed above represents another risk factor for a dysbalanced immune system and increased severity of inflammatory diseases. In this context, stress-induced maladaptations of the HPA axis and the autonomic nervous system seem to be central, as cortisol and catecholamines impact on immune cell trafficking, differentiation, proliferation, cytokine secretion and antibody production (Padgett and Glaser, 2003). Furthermore, lymphocytes including B and T cells can produce the ACTH precursor proopiomelanocortin and its derived peptides (Weigent and Blalock, 1995). These

examples demonstrate the close interplay between the immune system and the stress response, which is further supported by the finding of an increased production of pro-inflammatory and immune-regulatory cytokines, such as TNF- $\alpha$ , IL-6 and IFN- $\gamma$ , in students one day prior to a major academic exam (Maes et al., 1998). Thereby, psychological stress triggered cytokine-induced activation of the HPA axis paralleled by an increased risk to develop stress-induced disorders, like anxiety (Maes et al., 1998), depression (Quinn et al., 2020), and PTSD (Wang and Young, 2016). In line, IL-6 has been found to be a major stimulator of the HPA axis (Lyson and McCann, 1991; Mastorakos et al., 1994, 1993) and to predict the development of mental disorders like depression (Baune et al., 2012; Maes et al., 2011, 1998). As an example, bullied children suffer from long-term rise in C-reactive protein (CRP), a marker for systemic inflammation, which increased with the number of times being bullied (Copeland et al., 2014). Chronic rise in CRP is known to increase the risk of cardiovascular disease, ischemic stroke, metabolic disorders and mental health problems including depression (Kaptoge et al., 2010; Wolke and Lereya, 2015).

Thus, increasing levels of psychosocial stress in times of pandemics is thought to additionally challenge the immune system. Still, a direct correlation between the effects of pandemic-induced social restrictions and a rather severe course of disease, e.g. during the COVID-19 crisis, is missing. Moreover, clinical studies are mainly limited to peripheral analysis of immune marker, lacking the access to central levels.

### 5.2. Consequences of social isolation and psychosocial stress on the immune system in animals

#### Social isolation:

There is a plethora of preclinical studies on the effects of social isolation as well as psychosocial stress not only on the peripheral, but also the central immune system. For example, socially isolated hamsters showed impaired wound healing following an additional stressor compared to group housed conspecifics (Detillion et al., 2004). In male mice, long-term social isolation affected peripheral and central immunological parameters including increased pro-inflammatory TNF- $\alpha$  and decreased anti-inflammatory IL-10 plasma levels as well as microglia cell density in the dentate gyrus (Du Preez et al., 2020). In line, early-life social isolation induced an increase in microglia activation and expression of pro-inflammatory cytokines in the rat hippocampus accompanying depressive-like behavior (Wang et al., 2017). Treatment with minocycline, an antibiotic with antidepressant properties, was able to reduce microglial density in the PFC and hippocampus of adult rats with high trait anxiety (Schmidtner et al., 2019) and following early-life social isolation (Wang et al., 2017). Moreover, in male rats socially isolated for 7 weeks, an increased expression of the microglia marker Iba-1 in the PFC and NAc (Schiavone et al., 2009), and reduced hippocampal levels of IL-6 and IL-10 and of neurogenesis were found; this was linked to an altered gut microbiome composition (Dunphy-Doherty et al., 2018). Regarding the effects of isolation on the peripheral immune system, in male and female prairie voles, social isolation disrupted the innate immune response indicated by reduced in vitro bacteria killing ability and in females additionally increased aggressive behavior (Scotti et al., 2015).

Pair-bond disruption has recently been established as a model of social loss with significant effects not only on behavior discussed above, but also on the central immune system (Pohl et al., 2021, 2019). Thus, in male and female prairie voles sex- and brain region-specific effects of partner loss on the priming and morphological activation of microglia have been shown. In separated females, microglial activation was specifically reduced in the prelimbic cortex and the entire PVN, whereas in separated males this effect was exclusively found in the parvocellular PVN, where the neuroendocrine stress response is triggered (Pohl et al., 2021).

It is of special interest to note that physical exercise was able to partially reverse the adverse effects of post-weaning social isolation on

IL-1 $\beta$  expression in the dorsal hippocampus, cognition and neuronal survival in mice (Hueston et al., 2017). These potentially stress-buffering effects of physical activity are also limited during pandemic-associated social restrictions due to closed fitness centers, dusk-to-dawn curfew and, thus, banned outside team and other sportive activities.

#### *Chronic psychosocial stress:*

The discussed rodent models of chronic psychosocial stress (overcrowding, subordination or social defeat in males, and social instability in females) have also extensively been used to study the underlying mechanisms of the maladaptive effects of chronic stress on the immune system (Bartolomucci et al., 2001; DiSabato et al., 2020; Nie et al., 2018; Reber et al., 2016b, 2008, 2007, 2006; Schmidt et al., 2010). Three weeks exposure of male mice to CSC housing resulted not only in severe alterations in behavior, but also in robust immunological maladaptations at multiple levels. These effects included a general activation of the immune system, thymus atrophy, splenomegaly, reduction of regulatory T cells, decreased glucocorticoid signaling including glucocorticoid resistance of splenocytes, activation of stress-induced myeloid cells, resulting in chronic low-grade inflammation and even manifested colitis after 14 days (Foertsch et al., 2017; Foertsch and Reber, 2020; Langgartner et al., 2015; Reber et al., 2016a, 2016b, 2008, 2007; Schmidt et al., 2010). Likewise, CSC exposure as well as chronic intermittent psychosocial stress induced by social defeat and overcrowding triggered a more severe intestinal inflammation following dextran sulfate sodium, and increased IL-6, TNF- $\alpha$  and IFN- $\gamma$  secretion from the mesenteric lymph node cells (Reber et al., 2006, 2008). In female mice, chronic social instability reduced the expression of anti-inflammatory cytokines, like IL-10, and increased pro-/anti-inflammatory ratios of IL-1 $\beta$ /IL-10, IL-6/IL-10 and TNF- $\alpha$ /IL-10 in the hippocampus, which were accompanied by an increase in anxiety- and depressive-like behavior (Labaka et al., 2017). Moreover, in female adolescent rats social instability increased hippocampal NF $\kappa$ B1 expression, but attenuated its rise induced by an additional immune challenge. However, opposite effects were found on hippocampal IL-6 synthesis (McCormick et al., 2020). Recently, chronic social defeat-induced hippocampal IL-1 has been found to directly affect local glutamatergic neurons via actions at IL-1 receptors, thus possibly mediating social and cognitive deficits in mice (DiSabato et al., 2020).

In sum, there is substantial evidence that both social isolation as well as chronic psychosocial stress have significant adverse consequences on the immune system, which becomes less functional in situations of infection, inflammation or other diseases.

## 6. Importance of social support

The examples provided on the consequences of pandemic-induced social restrictions have one aspect in common: the lack of social support. Living in social groups is beneficial for many species, for increased survival, enhanced fitness of the group, and progression of brain development and cognitive abilities (Almberg et al., 2015; Donaldson and Young, 2008; Lamblin et al., 2017; Neumann, 2009). According to the social brain hypothesis originally conceived for primates, the growing complexity of social lives co-evolved with relative brain size, cognitive abilities, emotionality and vocal communication skills in primates, ungulates, carnivores and birds (Dunbar and Shultz, 2007; Whiten and Byrne, 1988). The evolution of complex social behaviors has been promoted by the activation of the reward system of the brain induced by social stimuli, positive reinforcing consequences of close social interactions on emotionality as well as improved mental and physical fitness, and a general health state. Thus, the display of social behaviors and the feeling of social integration result in the activation of the reward systems, and reward seeking is, thus, an important driving force for complex social behaviors (Caldwell and Albers, 2016).

There is profound evidence from animal and human studies that

rewarding social interactions and social support have acute and long-term beneficial effects on the individual physical and immunological fitness, and the emotional well-being, which finally protect against psychopathologies (Alipour et al., 2009; George et al., 1989; Han et al., 2019; Solomon et al., 1987; Zyrianova et al., 2006). Individuals that are engaged in all facets of close social interaction and consider themselves accepted in the group feel less stressed. Thus, the intensity of social support has been linked to the severity of stress-related somatic diseases, such as hypertension, atherosclerosis, cardiovascular diseases, asthma, cancer and stroke outcome (Brody, 2006; Castro and Matt, 1997; Cohen et al., 2015; Glass et al., 1993; Kamarck et al., 1990; Karelina and DeVries, 2011; Uchino et al., 1996; Wang et al., 2005). Moreover, in women diagnosed with breast cancer, social support increased quality of life and lowered psychiatric morbidity (Filazoglu and Griva, 2008; Lim and Zebrack, 2008; Sammarco and Konecny, 2008; Simpson et al., 2002). Therefore, it is not surprising that social support was found to improve the treatment success in COVID-19 patients (Yang et al., 2020). Interestingly, the beneficial effects of social support have been found to be more substantial in women than in men (Fiori and Denckla, 2012; Forster and Stoller, 1992; Manning et al., 2021).

One potential mechanism underlying the effects of social support is a reduction in circulating pro-inflammatory cytokines like CRP and IL-6 (Karelina and DeVries, 2011). In line, sensitivity to social disconnection has been correlated with increased pro-inflammatory cytokines including IL-6 and TNF- $\alpha$  (Moieni et al., 2015). Another central factor of the effects of social support is its ability to attenuate the response of the HPA axis, especially to an acute psychosocial stressor, resulting in reduced cortisol responses (Eisenberger et al., 2007; Häusser et al., 2012; DeVries et al., 2003; Heinrichs et al., 2003; Kikusui et al., 2006; Kirschbaum et al., 1995).

In pre-clinical studies, social support has been shown to promote stress resilience and to reduce some PTSD-like effects in rat models of multigenerational stressor exposure and PTSD, respectively (Faraji et al., 2017; Seetharaman et al., 2016). Moreover, social support can counteract chronic stress-induced increase in neuronal cell proliferation and epigenetic modulations in the rat hippocampus, suggesting an important role of social support in neurogenesis, neuroplasticity, neurotransmission and neuronal survival (Viana Borges et al., 2019).

Importantly, the OXT system with its prosocial and anti-stress effects has been shown to be an important mediator of the multiple aspects of social support.

## 7. The role of OXT in socio-emotional responses and social support

Various beneficial health effects of social housing and social support have been revealed to be mediated by the neuropeptide OXT (Neumann, 2009). Primarily synthesized in the paraventricular (PVN) and supra-optic (SON) nuclei of the hypothalamus OXT is released not only into the peripheral circulation, but also within distinct brain regions in response to various social stimuli in male and female individuals (Grinevich and Neumann, 2020; Jurek and Neumann, 2018; Landgraf and Neumann, 2004; Neumann, 2009; Neumann and Landgraf, 1989). Local OXT receptor-mediated signaling, in turn, is essential for the fine-tuned regulation of social behaviors including sexual, maternal, aggressive and juvenile play-fight behaviors, pair-bonding, social cognition and naturally occurring social preference behavior shown in rats, mice, voles and other mammals (Lukas et al., 2011b; Menon et al., 2018; Oettl et al., 2016; Oliveira et al., 2021; Zoicas et al., 2014; Bosch and Young, 2018; Donaldson and Young, 2008; Jong and Neumann, 2018; Jurek and Neumann, 2018). Of specific interest in this context is the finding that OXT neurons are even responsive to subtle social stimuli such as social investigation, auditory social stimuli and social touch in mice and rats, resulting in increased central release (Marlin et al., 2015; Menon et al., 2018; Tang et al., 2020b; Zoicas et al., 2014). In contrast, social isolation of rodents was found to reduce neuropeptide synthesis, the density of



OXT neuronal branching (Neumann and Grinevich, unpublished), and central OXT release (Heck et al., 2020; Ross et al., 2019; Zoicas et al., 2014).

Thus, although experimentally not accessible, it is likely that social interactions, hugging or talking to each other, and even subtle touch also stimulate the brain OXT system in humans. In support, elevated OXT concentrations in human blood or saliva as rough indicator of general OXT system activation were described not only in response to physical exercise such as running (Jong et al., 2015), but also to sexual and various social stimuli, such as interacting with the own dog (Carmichael et al., 1987; Demirci et al., 2016; Murphy et al., 1990; Nagasawa et al., 2009).

Also, increasing the availability of OXT within the brain and, thus, central OXT signaling by acute intranasal application of synthetic OXT promotes several aspects of social behavior including social cognition, empathy, trust and even xenophobia (Andari et al., 2010; Bernaerts et al., 2017; Ditzen et al., 2009; Gamer et al., 2010; Guastella et al., 2008; Lim and Young, 2006; McGraw and Young, 2010; for review see Grinevich and Neumann, 2020; Jurek and Neumann, 2018) further indicating a fundamental role of OXT in human social interactions. Interestingly, intranasal OXT may specifically affect regions of the social network comprising the amygdala, striatum, hippocampus, anterior and middle cingulate cortex, inferior frontal gyrus, and insular cortex (Paloyelis et al., 2016).

The activation of the brain OXT system even by subtle social stimuli is of particular relevance in the context of OXT as a mediator of the positive effects of social support on stress responsiveness, as the OXT system is closely linked to stress regulation. On the one hand, acute social and non-social stressors stimulate peripheral and/or central OXT release (Bernhard et al., 2018; Ebner et al., 2000; Hew-Butler et al., 2008; Jong et al., 2015; Pierrehumbert et al., 2010; Torner et al., 2017; Wigger and Neumann, 2002; Engelmann et al., 2004; Jurek and Neumann, 2018; Landgraf and Neumann, 2004), and such intracerebrally released OXT exerts stress-protecting, anxiolytic and pain-reducing effects (Bale et al., 2001; Blume et al., 2008; Eliava et al., 2016; Jurek et al., 2015; Neumann et al., 2000b, 2000a; Waldherr and Neumann, 2007). For example, brain OXT attenuates the responsiveness of the HPA axis (Neumann et al., 2000b) and regulates stress- or social trauma-induced social vigilance and social avoidance in a brain region-dependent manner (Duque-Wilckens et al., 2020; Zoicas et al., 2014). Moreover, acute administration of OXT rescued psychosocial stress-induced social avoidance (Lukas et al., 2011b), and chronic OXT applied in low dose partly prevents chronic stress-induced mal-adaptations (Peters et al., 2014). In line, administering OXT for 14 days via subcutaneous injections recued social isolation-induced increase in basal heart rate and depressive-like behavior in female prairie voles (Grippeo et al., 2009).

On the other hand, chronic psychosocial stress, social trauma in adulthood or early in life, as well as pair separation (Bosch et al., 2016; Frijling et al., 2015; Heim et al., 2009; Lukas et al., 2011a; Peters et al., 2014) result in mal-adaptations of the OXT system in animals and humans (for review see Jurek and Neumann, 2018; Neumann et al., 2000b; Olf et al., 2013).

## 8. The role of OXT in the regulation of the immune system

The findings of impaired functioning of the OXT system as a result of social isolation and psychosocial stress is of particular relevance during pandemics, the more as there is substantial evidence for the involvement of the OXT system in immune regulation. Thus, OXT has general positive effects on disease progression and exerts potent anti-nociceptive (Eliava et al., 2016; Lundeberg et al., 1994), anti-inflammatory and antioxidant (Moosmann and Behl, 2002; Wang et al., 2015) properties. It was further shown to alleviate tissue damage in models of renal (Tuğtepe et al., 2007) and hepatic (Düşünceli et al., 2008) ischemia, and of sepsis-induced multiple organ damage (İşeri et al., 2005a), skin injury

(İşeri et al., 2008) and colitis (İşeri et al., 2005b; Peters et al., 2014). In the context of COVID-19 it is important to mention that the anti-inflammatory effects of OXT involve organ protective effects as seen in mice, where it mitigated acute lung injury and multiorgan failure (İşeri et al., 2005b).

OXT receptors are located on macrophages, monocytes and endothelial cells, and OXT signaling reduces the secretion of inflammatory cytokines from these immune cells (Szeto et al., 2008). Thus, the primary anti-inflammatory properties of OXT are reflected by decreased levels of TNF $\alpha$  and IL-6 as well as decreased neutrophil infiltration to the site of injury (Düşünceli et al., 2008; İşeri et al., 2005b, 2005a; Tuğtepe et al., 2007). In line, elevated plasma OXT levels during early infection dampen excessive pro-inflammatory cytokine production (Soumier and Sirigu, 2020; Wang et al., 2015; Xia and Li, 2018). Interestingly, OXT and AVP have been shown to exert opposite regulatory effects on cellular homeostasis including mitochondria and reactive oxygen species, which are closely related to cellular inflammatory responses. While OXT is known to dampen inflammatory pathways like oxidative stress and protein translation abilities during cellular stress, AVP rather amplifies inflammatory responses (Biyikli et al., 2006; Klein et al., 2016; reviewed in Bordt et al., 2019). As OXT promotes, rather than suppresses, adaptive immune responses - in contrast to glucocorticoids - the interaction of OXT with the immune system has substantial health benefits (Buemann et al., 2020; Erdman and Poutahidis, 2016).

With the described functions of OXT it is not surprising that the neuropeptide is considered an essential mediator of the positive consequences of social support on mental and physical health (DeVries et al., 2007; Kikusui et al., 2006; Knox and Uvnäs-Moberg, 1998; Neumann, 2009; Ross et al., 2019). Evidence for an involvement of OXT mediating the effects of social touch on mental health comes from a study by Holt-Lundstad, which showed that in couples with high depressive symptomatology scores, peripheral OXT concentrations are elevated due to high stress levels, but warm touch abolished these high stress-induced levels of OXT linked to subclinical depression (Holt-Lundstad et al., 2011). In line, higher levels of plasma OXT were related to more positive communications between couples which was accompanied by faster wound healing (Gouin et al., 2010). Accordingly, central OXT signaling was found to mediate the beneficial effects of pair-housing on wound healing in hamsters (Detillion et al., 2004), and of social interactions on cerebral infarct size and inflammation, as blockade of OXT receptors prevented these effects (Karelina et al., 2011; Karelina and DeVries, 2011). Positive OXT-mediated effects of social support and social interactions have also been reported on the recovery from disease (Kikusui et al., 2006; Knox and Uvnäs-Moberg, 1998).

In several studies, the OXT system has also been found to influence the impact of loneliness. For example, variations of the OXT receptor gene have been associated with the susceptibility to loneliness (LeClair et al., 2016; Lucht et al., 2009). Moreover, in people reporting a high level of loneliness the beneficial effect of intranasal OXT on parasympathetic cardiac reactivity was diminished independent of stress hormone levels (Norman et al., 2011). In patients suffering from major depression, low OXT levels impede the buffering effect of social support (Tsai et al., 2019).

Social isolation has also been shown to be correlated with the erosion of telomere length - DNA-repetitive nucleotide segments at the ends of each chromosome in mammals that protect genetic material from degradation during somatic cell division in somatic cells (Aydinonat et al., 2014). In this context OXT was found to mediate the positive impact of social interactions on telomere length (Faraji et al., 2018).

In summary, given the multiple pro-social, anti-stress, anti-nociceptive and anti-inflammatory effects of OXT, and its substantial impact on mental and physical health, including immune resilience, the OXT system seems to be one of the major players central to the causes and consequences of corona-induced impairments of health. Consequently, social distancing, lack of social interactions and touch, which result in reduced activity of the OXT system and lack of the health-

protecting consequences of social support have far-reaching health consequences and affect recovery from disease.

## 9. Activation of the OXT system and OXT application as treatment options for pandemic-related social stress

It has been hypothesized that general lower levels of OXT are associated with increased severity of COVID-19 infection: People reported with lower OXT level such as men, elderly people and people with pre-existing conditions, were also reported with the most severe course of COVID-19 disease (Li et al., 2020a; CDC COVID-19 Response Team, 2020; Zhonghua et al., 2020; Marazziti et al., 2019; Elabd et al., 2014; Cochran et al., 2013; reviewed in Diep et al., 2020). Moreover, the pandemic-related social distancing results in a substantial inactivation of the OXT system in the general population. Accordingly, the question arises, how the activity state of OXT signaling can be elevated or at least maintained to prevent or reverse social isolation- or social stress-induced impairments of mental well-being and general health. Here, two options exist, either (i) to activate the endogenous OXT system, or (ii) to increase the availability of OXT by application of the synthetic nonapeptide. As discussed above, an efficient activation of the endogenous OXT can be achieved by, e.g., physical exercise, sexual stimulation, social interactions or intake of specific food supplements. For example, probiotics such as *Lactobacillus* bacteria were described to increase OXT levels and, thus, to affect the immune system (Andersson et al., 2016; Bharwani et al., 2017). However, more detailed studies are needed to substantiate these interesting findings. Similarly, whether subtle social interactions, for example via rather distant social media allowing at least visual and auditory social cues, stimulate the OXT system needs to be proven.

Intranasal application of synthetic OXT is another strategy to stimulate OXT signaling in the brain (and body), to ameliorate the adverse effects of pandemic-induced social isolation or psychosocial stress, and to increase the resilience of the immune system. In addition to the rather indirect health effects of OXT mediating the positive effects of social support, its potent anti-inflammatory and other properties described above indicate that OXT administration may become a helpful preventive and acute treatment strategy against COVID-19 infection, the more as, unfortunately, there is still no specific medication for COVID-19 patients available. In line, there is increasing evidence that peripheral OXT infusion may counteract the “cytokine storm” seen in COVID-19 patients via stimulation of the vagus nerve, which attenuates inflammation. Especially IL-6 is thought to rise COVID-19 symptoms including depression and anxiety and thus reduced inflammation including the IL-6/IL-6 receptor pathway might serve as a potential target for treatment of COVID-19 symptoms (Everett et al., 2021; Azabou et al., 2021; Bue-mann et al., 2020; Kappelmann et al., 2021). Moreover, as a natural hormone, OXT is safe and has already been routinely used in women in obstetric settings worldwide.

Nevertheless, we have to provide a word of caution for the chronic use of OXT: Chronic neuropeptide treatment and activation of OXT receptors may affect the endogenous OXT system, and result in down-regulation of OXT receptors (Bale et al., 2001; Peters et al., 2014) and in alternative OXT receptor-mediated signaling pathways (Winter et al., 2021).

## 10. Conclusion

During the COVID-19 pandemic, there is strong evidence for social distancing being an essential and useful sanction to reduce the spreading of SARS-CoV2 and to limit the national infection rates. Here, we provide evidence that pandemic-associated social restrictions, leading to either social isolation or home office-related psychosocial stress, impact on various aspects of physical and mental health. This together with the lack of social support as an important stress-buffering and health-promoting factor are likely to weaken the immune system, thus

worsening the course of disease and increasing its pathogenicity. Further, social isolation and lack of social support on the one hand, as well as social tension, bullying and domestic violence on the other are identified risk factors for the development of mental diseases across all ages. This has special impact on the low-risk group of children and adolescents, since their developing brain is highly vulnerable towards chronic psychosocial stress.

We further highlight the importance of the pro-social, anti-inflammatory and anti-stress properties of OXT acting as a mediator of the positive effects of social support. Thus, we suggest to increase the activity of the OXT system, either by application of the synthetic nonapeptide or by activation of the endogenous system, as a possible treatment option in times of pandemics.

## Conflict of interest

The authors declare that there is no conflict of interest.

## References

- Adam, E.K., Hawkey, L.C., Kudielka, B.M., Cacioppo, J.T., 2006. Day-to-day dynamics of experience-cortisol associations in a population-based sample of older adults. *Proc. Natl. Acad. Sci. USA* 103, 17058–17063. <https://doi.org/10.1073/pnas.0605053103>.
- Aguilera, G., 1994. Regulation of pituitary ACTH secretion during chronic stress. *Front. Neuroendocrinol.* 15, 321–350. <https://doi.org/10.1006/frne.1994.1013>.
- Ahmadpoor, P., Rostaing, L., 2020. Why the immune system fails to mount an adaptive immune response to a COVID-19 infection. *Transpl. Int.: Off. J. Eur. Soc. Organ Transplant.* <https://doi.org/10.1111/tri.13611>.
- Alipour, F., Sajadi, H., Forouzan, A., Nabavi, H., Khedmati, E., 2009. The role of social support in the anxiety and depression of elderly. *Iran. J. Ageing* 4, 0.
- Almberg, E.S., Cross, P.C., Dobson, A.P., Smith, D.W., Metz, M.C., Stahler, D.R., Hudson, P.J., 2015. Social living mitigates the costs of a chronic illness in a cooperative carnivore. *Ecol. Lett.* 18, 660–667. <https://doi.org/10.1111/ele.12444>.
- Almeida, J.D., Tyrrell, D.A., 1967. The morphology of three previously uncharacterized human respiratory viruses that grow in organ culture. *J. Gen. Virol.* 1, 175–178. <https://doi.org/10.1099/0022-1317-1-2-175>.
- Ambrée, O., Ruland, C., Scheu, S., Arolt, V., Alferink, J., 2018. Alterations of the innate immune system in susceptibility and resilience after social defeat stress. *Front. Behav. Neurosci.* 12, 141. <https://doi.org/10.3389/fnbeh.2018.00141>.
- Andari, E., Duhamel, J.-R., Zalla, T., Herbrecht, E., Leboyer, M., Sirigu, A., 2010. Promoting social behavior with oxytocin in high-functioning autism spectrum disorders. *Proc. Natl. Acad. Sci. USA* 107, 4389–4394. <https://doi.org/10.1073/pnas.0910249107>.
- Andersson, H., Tullberg, C., Ahméd, S., Hamberg, K., Lazou Ahrén, I., Molin, G., Sonesson, M., Håkansson, Å., 2016. Oral administration of *Lactobacillus plantarum* 299v reduces cortisol levels in human saliva during examination induced stress: a randomized, double-blind controlled trial. *Int. J. Microbiol.* 2016, 8469018 <https://doi.org/10.1155/2016/8469018>.
- Angst, J., Angst, F., Stassen, H.H., 1999. Suicide risk in patients with major depressive disorder. *J. Clin. Psychiatry* 60 (Suppl 2), 57–62 discussion 75-6, 113-6.
- Arakawa, H., 2005. Age dependent effects of space limitation and social tension on open-field behavior in male rats. *Physiol. Behav.* 84, 429–436. <https://doi.org/10.1016/j.physbeh.2005.01.008>.
- Armando, I., Carranza, A., Nishimura, Y., Hoe, K.L., Barontini, M., Terrón, J.A., Falcón-Neri, A., Ito, T., Juorio, A.V., Saavedra, J.M., 2001. Peripheral administration of an angiotensin II AT(1) receptor antagonist decreases the hypothalamic-pituitary-adrenal response to isolation stress. *Endocrinology* 142, 3880–3889. <https://doi.org/10.1210/endo.142.9.8366>.
- Aydinonat, D., Penn, D.J., Smith, S., Moodley, Y., Hoelzl, F., Knauer, F., Schwarzenberger, F., 2014. Social isolation shortens telomeres in African Grey parrots (*Psittacus erithacus erithacus*). *PLOS One* 9, e93839. <https://doi.org/10.1371/journal.pone.0093839>.
- Azabou, E., Bao, G., Bounab, R., Heming, N., Annane, D., 2021. Vagus nerve stimulation: a potential adjunct therapy for COVID-19. *Front. Med.* 8, 625836 <https://doi.org/10.3389/fmed.2021.625836>.
- Bale, T.L., Davis, A.M., Auger, A.P., Dorsa, D.M., McCarthy, M.M., 2001. CNS region-specific oxytocin receptor expression: importance in regulation of anxiety and sex behavior. *J. Neurosci.* 21, 2546–2552. <https://doi.org/10.1523/JNEUROSCI.21-07-02546.2001>.
- Balter, L.J.T., Raymond, J.E., Aldred, S., Drayson, M.T., van Veldhuijzen Zanten, J.J.C.S., Higgins, S., Bosch, J.A., 2019. Loneliness in healthy young adults predicts inflammatory responsiveness to a mild immune challenge in vivo. *Brain Behav., Immun.* 82, 298–301. <https://doi.org/10.1016/j.bbi.2019.08.196>.
- Bartolomucci, A., Palanza, P., Gaspani, L., Limiroli, E., Panerai, A.E., Ceresini, G., Poli, M.D., Parmigiani, S., 2001. Social status in mice: behavioral, endocrine and immune changes are context dependent. *Physiol. Behav.* 73, 401–410. [https://doi.org/10.1016/s0031-9384\(01\)00453-x](https://doi.org/10.1016/s0031-9384(01)00453-x).

- Basbaum, A.I., Fields, H.L., 1984. Endogenous pain control systems: brainstem spinal pathways and endorphin circuitry. *Annu. Rev. Neurosci.* 7, 309–338. <https://doi.org/10.1146/annurev.ne.07.030184.001521>.
- Baune, B.T., Smith, E., Reppermund, S., Air, T., Samaras, K., Lux, O., Brodaty, H., Sachdev, P., Trollor, J.N., 2012. Inflammatory biomarkers predict depressive, but not anxiety symptoms during aging: the prospective Sydney Memory and Aging Study. *Psychoneuroendocrinology* 37, 1521–1530. <https://doi.org/10.1016/j.psyneuen.2012.02.006>.
- Bennett, J.C., Surkan, P.J., Moulton, L.H., Fombonne, E., Melchior, M., 2020. Childhood social isolation and psychotic experiences in young adulthood: a community based study. *Eur. Child Adolesc. Psychiatry* 29, 1003–1010. <https://doi.org/10.1007/s00787-019-01417-2>.
- Bergman, B., Brismar, B., 1991. Suicide attempts by battered wives. *Acta Psychiatr. Scand.* 83, 380–384. <https://doi.org/10.1111/j.1600-0447.1991.tb05560.x>.
- Bernaerts, S., Prinsen, J., Berra, E., Bosmans, G., Steyaert, J., Alaerts, K., 2017. Long-term oxytocin administration enhances the experience of attachment. *Psychoneuroendocrinology* 78, 1–9. <https://doi.org/10.1016/j.psyneuen.2017.01.010>.
- Bernhard, A., van der Merwe, C., Ackermann, K., Martinelli, A., Neumann, I.D., Freitag, C.M., 2018. Adolescent oxytocin response to stress and its behavioral and endocrine correlates. *Horm. Behav.* 105, 157–165. <https://doi.org/10.1016/j.yhbeh.2018.08.010>.
- Berridge, C.W., Waterhouse, B.D., 2003. The locus coeruleus–noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. *Brain Res. Rev.* 42, 33–84. [https://doi.org/10.1016/S0165-0173\(03\)00143-7](https://doi.org/10.1016/S0165-0173(03)00143-7).
- Berton, O., Aguerre, S., Sarrieau, A., Mormede, P., Chaouloff, F., 1997. Differential effects of social stress on central serotonergic activity and emotional reactivity in Lewis and spontaneously hypertensive rats. *Neuroscience* 82, 147–159. [https://doi.org/10.1016/S0306-4522\(97\)00282-0](https://doi.org/10.1016/S0306-4522(97)00282-0).
- Berton, O., McClung, C.A., Dileone, R.J., Krishnan, V., Renthal, W., Russo, S.J., Graham, D., Tsankova, N.M., Bolanos, C.A., Rios, M., Monteggia, L.M., Self, D.W., Nestler, E.J., 2006. Essential role of BDNF in the mesolimbic dopamine pathway in social defeat stress. *Science* 311, 864–868. <https://doi.org/10.1126/science.1120972>.
- Bharwani, A., Mian, M.F., Surette, M.G., Bienenstock, J., Forsythe, P., 2017. Oral treatment with *Lactobacillus rhamnosus* attenuates behavioural deficits and immune changes in chronic social stress. *BMC Med.* 15, 7. <https://doi.org/10.1186/s12916-016-0771-7>.
- Biyikli, N.K., Tuğtepe, H., Sener, G., Velioglu-Ogünç, A., Cetinel, S., Midilloğlu, S., Gedik, N., Yeğen, B.C., 2006. Oxytocin alleviates oxidative renal injury in pyelonephritic rats via a neutrophil-dependent mechanism. *Peptides* 27, 2249–2257. <https://doi.org/10.1016/j.peptides.2006.03.029>.
- Blume, A., Bosch, O.J., Miklos, S., Torner, L., Wales, L., Waldherr, M., Neumann, I.D., 2008. Oxytocin reduces anxiety via ERK1/2 activation: local effect within the rat hypothalamic paraventricular nucleus. *Eur. J. Neurosci.* 27, 1947–1956. <https://doi.org/10.1111/j.1460-9568.2008.06184.x>.
- Bordt, E.A., Smith, C.J., Demarest, T.G., Bilbo, S.D., Kingsbury, M.A., 2019. Mitochondria, oxytocin, and vasopressin: unfolding the inflammatory protein response. *Neurotox. Res.* 36, 239–256. <https://doi.org/10.1007/s12640-018-9962-7>.
- Bosch, O.J., Young, L.J., 2018. Oxytocin and social relationships: from attachment to bond disruption. *Curr. Top. Behav. Neurosci.* 35, 97–117. [https://doi.org/10.1007/7854\\_2017\\_10](https://doi.org/10.1007/7854_2017_10).
- Bosch, O.J., Krömer, S.A., Neumann, I.D., 2006. Prenatal stress: opposite effects on anxiety and hypothalamic expression of vasopressin and corticotropin-releasing hormone in rats selectively bred for high and low anxiety. *Eur. J. Neurosci.* 23, 541–551. <https://doi.org/10.1111/j.1460-9568.2005.04576.x>.
- Bosch, O.J., Nair, H.P., Ahern, T.H., Neumann, I.D., Young, L.J., 2009. The CRF system mediates increased passive stress-coping behavior following the loss of a bonded partner in a monogamous rodent. *Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol.* 34, 1406–1415. <https://doi.org/10.1038/npp.2008.154>.
- Bosch, O.J., Dabrowska, J., Modi, M.E., Johnson, Z.V., Keebaugh, A.C., Barrett, C.E., Ahern, T.H., Guo, J., Grinevich, V., Rainnie, D.G., Neumann, I.D., Young, L.J., 2016. Oxytocin in the nucleus accumbens shell reverses CRFR2-evoked passive stress-coping after partner loss in monogamous male prairie voles. *Psychoneuroendocrinology* 64, 66–78. <https://doi.org/10.1016/j.psyneuen.2015.11.011>.
- Boserup, B., McKenney, M., Elkbulli, A., 2020. Alarming trends in US domestic violence during the COVID-19 pandemic. *Am. J. Emerg. Med.* <https://doi.org/10.1016/j.ajem.2020.04.077>.
- Bradbury-Jones, C., Isham, L., 2020. The pandemic paradox: the consequences of COVID-19 on domestic violence. *J. Clin. Nurs.* <https://doi.org/10.1111/jocn.15296>.
- British Red Cross. Life after lockdown: Tackling loneliness among those left behind. URL: (<https://www.redcross.org.uk/-/media/documents/about-us/research-publication/s/health-and-social-care/life-after-lockdown-tackling-loneliness-among-those-left-behind-report.pdf>) (Accessed 19 June 2020).
- Brody, S., 2006. Blood pressure reactivity to stress is better for people who recently had penile-vaginal intercourse than for people who had other or no sexual activity. *Biol. Psychol.* 71, 214–222. <https://doi.org/10.1016/j.biopsycho.2005.03.005>.
- Brooks, S.K., Webster, R.K., Smith, L.E., Woodland, L., Wessely, S., Greenberg, N., Rubin, G.J., 2020. The psychological impact of quarantine and how to reduce it: rapid review of the evidence. *Lancet* 395, 912–920. [https://doi.org/10.1016/S0140-6736\(20\)30460-8](https://doi.org/10.1016/S0140-6736(20)30460-8).
- Brummett, B.H., Barefoot, J.C., Siegler, I.C., Clapp-Channing, N.E., Lytle, B.L., Bosworth, H.B., Williams, R.B., Mark, D.B., 2001. Characteristics of socially isolated patients with coronary artery disease who are at elevated risk for mortality. *Psychosom. Med.* 63, 267–272. <https://doi.org/10.1097/00006842-200103000-00010>.
- Buemann, B., Marazziti, D., Uvnäs-Moberg, K., 2020. Can intravenous oxytocin infusion counteract hyperinflammation in COVID-19 infected patients? *World J. Biol. Psychiatry: Off. J. World Fed. Soc. Biol. Psychiatry* 1–12. <https://doi.org/10.1080/15622975.2020.1814408>.
- Byambasuren, O., Cardona, M., Bell, K., Clark, J., McLaws, M.-L., Glasziou, P., 2020. Estimating the extent of asymptomatic COVID-19 and its potential for community transmission: systematic review and meta-analysis. *Off. J. Assoc. Med. Microbiol. Infect. Dis. Can.* 5, 223–234. <https://doi.org/10.3138/jammi-2020-0030>.
- Caballero-Domínguez, C.C., Jiménez-Villamizar, M.P., Campo-Arias, A., 2020. Suicide risk during the lockdown due to coronavirus disease (COVID-19) in Colombia. *Death Stud.* 1–6. <https://doi.org/10.1080/07481187.2020.1784312>.
- Cacioppo, J.T., Hughes, M.E., Waite, L.J., Hawkey, L.C., Thisted, R.A., 2006. Loneliness as a specific risk factor for depressive symptoms: cross-sectional and longitudinal analyses. *Psychol. Aging* 21, 140–151. <https://doi.org/10.1037/0882-7974.21.1.140>.
- Cacioppo, J.T., Hawkey, L.C., Thisted, R.A., 2010. Perceived social isolation makes me sad: 5-year cross-lagged analyses of loneliness and depressive symptomatology in the Chicago Health, Aging, and Social Relations Study. *Psychol. Aging* 25, 453–463. <https://doi.org/10.1037/a0017216>.
- Caldwell, H.K., Albers, H.E., 2016. Oxytocin, vasopressin, and the motivational forces that drive social behaviors. *Curr. Top. Behav. Neurosci.* 27, 51–103. [https://doi.org/10.1007/7854\\_2015\\_390](https://doi.org/10.1007/7854_2015_390).
- Campbell, A.M., 2020. An increasing risk of family violence during the Covid-19 pandemic: strengthening community collaborations to save lives. *Forensic Sci. Int.: Rep.* 2, 100089. <https://doi.org/10.1016/j.fsr.2020.100089>.
- Campbell, J.C., 2002. Health consequences of intimate partner violence. *Lancet* 359, 1331–1336. [https://doi.org/10.1016/S0140-6736\(02\)08336-8](https://doi.org/10.1016/S0140-6736(02)08336-8).
- Carmichael, M.S., Humbert, R., Dixen, J., Palmisano, G., Greenleaf, W., Davidson, J.M., 1987. Plasma oxytocin increases in the human sexual response. *J. Clin. Endocrinol. Metab.* 64, 27–31. <https://doi.org/10.1210/jcem-64-1-27>.
- Caspi, A., Harrington, H., Moffitt, T.E., Milne, B.J., Poulton, R., 2006. Socially isolated children 20 years later: risk of cardiovascular disease. *Arch. Pediatr. Adolesc. Med.* 160, 805–811. <https://doi.org/10.1001/archpedi.160.8.805>.
- Castle, S.C., 2000. Clinical relevance of age-related immune dysfunction. *Clin. Infect. Dis.: Off. Publ. Infect. Dis. Soc. Am.* 31, 578–585. <https://doi.org/10.1086/313947>.
- Castro, W.L.R., Matt, K.S., 1997. Neuroendocrine Correlates of Separation Stress in the Siberian Dwarf Hamster (*Phodopus sungorus*). *Physiol. Behav.* 61, 477–484. [https://doi.org/10.1016/S0031-9384\(96\)00456-8](https://doi.org/10.1016/S0031-9384(96)00456-8).
- Catalá-Miñana, A., Lila, M., Oliver, A., Vivo, J.-M., Galiana, L., Gracia, E., 2017. Contextual factors related to alcohol abuse among intimate partner violence offenders. *Subst. Use Misuse* 52, 294–302. <https://doi.org/10.1080/10826084.2016.1225097>.
- CDC COVID-19 Response Team, 2020. Severe Outcomes Among Patients with Coronavirus Disease 2019 (COVID-19) – United States, February 12–March 16, 2020. *Morb. Mortal. Wkly. Rep.* 69, 343–346. <https://doi.org/10.15585/mmwr.mm6912e2>.
- CEBM, 2020. COVID-19: What proportion are asymptomatic? (<https://www.cebm.net/covid-19/covid-19-what-proportion-are-asymptomatic/>).
- Channappanavar, R., Perlman, S., 2017. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. *Semin. Immunopathol.* 39, 529–539. <https://doi.org/10.1007/s00281-017-0629-x>.
- Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Han, Y., Qiu, Y., Wang, J., Liu, Y., Wei, Y., Xia, J., Yu, T., Zhang, X., Zhang, L., 2020. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 395, 507–513. [https://doi.org/10.1016/S0140-6736\(20\)30211-7](https://doi.org/10.1016/S0140-6736(20)30211-7).
- Clair, R., Gordon, M., Kroon, M., Reilly, C., 2021. The effects of social isolation on well-being and life satisfaction during pandemic. *Humanit Soc. Sci. Commun.* 8. <https://doi.org/10.1057/s41599-021-00710-3>.
- Cochran, D.M., Fallon, D., Hill, M., Frazier, J.A., 2013. The role of oxytocin in psychiatric disorders: a review of biological and therapeutic research findings. *Harv. Rev. Psychiatry* 21, 219–247. <https://doi.org/10.1097/HRP.0b013e3182a75b7d>.
- Cohen, S., Janicki-Deverts, D., Turner, R.B., Doyle, W.J., 2015. Does hugging provide stress-buffering social support? A study of susceptibility to upper respiratory infection and illness. *Psychol. Sci.* 26, 135–147. <https://doi.org/10.1177/0956797614559284>.
- Cole, S.W., Hawkey, L.C., Arevalo, J.M.G., Cacioppo, J.T., 2011. Transcript origin analysis identifies antigen-presenting cells as primary targets of socially regulated gene expression in leukocytes. *Proc. Natl. Acad. Sci. USA* 108, 3080–3085. <https://doi.org/10.1073/pnas.1014218108>.
- Copeland, W.E., Wolke, D., Lereya, S.T., Shanahan, L., Worthman, C., Costello, E.J., 2014. Childhood bullying involvement predicts low-grade systemic inflammation into adulthood. *Proc. Natl. Acad. Sci. USA* 111, 7570–7575. <https://doi.org/10.1073/pnas.1323641111>.
- Cusinato, M., Iannattone, S., Spoto, A., Poli, M., Moretti, C., Gatta, M., Miscioscia, M., 2020. Stress, resilience, and well-being in Italian children and their parents during the COVID-19 pandemic. *Int. J. Environ. Res. Public Health* 17. <https://doi.org/10.3390/ijerph17228297>.
- Davidson, L.M., Baum, A., 1986. Chronic stress and posttraumatic stress disorders. *J. Consult. Clin. Psychol.* 54, 303–308. <https://doi.org/10.1037/0022-006X.54.3.303>.
- Delves, P.J., Roitt, I.M., 2000. The immune system. First of two parts. *N. Engl. J. Med.* 343, 37–49. <https://doi.org/10.1056/NEJM200007063430107>.

- Demirci, E., Ozmen, S., Kilic, E., Oztop, D.B., 2016. The relationship between aggression, empathy skills and serum oxytocin levels in male children and adolescents with attention deficit and hyperactivity disorder. *Behav. Pharmacol.* 27, 681–688. <https://doi.org/10.1097/FBP.0000000000000234>.
- Detillion, C.E., Craft, T.K.S., Glasper, E.R., Prendergast, B.J., DeVries, A.C., 2004. Social facilitation of wound healing. *Psychoneuroendocrinology* 29, 1004–1011. <https://doi.org/10.1016/j.psyneuen.2003.10.003>.
- DeVries, A., Glasper, E.R., Detillion, C.E., 2003. Social modulation of stress responses. *Physiol. Behav.* 79, 399–407. [https://doi.org/10.1016/S0031-9384\(03\)00152-5](https://doi.org/10.1016/S0031-9384(03)00152-5).
- DeVries, A.C., Craft, T.K.S., Glasper, E.R., Neigh, G.N., Alexander, J.K., 2007. 2006 Curt P. Richter award winner: social influences on stress responses and health. *Psychoneuroendocrinology* 32, 587–603. <https://doi.org/10.1016/j.psyneuen.2007.04.007>.
- DeWall, C.N., Baumeister, R.F., 2006. Alone but feeling no pain: effects of social exclusion on physical pain tolerance and pain threshold, affective forecasting, and interpersonal empathy. *J. Personal. Soc. Psychol.* 91, 1–15. <https://doi.org/10.1037/0022-3514.91.1.1>.
- Diep, P.-T., Buemann, B., Carter, C.S., 2020. Oxytocin, a possible treatment for COVID-19? Everything to gain, nothing to lose. *Clin. Neuropsychiatry* 17, 1. <https://doi.org/10.36131/CNEPUB20201703>.
- DiSabato, D.J., Nemeth, D.P., Liu, X., Witcher, K.G., O'Neil, S.M., Oliver, B., Bray, C.E., Sheridan, J.F., Godbout, J.P., Quan, N., 2020. Interleukin-1 receptor on hippocampal neurons drives social withdrawal and cognitive deficits after chronic social stress. *Mol. Psychiatry*. <https://doi.org/10.1038/s41380-020-0788-3>.
- Ditzen, B., Schaefer, M., Gabriel, B., Bodenmann, G., Ehler, U., Heinrichs, M., 2009. Intranasal oxytocin increases positive communication and reduces cortisol levels during couple conflict. *Biol. Psychiatry* 65, 728–731. <https://doi.org/10.1016/j.biopsych.2008.10.011>.
- Doane, L.D., Adam, E.K., 2010. Loneliness and cortisol: momentary, day-to-day, and trait associations. *Psychoneuroendocrinology* 35, 430–441. <https://doi.org/10.1016/j.psyneuen.2009.08.005>.
- Donaldson, Z.R., Young, L.J., 2008. Oxytocin, vasopressin, and the neurogenetics of sociality. *Science* 322, 900–904. <https://doi.org/10.1126/science.1158668>.
- Donovan, M., Mackey, C.S., Platt, G.N., Rounds, J., Brown, A.N., Trickey, D.J., Liu, Y., Jones, K.M., Wang, Z., 2020. Social isolation alters behavior, the gut-immune-brain axis, and neurochemical circuits in male and female prairie voles. *Neurobiol. Stress* 13, 100278. <https://doi.org/10.1016/j.jynstr.2020.100278>.
- Du Preez, A., Law, T., Onorato, D., Lim, Y.M., Eiben, P., Musaeelyan, K., Egeland, M., Hye, A., Zunszain, P.A., Thuret, S., Pariante, C.M., Fernandes, C., 2020. The type of stress matters: repeated injection and permanent social isolation stress in male mice have a differential effect on anxiety- and depressive-like behaviours, and associated biological alterations. *Transl. Psychiatry* 10, 325. <https://doi.org/10.1038/s41398-020-01000-3>.
- Dubey, S., Biswas, P., Ghosh, R., Chatterjee, S., Dubey, M.J., Chatterjee, S., Lahiri, D., Lavie, C.J., 2020. Psychosocial impact of COVID-19. *Diabetes Metab. Syndr.* 14, 779–788. <https://doi.org/10.1016/j.dsx.2020.05.035>.
- Duffy, S.S., Keating, B.A., Perera, C.J., Moalem-Taylor, G., 2018. The role of regulatory T cells in nervous system pathologies. *J. Neurosci. Res.* 96, 951–968. <https://doi.org/10.1002/jnr.24073>.
- Dunbar, R.I.M., Shultz, S., 2007. Evolution in the social brain. *Science* 317, 1344–1347. <https://doi.org/10.1126/science.1145463>.
- Dunphy-Doherty, F., O'Mahony, S.M., Peterson, V.L., O'Sullivan, O., Crispie, F., Cotter, P.D., Wigmore, P., King, M.V., Cryan, J.F., Fone, K.C.F., 2018. Post-weaning social isolation of rats leads to long-term disruption of the gut microbiota-immune-brain axis. *Brain Behav. Immun.* 68, 261–273. <https://doi.org/10.1016/j.bbi.2017.10.024>.
- Duque-Wilckens, N., Torres, L.Y., Yokoyama, S., Minie, V.A., Tran, A.M., Petkova, S.P., Hao, R., Ramos-Macieli, S., Rios, R.A., Jackson, K., Flores-Ramirez, F.J., Garcia-Carachure, I., Pesavento, P.A., Iniguez, S.D., Grinevich, V., Trainor, B.C., 2020. Extrahypothalamic oxytocin neurons drive stress-induced social vigilance and avoidance. *Proc. Natl. Acad. Sci. USA* 117, 26406–26413. <https://doi.org/10.1073/pnas.2011890117>.
- Düşünceli, F., İseri, S.O., Ercan, F., Gedik, N., Yeğen, C., Yeğen, B.C., 2008. Oxytocin alleviates hepatic ischemia-reperfusion injury in rats. *Peptides* 29, 1216–1222. <https://doi.org/10.1016/j.peptides.2008.02.010>.
- Ebner, K., Wotjak, C.T., Landgraf, R., Engelmann, M., 2000. A single social defeat experience selectively stimulates the release of oxytocin, but not vasopressin, within the septal brain area of male rats. *Brain Res.* 872, 87–92. [https://doi.org/10.1016/S0006-8993\(00\)02464-1](https://doi.org/10.1016/S0006-8993(00)02464-1).
- Eisenberger, N.I., Taylor, S.E., Gable, S.L., Hilmert, C.J., Lieberman, M.D., 2007. Neural pathways link social support to attenuated neuroendocrine stress responses. *NeuroImage* 35, 1601–1612. <https://doi.org/10.1016/j.neuroimage.2007.01.038>.
- Eisenberger, N.I., Inagaki, T.K., Rameson, L.T., Mashal, N.M., Irwin, M.R., 2009. An fMRI study of cytokine-induced depressed mood and social pain: the role of sex differences. *NeuroImage* 47, 881–890. <https://doi.org/10.1016/j.neuroimage.2009.04.040>.
- Eisenberger, N.I., Inagaki, T.K., Mashal, N.M., Irwin, M.R., 2010. Inflammation and social experience: an inflammatory challenge induces feelings of social disconnection in addition to depressed mood. *Brain Behav. Immun.* 24, 558–563. <https://doi.org/10.1016/j.bbi.2009.12.009>.
- Elabed, C., Cousin, W., Upadhyayula, P., Chen, R.Y., Chooljian, M.S., Li, J., Kung, S., Jiang, K.P., Conboy, I.M., 2014. Oxytocin is an age-specific circulating hormone that is necessary for muscle maintenance and regeneration. *Nat. Commun.* 5, 4082. <https://doi.org/10.1038/ncomms5082>.
- Eliava, M., Melchior, M., Knobloch-Bollmann, H.S., Wahis, J., Da Silva Gouveia, M., Tang, Y., Ciobanu, A.C., Del Triana Rio, R., Roth, L.C., Althammer, F., Chavant, V., Goumon, Y., Gruber, T., Petit-Demoulière, N., Busnelli, M., Chini, B., Tan, L.L., Mitre, M., Froemke, R.C., Chao, M.V., Giese, G., Sprengel, R., Kuner, R., Poisbeau, P., Seeburg, P.H., Stoop, R., Charlet, A., Grinevich, V., 2016. A new population of parvocellular oxytocin neurons controlling magnocellular neuron activity and inflammatory pain processing. *Neuron* 89, 1291–1304. <https://doi.org/10.1016/j.neuron.2016.01.041>.
- Engelmann, M., Landgraf, R., Wotjak, C.T., 2004. The hypothalamic-neurohypophysial system regulates the hypothalamic-pituitary-adrenal axis under stress: an old concept revisited. *Front. Neuroendocrinol.* 25, 132–149. <https://doi.org/10.1016/j.yfrne.2004.09.001>.
- Erdman, S.E., Pouthahidis, T., 2016. Microbes and oxytocin: benefits for host physiology and behavior. *Int. Rev. Neurobiol.* 131, 91–126. <https://doi.org/10.1016/bs.irn.2016.07.004>.
- Ernst, J.M., Cacioppo, J.T., 1999. Lonely hearts: psychological perspectives on loneliness. *Appl. Prev. Psychol.* 8, 1–22. [https://doi.org/10.1016/S0962-1849\(99\)80008-0](https://doi.org/10.1016/S0962-1849(99)80008-0).
- Everett, N.A., Turner, A.J., Costa, P.A., Baracz, S.J., Cornish, J.L., 2021. The vagus nerve mediates the suppressing effects of peripherally administered oxytocin on methamphetamine self-administration and seeking in rats. *Neuropsychopharmacology: Off. Publ. Am. Coll. Neuropsychopharmacol.* 46, 297–304. <https://doi.org/10.1038/s41386-020-0719-7>.
- Faraji, J., Soltanpour, N., Lotfi, H., Moeeni, R., Moharreri, A.-R., Roudaki, S., Hosseini, S.A., Olson, D.M., Abdollahi, A.-A., Soltanpour, N., Mohajerani, M.H., Metz, G.A.S., 2017. Lack of social support raises stress vulnerability in rats with a history of ancestral stress. *Sci. Rep.* 7, 5277. <https://doi.org/10.1038/s41598-017-05440-8>.
- Faraji, J., Karimi, M., Soltanpour, N., Moharreri, A., Rouhadeh, Z., Lotfi, H., Hosseini, S.A., Jafari, S.Y., Roudaki, S., Moeeni, R., Metz, G.A., 2018. Oxytocin-mediated social enrichment promotes longer telomeres and novelty seeking. *eLife* 7. <https://doi.org/10.7554/eLife.40262>.
- Filazoglu, G., Griva, K., 2008. Coping and social support and health related quality of life in women with breast cancer in Turkey. *Psychol. Health Med.* 13, 559–573. <https://doi.org/10.1080/13548500701767353>.
- Fiori, K.L., Denckla, C.A., 2012. Social support and mental health in middle-aged men and women: a multidimensional approach. *J. Aging Health* 24, 407–438. <https://doi.org/10.1177/0898264311425087>.
- Foertsch, S., Reber, S.O., 2020. The role of physical trauma in social stress-induced immune activation. *Neurosci. Biobehav. Rev.* 113, 169–178. <https://doi.org/10.1016/j.neubiorev.2020.02.025>.
- Foertsch, S., Füchsl, A.M., Faller, S.D., Hölzer, H., Langgartner, D., Messmann, J., Straub, G., Reber, S.O., 2017. Splenic glucocorticoid resistance following psychosocial stress requires physical injury. *Sci. Rep.* 7, 15730. <https://doi.org/10.1038/s41598-017-15897-2>.
- Fone, K.C.F., Porkess, M.V., 2008. Behavioural and neurochemical effects of post-weaning social isolation in rodents—relevance to developmental neuropsychiatric disorders. *Neurosci. Biobehav. Rev.* 32, 1087–1102. <https://doi.org/10.1016/j.neubiorev.2008.03.003>.
- Forster, L.E., Stoller, E.P., 1992. The impact of social support on mortality: a seven-year follow-up of older men and women. *J. Appl. Gerontol.* 11, 173–186. <https://doi.org/10.1177/073346489201100204>.
- Forte, G., Favieri, F., Tambelli, R., Casagrande, M., 2020. COVID-19 pandemic in the Italian population: validation of a post-traumatic stress disorder questionnaire and prevalence of PTSD symptomatology. *Int. J. Environ. Res. Public Health* 17. <https://doi.org/10.3390/ijerph17114151>.
- Frijling, J.L., van Zuiden, M., Nawijn, L., Koch, S.B.J., Neumann, I.D., Veltman, D.J., Olff, M., 2015. Salivary oxytocin and vasopressin levels in police officers with and without post-traumatic stress disorder. *J. Neuroendocrinol.* 27, 743–751. <https://doi.org/10.1111/jne.12300>.
- Füchsl, A.M., Langgartner, D., Reber, S.O., 2013. Mechanisms underlying the increased plasma ACTH levels in chronic psychosocially stressed male mice. *PLOS One* 8, e84161. <https://doi.org/10.1371/journal.pone.0084161>.
- Gądek-Michalska, A., Tadeusz, J., Bugajski, A., Bugajski, J., 2019. Chronic isolation stress affects subsequent crowding stress-induced brain nitric oxide synthase (NOS) isoforms and hypothalamic-pituitary-adrenal (HPA) axis responses. *Neurotox. Res.* 36, 523–539. <https://doi.org/10.1007/s12640-019-00067-1>.
- Galea, S., Abdalla, S.M., 2020. COVID-19 pandemic, unemployment, and civil unrest: underlying deep racial and socioeconomic divides. *JAMA*. <https://doi.org/10.1001/jama.2020.11132>.
- Gamer, M., Zurowski, B., Büchel, C., 2010. Different amygdala subregions mediate valence-related and attentional effects of oxytocin in humans. *Proc. Natl. Acad. Sci. USA* 107, 9400–9405. <https://doi.org/10.1073/pnas.1000985107>.
- George, L.K., Blazer, D.G., Hughes, D.C., Fowler, N., 1989. Social support and the outcome of major depression. *Br. J. Psychiatry: J. Ment. Sci.* 154, 478–485. <https://doi.org/10.1192/bjp.154.4.478>.
- Ginzburg, K., Ein-Dor, T., Solomon, Z., 2010. Comorbidity of posttraumatic stress disorder, anxiety and depression: a 20-year longitudinal study of war veterans. *J. Affect. Disord.* 123, 249–257. <https://doi.org/10.1016/j.jad.2009.08.006>.
- Glass, T.A., Matchar, D.B., Belyea, M., Feussner, J.R., 1993. Impact of social support on outcome in first stroke. *Stroke* 24, 64–70. <https://doi.org/10.1161/01.STR.24.1.64>.
- Golden, S.A., Covington, H.E., Berton, O., Russo, S.J., 2011. A standardized protocol for repeated social defeat stress in mice. *Nat. Protoc.* 6, 1183–1191. <https://doi.org/10.1038/nprot.2011.361>.
- Golding, J.M., 1999. *J. Fam. Violence* 14, 99–132. <https://doi.org/10.1023/A:1022079418229>.
- Gouin, J.-P., Carter, C.S., Pournajafi-Nazarloo, H., Glaser, R., Malarkey, W.B., Loving, T. J., Stowell, J., Kiecolt-Glaser, J.K., 2010. Marital behavior, oxytocin, vasopressin,

- and wound healing. *Psychoneuroendocrinology* 35, 1082–1090. <https://doi.org/10.1016/j.psyneuen.2010.01.009>.
- Gove, W.R., Hughes, M., Galle, O.R., 1979. Overcrowding in the home: an empirical investigation of its possible pathological consequences. *Am. Sociol. Rev.* 44, 59. <https://doi.org/10.2307/2094818>.
- Grinevich, V., Neumann, I.D., 2020. Brain oxytocin: how puzzle stones from animal studies translate into psychiatry. *Mol. Psychiatry*. <https://doi.org/10.1038/s41380-020-0802-9>.
- Grippo, A.J., Wu, K.D., Hassan, I., Carter, C.S., 2008. Social isolation in prairie voles induces behaviors relevant to negative affect: toward the development of a rodent model focused on co-occurring depression and anxiety. *Depress Anxiety* 25, E17–E26. <https://doi.org/10.1002/da.20375>.
- Grippo, A.J., Trahanas, D.M., Zimmerman, R.R., Porges, S.W., Carter, C.S., 2009. Oxytocin protects against negative behavioral and autonomic consequences of long-term social isolation. *Psychoneuroendocrinology* 34, 1542–1553. <https://doi.org/10.1016/j.psyneuen.2009.05.017>.
- Grippo, A.J., Carter, C.S., McNeal, N., Chandler, D.L., Larocca, M.A., Bates, S.L., Porges, S.W., 2011. 24-hour autonomic dysfunction and depressive behaviors in an animal model of social isolation: implications for the study of depression and cardiovascular disease. *Psychosom. Med.* 73, 59–66. <https://doi.org/10.1097/PSY.0b013e31820019e4>.
- Groß, S., Jahn, C., Cushman, S., Bär, C., Thum, T., 2020. SARS-CoV-2 receptor ACE2-dependent implications on the cardiovascular system: From basic science to clinical implications. *J. Mol. Cell. Cardiol.* 144, 47–53. <https://doi.org/10.1016/j.yjmcc.2020.04.031>.
- Gruver, A.L., Sempowski, G.D., 2008. Cytokines, leptin, and stress-induced thymic atrophy. *J. Leukoc. Biol.* 84, 915–923. <https://doi.org/10.1189/jlb.0108025>.
- Guastella, A.J., Mitchell, P.B., Mathews, F., 2008. Oxytocin enhances the encoding of positive social memories in humans. *Biol. Psychiatry* 64, 256–258. <https://doi.org/10.1016/j.biopsych.2008.02.008>.
- Guerra Lund, R., Manica, S., Mânica, G., 2020. Collateral issues in times of covid-19: child abuse, domestic violence and femicide. *RBOL* 7. <https://doi.org/10.21117/rbol-v7n22020-318>.
- Guessoum, S.B., Lachal, J., Radjack, R., Carretier, E., Minassian, S., Benoit, L., Moro, M. R., 2020. Adolescent psychiatric disorders during the COVID-19 pandemic and lockdown. *Psychiatry Res.* 291, 113264. <https://doi.org/10.1016/j.psychres.2020.113264>.
- Gunaydin, L.A., Deisseroth, K., 2014. Dopaminergic dynamics contributing to social behavior. *Cold Spring Harb. Symp. Quant. Biol.* 79, 221–227. <https://doi.org/10.1101/sqb.2014.79.024711>.
- Hackett, R.A., Hamer, M., Endrighi, R., Brydon, L., Steptoe, A., 2012. Loneliness and stress-related inflammatory and neuroendocrine responses in older men and women. *Psychoneuroendocrinology* 37, 1801–1809. <https://doi.org/10.1016/j.psyneuen.2012.03.016>.
- Haller, J., Harold, G., Sandi, C., Neumann, I.D., 2014. Effects of adverse early-life events on aggression and anti-social behaviours in animals and humans. *J. Neuroendocrinol.* 26, 724–738. <https://doi.org/10.1111/jne.12182>.
- Han, K.-M., Park, J.Y., Park, H.E., An, S.R., Lee, E.H., Yoon, H.-K., Ko, Y.-H., 2019. Social support moderates association between posttraumatic growth and trauma-related psychopathologies among victims of the Sewol Ferry Disaster. *Psychiatry Res.* 272, 507–514. <https://doi.org/10.1016/j.psychres.2018.12.168>.
- Harvey, B.H., Regenass, W., Dreyer, W., Möller, M., 2019. Social isolation rearing-induced anxiety and response to agomelatine in male and female rats: role of corticosterone, oxytocin, and vasopressin. *J. Psychopharmacol. (Oxf., Engl.)* 33, 640–646. <https://doi.org/10.1177/0269881119826783>.
- Häusser, J.A., Kattenstroth, M., van Dick, R., Mojzisch, A., 2012. “We” are not stressed: social identity in groups buffers neuroendocrine stress reactions. *J. Exp. Soc. Psychol.* 48, 973–977. <https://doi.org/10.1016/j.jesp.2012.02.020>.
- Hawley, L.C., Cacioppo, J.T., 2004. Stress and the aging immune system. *Brain Behav. Immun.* 18, 114–119. <https://doi.org/10.1016/j.bbi.2003.09.005>.
- Hawley, L.C., Masi, C.M., Berry, J.D., Cacioppo, J.T., 2006. Loneliness is a unique predictor of age-related differences in systolic blood pressure. *Psychol. Aging* 21, 152–164. <https://doi.org/10.1037/0882-7974.21.1.152>.
- Hawley, L.C., Bosch, J.A., Engeland, C.G., Marucha, P.T., Cacioppo, J.T., 2007. Loneliness, dysphoria, stress and immunity: a role for cytokines. *Cytokine: Stress Immun.* 67–85.
- Heck, A.L., Sheng, J.A., Miller, A.M., Stover, S.A., Bales, N.J., Tan, S.M.L., Daniels, R.M., Fleury, T.K., Handa, R.J., 2020. Social isolation alters hypothalamic pituitary adrenal axis activity after chronic variable stress in male C57BL/6 mice. *Stress* 23, 457–465. <https://doi.org/10.1080/10253890.2020.1733962>.
- Heim, C., Nemeroff, C.B., 2001. The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. *Biol. Psychiatry* 49, 1023–1039. [https://doi.org/10.1016/S0006-3223\(01\)01157-X](https://doi.org/10.1016/S0006-3223(01)01157-X).
- Heim, C., Newport, D.J., Heit, S., Graham, Y.P., Wilcox, M., Bonsall, R., Miller, A.H., Nemeroff, C.B., 2000. Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. *JAMA* 284, 592–597. <https://doi.org/10.1001/jama.284.5.592>.
- Heim, C., Young, L.J., Newport, D.J., Mletzko, T., Miller, A.H., Nemeroff, C.B., 2009. Lower CSF oxytocin concentrations in women with a history of childhood abuse. *Mol. Psychiatry* 14, 954–958. <https://doi.org/10.1038/mp.2008.112>.
- Heinrichs, M., Baumgartner, T., Kirschbaum, C., Ehler, U., 2003. Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress. *Biol. Psychiatry* 54, 1389–1398. [https://doi.org/10.1016/S0006-3223\(03\)00465-7](https://doi.org/10.1016/S0006-3223(03)00465-7).
- Heinrichs, S.C., Pich, E.M., Miczek, K.A., Britton, K.T., Koob, G.F., 1992. Corticotropin-releasing factor antagonist reduces emotionality in socially defeated rats via direct neurotropic action. *Brain Res.* 581, 190–197. [https://doi.org/10.1016/0006-8993\(92\)90708-H](https://doi.org/10.1016/0006-8993(92)90708-H).
- Hew-Butler, T., Noakes, T.D., Soldin, S.J., Verbalis, J.G., 2008. Acute changes in endocrine and fluid balance markers during high-intensity, steady-state, and prolonged endurance running: unexpected increases in oxytocin and brain natriuretic peptide during exercise. *Eur. J. Endocrinol.* 159, 729–737. <https://doi.org/10.1530/EJE-08-0064>.
- Heyne, A., 1996. The development of opiate addiction in the rat. *Pharmacol. Biochem. Behav.* 53, 11–25. [https://doi.org/10.1016/0091-3057\(95\)00193-X](https://doi.org/10.1016/0091-3057(95)00193-X).
- Hodes, G.E., Pfau, M.L., Leboeuf, M., Golden, S.A., Christoffel, D.J., Bregman, D., Rebusi, N., Heshmati, M., Aleyasin, H., Warren, B.L., Lebonoté, B., Horn, S., Lapidus, K.A., Stelzhammer, V., Wong, E.H.F., Bahn, S., Krishnan, V., Bolaños-Guzman, C.A., Murrrough, J.W., Merad, M., Russo, S.J., 2014. Individual differences in the peripheral immune system promote resilience versus susceptibility to social stress. *Proc. Natl. Acad. Sci. USA* 111, 16136–16141. <https://doi.org/10.1073/pnas.1415191111>.
- Hollins Martin, C.J., Martin, C., 2010. Bully for you: harassment and bullying in the workplace. *Br. J. Midwifery* 18, 25–31. <https://doi.org/10.12968/bjom.2010.18.1.45812>.
- Holt-Lunstad, J., Smith, T.B., Layton, J.B., 2010. Social relationships and mortality risk: a meta-analytic review. *PLoS Med.* 7, e1000316. <https://doi.org/10.1371/journal.pmed.1000316>.
- Holt-Lunstad, J., Birmingham, W., Light, K.C., 2011. The influence of depressive symptomatology and perceived stress on plasma and salivary oxytocin before, during and after a support enhancement intervention. *Psychoneuroendocrinology* 36, 1249–1256. <https://doi.org/10.1016/j.psyneuen.2011.03.007>.
- Howard, L.M., Trevillion, K., Agnew-Davies, R., 2010. Domestic violence and mental health. *Int. Rev. Psychiatry* 22, 525–534. <https://doi.org/10.3109/09540261.2010.512283>.
- Huang, K.-J., Su, I.-J., Theron, M., Wu, Y.-C., Lai, S.-K., Liu, C.-C., Lei, H.-Y., 2005. An interferon-gamma-related cytokine storm in SARS patients. *J. Med. Virol.* 75, 185–194. <https://doi.org/10.1002/jmv.20255>.
- Hueston, C.M., Cryan, J.F., Nolan, Y.M., 2017. Adolescent social isolation stress unmasks the combined effects of adolescent exercise and adult inflammation on hippocampal neurogenesis and behavior. *Neuroscience* 365, 226–236. <https://doi.org/10.1016/j.neuroscience.2017.09.020>.
- Huhman, K.L., Bunnell, B.N., Mougey, E.H., Meyerhoff, J.L., 1990. Effects of social conflict on POMC-derived peptides and glucocorticoids in male golden hamsters. *Physiol. Behav.* 47, 949–956. [https://doi.org/10.1016/0031-9384\(90\)90023-W](https://doi.org/10.1016/0031-9384(90)90023-W).
- Hwang, T.-J., Rabheru, K., Peisah, C., Reichman, W., Ikeda, M., 2020. Loneliness and social isolation during the COVID-19 pandemic. *Int. Psychogeriatr.* 32, 1217–1220. <https://doi.org/10.1017/S1041610220000988>.
- Ieraci, A., Mallei, A., Popoli, M., 2016. Social isolation stress induces anxious-depressive-like behavior and alterations of neuroplasticity-related genes in adult male mice. *Neural Plast.* 2016, 6212983. <https://doi.org/10.1155/2016/6212983>.
- Ikemoto, S., 2007. Dopamine reward circuitry: two projection systems from the ventral midbrain to the nucleus accumbens-olfactory tubercle complex. *Brain Res. Rev.* 56, 27–78. <https://doi.org/10.1016/j.brainresrev.2007.05.004>.
- Ireland, J.L., Power, C.L., 2004. Attachment, emotional loneliness, and bullying behaviour: A study of adult and young offenders. *Aggr. Behav.* 30, 298–312. <https://doi.org/10.1002/ab.20035>.
- Işeri, S.O., Sener, G., Sağlam, B., Gedik, N., Ercan, F., Yeğen, B.C., 2005a. Oxytocin protects against sepsis-induced multiple organ damage: role of neutrophils. *J. Surg. Res.* 126, 73–81. <https://doi.org/10.1016/j.jss.2005.01.021>.
- Işeri, S.O., Sener, G., Sağlam, B., Gedik, N., Ercan, F., Yeğen, B.C., 2005b. Oxytocin ameliorates oxidative colonic inflammation by a neutrophil-dependent mechanism. *Spectroscopy* 26, 483–491. <https://doi.org/10.1016/j.peptides.2004.10.005>.
- Işeri, S.O., Gedik, I.E., Erzik, C., Uslu, B., Arbak, S., Gedik, N., Yeğen, B.C., 2008. Oxytocin ameliorates skin damage and oxidant gastric injury in rats with thermal trauma. *Burn. J. Int. Soc. Burn Inj.* 34, 361–369. <https://doi.org/10.1016/j.burns.2007.03.022>.
- Janevay, C., Travers, P., 2005. *Immunobiology: The Immune System in Health and Disease; [CD-ROM Inside; Animations, Videos and Figures from the Book, sixth ed. Garland Science, New York, p. 823.*
- Jankowski, M., Bissonauth, V., Gao, L., Gangal, M., Wang, D., Danalache, B., Wang, Y., Stroyanova, E., Cloutier, G., Blaise, G., Gutkowska, J., 2010. Anti-inflammatory effect of oxytocin in rat myocardial infarction. *Basic Res. Cardiol.* 105, 205–218. <https://doi.org/10.1007/s00395-009-0076-5>.
- Jaremka, L.M., Fagundes, C.P., Glaser, R., Bennett, J.M., Malarkey, W.B., Kiecolt-Glaser, J.K., 2013a. Loneliness predicts pain, depression, and fatigue: understanding the role of immune dysregulation. *Psychoneuroendocrinology* 38, 1310–1317. <https://doi.org/10.1016/j.psyneuen.2012.11.016>.
- Jaremka, L.M., Fagundes, C.P., Peng, J., Bennett, J.M., Glaser, R., Malarkey, W.B., Kiecolt-Glaser, J.K., 2013b. Loneliness promotes inflammation during acute stress. *Psychol. Sci.* 24, 1089–1097. <https://doi.org/10.1177/0956797612464059>.
- Jong, T.R., de Menon, R., Bludau, A., Grund, T., Biermeier, V., Klampfl, S.M., Jurek, B., Bosch, O.J., Hellhammer, J., Neumann, I.D., 2015. Salivary oxytocin concentrations in response to running, sexual self-stimulation, breastfeeding and the TSST: The Regensburg Oxytocin Challenge (ROC) study. *Psychoneuroendocrinology* 62, 381–388. <https://doi.org/10.1016/j.psyneuen.2015.08.027>.
- Jong, T.R., de Neumann, I.D., 2018. Oxytocin and aggression. *Curr. Top. Behav. Neurosci.* 35, 175–192. [https://doi.org/10.1007/7854\\_2017\\_13](https://doi.org/10.1007/7854_2017_13).
- Jurek, B., Neumann, I.D., 2018. The oxytocin receptor: from intracellular signaling to behavior. *Physiol. Rev.* 98, 1805–1908. <https://doi.org/10.1152/physrev.00031.2017>.

- Jurek, B., Slattery, D.A., Hiraoka, Y., Liu, Y., Nishimori, K., Aguilera, G., Neumann, I.D., van den Burg, E.H., 2015. Oxytocin regulates stress-induced Crf gene transcription through CREB-regulated transcription coactivator 3. *J. Neurosci.* 35, 12248–12260. <https://doi.org/10.1523/JNEUROSCI.1345-14.2015>.
- Kaiser, S., Sachser, N., 1998. The social environment during pregnancy and lactation affects the female offspring's endocrine status and behaviour in guinea pigs. *Physiol. Behav.* 63, 361–366. [https://doi.org/10.1016/S0031-9384\(97\)00435-6](https://doi.org/10.1016/S0031-9384(97)00435-6).
- Kaiser, S., Sachser, N., 2005. The effects of prenatal social stress on behaviour: mechanisms and function. *Neurosci. Biobehav. Rev.* 29, 283–294. <https://doi.org/10.1016/j.neubiorev.2004.09.015>.
- Kamal, N.M., Othman, N., 2020. Depression, anxiety, and stress in the time of COVID-19 pandemic in Kurdistan Region, Iraq. *KJAR* 37–44. <https://doi.org/10.24017/covid.5>.
- Kamarck, T.W., Manuck, S.B., Jennings, J.R., 1990. Social support reduces cardiovascular reactivity to psychological challenge: a laboratory model. *Psychosom. Med.* 52, 42–58. <https://doi.org/10.1097/00006842-199001000-00004>.
- Kappelman, N., Dantzer, R., Khandaker, G.M., 2021. Interleukin-6 as potential mediator of long-term neuropsychiatric symptoms of COVID-19. *Psychoneuroendocrinology* 131, 105295. <https://doi.org/10.1016/j.psyneuen.2021.105295>.
- Kaptoge, S., Di Angelantonio, E., Lowe, G., Pepys, M.B., Thompson, S.G., Collins, R., Danesh, J., 2010. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. *Lancet* 375, 132–140. [https://doi.org/10.1016/S0140-6736\(09\)61717-7](https://doi.org/10.1016/S0140-6736(09)61717-7).
- Karailiev, P., Hlavacova, N., Chmelova, M., Homer, N.Z.M., Jezova, D., 2021. Tight junction proteins in the small intestine and prefrontal cortex of female rats exposed to stress of chronic isolation starting early in life. *Neurogastroenterology and motility: the official journal of the European Gastrointestinal Motility Society* 33, e14084. <https://doi.org/10.1111/nmo.14084>.
- Karelina, K., DeVries, A.C., 2011. Modeling social influences on human health. *Psychosom. Med.* 73, 67–74. <https://doi.org/10.1097/PSY.0b013e3182002116>.
- Karelina, K., Stuller, K.A., Jarrett, B., Zhang, N., Wells, J., Norman, G.J., DeVries, A.C., 2011. Oxytocin mediates social neuroprotection after cerebral ischemia. *Stroke* 42, 3606–3611. <https://doi.org/10.1161/STROKEAHA.111.628008>.
- Kaslow, N.J., Thompson, M.P., Okun, A., Price, A., Young, S., Bender, M., Wyckoff, S., Twomey, H., Goldin, J., Parker, R., 2002. Risk and protective factors for suicidal behavior in abused African American women. *J. Consult. Clin. Psychol.* 70, 311–319. <https://doi.org/10.1037/0022-006X.70.2.311>.
- Keeney, A., Jessop, D.S., Harbuz, M.S., Marsden, C.A., Hogg, S., Blackburn-Munro, R.E., 2006. Differential effects of acute and chronic social defeat stress on hypothalamic-pituitary-adrenal axis function and hippocampal serotonin release in mice. *J. Neuroendocrinol.* 18, 330–338. <https://doi.org/10.1111/j.1365-2826.2006.01422.x>.
- Keeney, A.J., Hogg, S., 1999. Behavioural consequences of repeated social defeat in the mouse: preliminary evaluation of a potential animal model of depression. *Behav. Pharmacol.* 10, 753–764. <https://doi.org/10.1097/00008877-199912000-00007>.
- Kelly, H., 2011. The classical definition of a pandemic is not elusive. *Bull. World Health Organ.* 89, 540–541. <https://doi.org/10.2471/BLT.11.088815>.
- Khan, A., Leventhal, R.M., Khan, S., Brown, W.A., 2002. Suicide risk in patients with anxiety disorders: a meta-analysis of the FDA database. *J. Affect. Disord.* 68, 183–190. [https://doi.org/10.1016/S0165-0327\(01\)00354-8](https://doi.org/10.1016/S0165-0327(01)00354-8).
- Kiecolt-Glaser, J.K., Ricker, D., George, J., Messick, G., Speicher, C.E., Garner, W., Glaser, R., 1984. Urinary cortisol levels, cellular immunocompetency, and loneliness in psychiatric inpatients. *Psychosom. Med.* 46, 15–23. <https://doi.org/10.1097/00006842-198401000-00004>.
- Kikusui, T., Winslow, J.T., Mori, Y., 2006. Social buffering: relief from stress and anxiety. *Philos. Trans. R. Soc. Lond. Ser. B Biol. Sci.* 361, 2215–2228. <https://doi.org/10.1098/rstb.2006.1941>.
- Kirschbaum, C., Klauer, T., Filipp, S.H., Hellhammer, D.H., 1995. Sex-specific effects of social support on cortisol and subjective responses to acute psychologic stress. *Psychosom. Med.* 57, 23–31. <https://doi.org/10.1097/00006842-199501000-00004>.
- Klein, B.Y., Tamir, H., Hirschberg, D.L., Ludwig, R.J., Glickstein, S.B., Myers, M.M., Welch, M.G., 2016. Oxytocin opposes effects of bacterial endotoxin on ER-stress signaling in Caco2BB gut cells. *Biochim. Biophys. Acta* 1860, 402–411. <https://doi.org/10.1016/j.bbagen.2015.10.025>.
- Knox, S.S., Uvnäs-Moberg, K., 1998. Social isolation and cardiovascular disease: an atherosclerotic pathway? *Psychoneuroendocrinology* 23, 877–890. [https://doi.org/10.1016/S0306-4530\(98\)00061-4](https://doi.org/10.1016/S0306-4530(98)00061-4).
- Kofler, J., Wiley, C.A., 2011. Microglia: key innate immune cells of the brain. *Toxicol. Pathol.* 39, 103–114. <https://doi.org/10.1177/0192623310387619>.
- Koike, H., Ibi, D., Mizoguchi, H., Nagai, T., Nitta, A., Takuma, K., Nabeshima, T., Yoneda, Y., Yamada, K., 2009. Behavioral abnormality and pharmacologic response in social isolation-reared mice. *Behav. Brain Res.* 202, 114–121. <https://doi.org/10.1016/j.bbr.2009.03.028>.
- Kola, L., Kohrt, B.A., Hanlon, C., Naslund, J.A., Sikander, S., Balaji, M., Benjet, C., Cheung, E.Y.L., Eaton, J., Gonsalves, P., Hailemariam, M., Luitel, N.P., Machado, D. B., Misganaw, E., Omigbodun, O., Roberts, T., Salisbury, T.T., Shidhaye, R., Sunkel, C., Ugo, V., van Rensburg, A.J., Gureje, O., Pathare, S., Saxena, S., Thornicroft, G., Patel, V., 2021. COVID-19 mental health impact and responses in low-income and middle-income countries: reimagining global mental health. *Lancet Psychiatry* 8, 535–550. [https://doi.org/10.1016/S2215-0366\(21\)00025-0](https://doi.org/10.1016/S2215-0366(21)00025-0).
- Konecka, A.M., Sroczyńska, I., 1990. Stressors and pain sensitivity in CFW mice. Role of opioid peptides. *Arch. Int. Physiol. Biochim.* 98, 245–252. <https://doi.org/10.3109/13813459009113984>.
- Krishnan, V., Han, M.-H., Graham, D.L., Berton, O., Renthal, W., Russo, S.J., Laplant, Q., Graham, A., Lutter, M., Lagace, D.C., Ghose, S., Reister, R., Tannous, P., Green, T.A., Neve, R.L., Chakravarty, S., Kumar, A., Eisch, A.J., Self, D.W., Lee, F.S., Tammenga, C.A., Cooper, D.C., Gershenfeld, H.K., Nestler, E.J., 2007. Molecular adaptations underlying susceptibility and resistance to social defeat in brain reward regions. *Cell* 131, 391–404. <https://doi.org/10.1016/j.cell.2007.09.018>.
- Kronen, C.H., Kubzansky, L.D., Schernhammer, E.S., Holmes, M.D., Kawachi, I., 2006. Social networks, social support, and survival after breast cancer diagnosis. *J. Clin. Oncol.: Off. J. Am. Soc. Clin. Oncol.* 24, 1105–1111. <https://doi.org/10.1200/JCO.2005.04.2846>.
- Labaka, A., Gómez-Lázaro, E., Vegas, O., Pérez-Tejada, J., Arregi, A., Garmendia, L., 2017. Reduced hippocampal IL-10 expression, altered monoaminergic activity and anxiety and depressive-like behavior in female mice subjected to chronic social instability stress. *Behav. Brain Res.* 335, 8–18. <https://doi.org/10.1016/j.bbr.2017.08.002>.
- Lambin, M., Murawski, C., Whittle, S., Fornito, A., 2017. Social connectedness, mental health and the adolescent brain. *Neurosci. Biobehav. Rev.* 80, 57–68. <https://doi.org/10.1016/j.neubiorev.2017.05.010>.
- Landgraf, R., Neumann, I.D., 2004. Vasopressin and oxytocin release within the brain: a dynamic concept of multiple and variable modes of neuropeptide communication. *Front. Neuroendocrinol.* 25, 150–176. <https://doi.org/10.1016/j.yfrne.2004.05.001>.
- Langgartner, D., Füchsl, A.M., Uschold-Schmidt, N., Slattery, D.A., Reber, S.O., 2015. Chronic subordinate colony housing paradigm: a mouse model to characterize the consequences of insufficient glucocorticoid signaling. *Front. Psychiatry* 6, 18. <https://doi.org/10.3389/fpsy.2015.00018>.
- Le Merer, J., Becker, J.A.J., Befort, K., Kieffer, B.L., 2009. Reward processing by the opioid system in the brain. *Physiol. Rev.* 89, 1379–1412. <https://doi.org/10.1152/physrev.00005.2009>.
- LeClair, J., Sasaki, J.Y., Ishii, K., Shinada, M., Kim, H.S., 2016. Gene-culture interaction: influence of culture and oxytocin receptor gene (OXTR) polymorphism on loneliness. *Cult. Brain* 4, 21–37. <https://doi.org/10.1007/s40167-016-0034-7>.
- Lee, A.M., Wong, J.G.W.S., McAlonan, G.M., Cheung, V., Cheung, C., Sham, P.C., Chu, C.-M., Wong, P.-C., Tsang, K.W.T., Chua, S.E., 2007. Stress and psychological distress among SARS survivors 1 year after the outbreak. *Can. J. Psychiatry Rev. Can. Psychiatr.* 52, 233–240. <https://doi.org/10.1177/070674370705200405>.
- Li, L.-Q., Huang, T., Wang, Y.-Q., Wang, Z.-P., Liang, Y., Huang, T.-B., Zhang, H.-Y., Sun, W., Wang, Y., 2020a. COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. *J. Med. Virol.* 92, 577–583. <https://doi.org/10.1002/jmv.25757>.
- Li, M.-Y., Li, L., Zhang, Y., Wang, X.-S., 2020b. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. *Infect. Dis. Poverty* 9, 45. <https://doi.org/10.1186/s40249-020-00662-x>.
- Lim, J., Zebrack, B., 2008. Different pathways in social support and quality of life between Korean American and Korean breast and gynecological cancer survivors. *Qual. Life Res.: Int. J. Qual. Life Asp. Treat., Care Rehabil.* 17, 679–689. <https://doi.org/10.1007/s11136-008-9343-4>.
- Lim, M.M., Young, L.J., 2006. Neuropeptidergic regulation of affiliative behavior and social bonding in animals. *Horm. Behav.* 50, 506–517. <https://doi.org/10.1016/j.yhbeh.2006.06.028>.
- Lima, C.K.T., Carvalho, P.Md.M., Lima, Id.A.A.S., Nunes, J.V.Ad.O., Saraiva, J.S., Souza, R. Ide, da Silva, C.G.L., Neto, M.L.R., 2020. The emotional impact of Coronavirus 2019-nCoV (new Coronavirus disease). *Psychiatry Res.* 287, 112915. <https://doi.org/10.1016/j.psychres.2020.112915>.
- Liu, C.H., Zhang, E., Wong, G.T.F., Hyun, S., Hahn, H.C., 2020. Factors associated with depression, anxiety, and PTSD symptomatology during the COVID-19 pandemic: clinical implications for U.S. young adult mental health. *Psychiatry Res.* 290, 113172. <https://doi.org/10.1016/j.psychres.2020.113172>.
- Liu, Y., Yue, S., Hu, X., Zhu, J., Wu, Z., Wang, J., Wu, Y., 2021. Associations between feelings/behaviors during COVID-19 pandemic lockdown and depression/anxiety after lockdown in a sample of Chinese children and adolescents. *J. Affect. Disord.* 284, 98–103. <https://doi.org/10.1016/j.jad.2021.02.001>.
- Lopez-Duran, N.L., McGinnis, E., Kuhlman, K., Geiss, E., Vaxgar, I., Mayer, S., 2015. HPA-axis stress reactivity in youth depression: evidence of impaired regulatory processes in depressed boys. *Stress* 18, 545–553. <https://doi.org/10.3109/10253890.2015.1053455>.
- Lucas, S., Jernbro, C., Tindberg, Y., Janson, S., 2016. Bully, bullied and abused. Associations between violence at home and bullying in childhood. *Scand. J. Public Health* 44, 27–35. <https://doi.org/10.1177/1403494815610238>.
- Lucht, M.J., Barnow, S., Sonnenfeld, C., Rosenberger, A., Grabe, H.J., Schroeder, W., Völzke, H., Freyberger, H.J., Herrmann, F.H., Kroemer, H., Roskopf, D., 2009. Associations between the oxytocin receptor gene (OXTR) and affect, loneliness and intelligence in normal subjects. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* 33, 860–866. <https://doi.org/10.1016/j.pnpbp.2009.04.004>.
- Lukas, M., Bredewold, R., Landgraf, R., Neumann, I.D., Veenema, A.H., 2011a. Early life stress impairs social recognition due to a blunted response of vasopressin release within the septum of adult male rats. *Psychoneuroendocrinology* 36, 843–853. <https://doi.org/10.1016/j.psyneuen.2010.11.007>.
- Lukas, M., Toth, I., Reber, S.O., Slattery, D.A., Veenema, A.H., Neumann, I.D., 2011b. The neuropeptide oxytocin facilitates pro-social behavior and prevents social avoidance in rats and mice. *Neuropsychopharmacol.: Off. Publ. Am. Coll. Neuropsychopharmacol.* 36, 2159–2168. <https://doi.org/10.1038/npp.2011.95>.
- Lundeberg, T., Uvnäs-Moberg, K., Ågren, G., Bruzelius, G., 1994. Anti-nociceptive effects of oxytocin in rats and mice. *Neurosci. Lett.* 170, 153–157. [https://doi.org/10.1016/0304-3940\(94\)90262-3](https://doi.org/10.1016/0304-3940(94)90262-3).

- Lyson, K., McCann, S.M., 1991. The effect of interleukin-6 on pituitary hormone release in vivo and in vitro. *Neuroendocrinology* 54, 262–266. <https://doi.org/10.1159/000125884>.
- Machin, A.J., Dunbar, R., 2011. The brain opioid theory of social attachment: a review of the evidence. *Behav* 148, 985–1025. <https://doi.org/10.1163/000579511X596624>.
- Madhav, N., Oppenheim, B., Gallivan, M., Mulembakani, P., Rubin, E., Wolfe, N., 2017. *Disease Control Priorities: Improving Health and Reducing Poverty: Pandemics: Risks, Impacts, and Mitigation*, third ed. Washington (DC).
- Maes, M., Song, C., Lin, A., Jongh, R., de, van Gastel, A., Kenis, G., Bosmans, E., Meester, I., de, Benoy, I., Neels, H., Demedts, P., Janca, A., Scharpé, S., Smith, R.S., 1998. The effects of psychological stress on humans: increased production of pro-inflammatory. *Cytokines a Th1- Response Stress-Induc. Anxiety Cytokine* 10, 313–318. <https://doi.org/10.1006/cyto.1997.0290>.
- Maes, M., Kubera, M., Obuchowiczwa, E., Goehler, L., Brzeszcz, J., 2011. Depression's multiple comorbidities explained by (neuro)inflammatory and oxidative & nitrosative stress pathways. *Neuro Endocrinol. Lett.* 32, 7–24.
- Maner, J.K., DeWall, C.N., Baumeister, R.F., Schaller, M., 2007. Does social exclusion motivate interpersonal reconnection? Resolving the “porcupine problem”. *J. Personal. Soc. Psychol.* 92, 42–55. <https://doi.org/10.1037/0022-3514.92.1.42>.
- Manning, K.J., Chan, G., Steffens, D.C., Pierce, C.W., Potter, G.G., 2021. The interaction of personality and social support on prospective suicidal ideation in men and women with late-life depression. *Am. J. Geriatr. Psychiatry: Off. J. Am. Assoc. Geriatr. Psychiatry* 29, 66–77. <https://doi.org/10.1016/j.jagp.2020.03.018>.
- Manzar, M.D., AlBougami, A., Usman, N., Mamun, M.A., 2020. COVID-19 Suicide among Adolescents and Youths during the Lockdown: An Exploratory Study based on Media Reports.
- Marazziti, D., Baroni, S., Mucci, F., Piccinni, A., Moroni, I., Giannaccini, G., Carmassi, C., Massimetti, E., Dell’Osso, L., 2019. Sex-related differences in plasma oxytocin levels in humans. *Clin. Pract. Epidemiol. Ment. Health.: CP EMH* 15, 58–63. <https://doi.org/10.2174/1745017901915010058>.
- Marlin, B.J., Mitre, M., D’Amour, J.A., Chao, M.V., Froemke, R.C., 2015. Oxytocin enables maternal behaviour by balancing cortical inhibition. *Nature* 520, 499–504. <https://doi.org/10.1038/nature14402>.
- Marsland, A., Bachen, E., Cohen, S., Rabin, B., Manuck, S., 2002. Stress, immune reactivity and susceptibility to infectious disease. *Physiol. Behav.* 77, 711–716. [https://doi.org/10.1016/S0031-9384\(02\)00923-X](https://doi.org/10.1016/S0031-9384(02)00923-X).
- Martinez, M., Phillips, P.J., Herbert, J., 1998. Adaptation in patterns of c-fos expression in the brain associated with exposure to either single or repeated social stress in male rats. *Eur. J. Neurosci.* 10, 20–33. <https://doi.org/10.1046/j.1460-9568.1998.00011.x>.
- Masis-Calvo, M., Schmidtner, A.K., Moura Oliveira, V.E., de, Grossmann, C.P., Jong, T.R., de, Neumann, I.D., 2018. Animal models of social stress: the dark side of social interactions. *Stress* 21, 417–432. <https://doi.org/10.1080/10253890.2018.1462327>.
- Masters, P.S., 2006. In: *The Molecular Biology of Coronaviruses*, vol. 66. Elsevier, pp. 193–292.
- Mastorakos, G., Chrousos, G.P., Weber, J.S., 1993. Recombinant interleukin-6 activates the hypothalamic-pituitary-adrenal axis in humans. *J. Clin. Endocrinol. Metab.* 77, 1690–1694. <https://doi.org/10.1210/jcem.77.6.8263159>.
- Mastorakos, G., Weber, J.S., Magiakou, M.A., Gunn, H., Chrousos, G.P., 1994. Hypothalamic-pituitary-adrenal axis activation and stimulation of systemic vasopressin secretion by recombinant interleukin-6 in humans: potential implications for the syndrome of inappropriate vasopressin secretion. *J. Clin. Endocrinol. Metab.* 79, 934–939. <https://doi.org/10.1210/jcem.79.4.7962300>.
- Matsumoto, K., Pinna, G., Putia, G., Guidotti, A., Costa, E., 2005. Social isolation stress-induced aggression in mice: a model to study the pharmacology of neurosteroidogenesis. *Stress* 8, 85–93. <https://doi.org/10.1080/10253890500159022>.
- Matthews, G.A., Tye, K.M., 2019. Neural mechanisms of social homeostasis. *Ann. N. Y. Acad. Sci.* 1457, 5–25. <https://doi.org/10.1111/nyas.14016>.
- McCormick, C.M., Smith, K., Baumbach, J.L., Lima, A.P.N., de, Shaver, M., Hodges, T.E., Marcolin, M.L., Ismail, N., 2020. Adolescent social instability stress leads to immediate and lasting sex-specific changes in the neuroendocrine-immune-gut axis in rats. *Horm. Behav.* 126, 104845. <https://doi.org/10.1016/j.yhbeh.2020.104845>.
- McGraw, L.A., Young, L.J., 2010. The prairie vole: an emerging model organism for understanding the social brain. *Trends Neurosci.* 33, 103–109. <https://doi.org/10.1016/j.tins.2009.11.006>.
- Mednick, S.A., Machon, R.A., Huttunen, M.O., Bonett, D., 1988. Adult schizophrenia following prenatal exposure to an influenza epidemic. *Arch. Gen. Psychiatry* 45, 189–192. <https://doi.org/10.1001/archpsyc.1988.01800260109013>.
- Mehta, P., McAuley, D.F., Brown, M., Sanchez, E., Tattersall, R.S., Manson, J.J., 2020. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 395, 1033–1034. [https://doi.org/10.1016/S0140-6736\(20\)30628-0](https://doi.org/10.1016/S0140-6736(20)30628-0).
- Meltzer, H., Bebbington, P., Dennis, M.S., Jenkins, R., McManus, S., Brugha, T.S., 2013. Feelings of loneliness among adults with mental disorder. *Soc. Psychiatry Psychiatr. Epidemiol.* 48, 5–13. <https://doi.org/10.1007/s00127-012-0515-8>.
- Menon, R., Grund, T., Zoicas, I., Althammer, F., Fiedler, D., Biermeier, V., Bosch, O.J., Hiraoka, Y., Nishimori, K., Eliava, M., Grinevich, V., Neumann, I.D., 2018. Oxytocin signaling in the lateral septum prevents social fear during lactation. *Curr. Biol.* 28 (1066–1078), e6. <https://doi.org/10.1016/j.cub.2018.02.044>.
- Moieni, M., Irwin, M.R., Jevtic, I., Breen, E.C., Cho, H.J., Arevalo, J.M.G., Ma, J., Cole, S.W., Eisenberger, N.I., 2015. Trait sensitivity to social disconnection enhances pro-inflammatory responses to a randomized controlled trial of endotoxin. *Psychoneuroendocrinology* 62, 336–342. <https://doi.org/10.1016/j.psyneuen.2015.08.020>.
- Moosmann, B., Behl, C., 2002. Secretory peptide hormones are biochemical antioxidants: structure-activity relationship. *Mol. Pharmacol.* 61, 260–268. <https://doi.org/10.1124/mol.61.2.260>.
- Morgan, C., Fisher, H., 2007. Environment and schizophrenia: environmental factors in schizophrenia: childhood trauma—a critical review. *Schizophr. Bull.* 33, 3–10. <https://doi.org/10.1093/schbul/sbl053>.
- Mumtaz, F., Khan, M.I., Zubair, M., Dehpour, A.R., 2018. Neurobiology and consequences of social isolation stress in animal model—A comprehensive review. *Biomed. Pharmacother. = Biomedecine Pharmacother.* 105, 1205–1222. <https://doi.org/10.1016/j.biopha.2018.05.086>.
- Murphy, M.R., Checkley, S.A., Seckl, J.R., Lightman, S.L., 1990. Naloxone inhibits oxytocin release at orgasm in man. *J. Clin. Endocrinol. Metab.* 71, 1056–1058. <https://doi.org/10.1210/jcem-71-4-1056>.
- Nagasawa, M., Kikusui, T., Onaka, T., Ohta, M., 2009. Dog’s gaze at its owner increases owner’s urinary oxytocin during social interaction. *Horm. Behav.* 55, 434–441. <https://doi.org/10.1016/j.yhbeh.2008.12.002>.
- Naranjo, J.R., Fuentes, J.A., 1985. Association between hypoalgesia and hypertension in rats after short-term isolation. *Neuropharmacology* 24, 167–171. [https://doi.org/10.1016/0028-3908\(85\)90176-5](https://doi.org/10.1016/0028-3908(85)90176-5).
- Natoli, S., Oliveira, V., Calabresi, P., Maia, L.F., Pisani, A., 2020. Does SARS-Cov-2 invade the brain? Translational lessons from animal models. *Eur. J. Neurol.* <https://doi.org/10.1111/ene.14277>.
- Neelsen, S., Stratmann, T., 2012. Long-run effects of fetal influenza exposure: evidence from Switzerland. *Soc. Sci. Med.* (1982) 74, 58–66. <https://doi.org/10.1016/j.socscimed.2011.09.039>.
- Neumann, I., Landgraf, R., 1989. Septal and hippocampal release of oxytocin, but not vasopressin, in the conscious lactating rat during suckling. *J. Neuroendocrinol.* 1, 305–308. <https://doi.org/10.1111/j.1365-2826.1989.tb00120.x>.
- Neumann, I.D., 2009. The advantage of social living: brain neuropeptides mediate the beneficial consequences of sex and motherhood. *Front. Neuroendocrinol.* 30, 483–496. <https://doi.org/10.1016/j.yfrne.2009.04.012>.
- Neumann, I.D., Landgraf, R., 2012. Balance of brain oxytocin and vasopressin: implications for anxiety, depression, and social behaviors. *Trends Neurosci.* 35, 649–659. <https://doi.org/10.1016/j.tins.2012.08.004>.
- Neumann, I.D., Torner, L., Wigger, A., 2000a. Brain oxytocin: differential inhibition of neuroendocrine stress responses and anxiety-related behaviour in virgin, pregnant and lactating rats. *Neuroscience* 95, 567–575. [https://doi.org/10.1016/S0306-4522\(99\)00433-9](https://doi.org/10.1016/S0306-4522(99)00433-9).
- Neumann, I.D., Wigger, A., Torner, L., Holsboer, F., Landgraf, R., 2000b. Brain oxytocin inhibits basal and stress-induced activity of the hypothalamo-pituitary-adrenal axis in male and female rats: partial action within the paraventricular nucleus. *J. Neuroendocrinol.* 12, 235–243. <https://doi.org/10.1046/j.1365-2826.2000.00442.x>.
- Nie, X., Kitaoka, S., Tanaka, K., Segi-Nishida, E., Imoto, Y., Ogawa, A., Nakano, F., Tomohiro, A., Nakayama, K., Taniguchi, M., Mimori-Kiyosue, Y., Kakizuka, A., Narumiya, S., Furiyashiki, T., 2018. The innate immune receptors TLR2/4 mediate repeated social defeat stress-induced social avoidance through prefrontal microglial activation. *Neuron* 99 (464–479), e7. <https://doi.org/10.1016/j.neuron.2018.06.035>.
- Nomura, S., Kawashima, T., Yoneoka, D., Tanoue, Y., Eguchi, A., Gilmour, S., Kawamura, Y., Harada, N., Hashizume, M., 2021. Trends in suicide in Japan by gender during the COVID-19 pandemic, up to September 2020. *Psychiatry Res.* 295, 113622. <https://doi.org/10.1016/j.psychres.2020.113622>.
- Norman, G.J., Cacioppo, J.T., Morris, J.S., Malarkey, W.B., Bertson, G.G., DeVries, A.C., 2011. Oxytocin increases autonomic cardiac control: moderation by loneliness. *Biol. Psychol.* 86, 174–180. <https://doi.org/10.1016/j.biopsycho.2010.11.006>.
- Nuyki, K.D., Beiderbeck, D.I., Lukas, M., Neumann, I.D., Reber, S.O., 2012. Chronic subordinate colony housing (CSC) as a model of chronic psychosocial stress in male rats. *PLoS One* 7, e52371. <https://doi.org/10.1371/journal.pone.0052371>.
- O’Callaghan, E., Sham, P., Takei, N., Murray, R., Glover, G., 1991. Schizophrenia after prenatal exposure to 1957 A2 influenza epidemic. *Lancet* 337, 1248–1250. [https://doi.org/10.1016/0140-6736\(91\)92919-S](https://doi.org/10.1016/0140-6736(91)92919-S).
- Oettl, L.-L., Ravi, N., Schneider, M., Scheller, M.F., Schneider, P., Mitre, M., Da Silva Gouveia, M., Froemke, R.C., Chao, M.V., Young, W.S., Meyer-Lindenberg, A., Grinevich, V., Shusterman, R., Kelsch, W., 2016. Oxytocin enhances social recognition by modulating cortical control of early olfactory processing. *Neuron* 90, 609–621. <https://doi.org/10.1016/j.neuron.2016.03.033>.
- Ohline, S.M., Abraham, W.C., 2019. Environmental enrichment effects on synaptic and cellular physiology of hippocampal neurons. *Neuropharmacology* 145, 3–12. <https://doi.org/10.1016/j.neuropharm.2018.04.007>.
- O’Keefe, L.M., Doran, S.J., Mwilambwe-Tshilobo, L., Conti, L.H., Venna, V.R., McCullough, L.D., 2014. Social isolation after stroke leads to depressive-like behavior and decreased BDNF levels in mice. *Behav. Brain Res.* 260, 162–170. <https://doi.org/10.1016/j.bbr.2013.10.047>.
- Olf, M., Frijling, J.L., Kubzansky, L.D., Bradley, B., Ellenbogen, M.A., Cardoso, C., Bartz, J.A., Yee, J.R., van Zuiden, M., 2013. The role of oxytocin in social bonding, stress regulation and mental health: an update on the moderating effects of context and interindividual differences. *Psychoneuroendocrinology* 38, 1883–1894. <https://doi.org/10.1016/j.psyneuen.2013.06.019>.
- Oliveira, V.Ed.M., Neumann, I.D., Jong, T.R. de, 2019. Post-weaning social isolation exacerbates aggression in both sexes and affects the vasopressin and oxytocin system in a sex-specific manner. *Neuropharmacology* 156, 107504. <https://doi.org/10.1016/j.neuropharm.2019.01.019>.
- Oliveira, V.Ed.M., Lukas, M., Wolf, H.N., Durante, E., Lorenz, A., Mayer, A.-L., Bludau, A., Bosch, O.J., Grinevich, V., Egger, V., Jong, T.R. de, Neumann, I.D., 2021. Oxytocin and vasopressin within the ventral and dorsal lateral septum modulate

- aggression in female rats. *Nat. Commun.* 12, 2900. <https://doi.org/10.1038/s41467-021-23064-5>.
- Oliveira-Pelegrin, G.R., Saia, R.S., Cárnio, E.C., Rocha, M.J.A., 2013. Oxytocin affects nitric oxide and cytokine production by sepsis-sensitized macrophages. *Neuroimmunomodulation* 20, 65–71. <https://doi.org/10.1159/000345044>.
- Ou, X., Liu, Y., Lei, X., Li, P., Mi, D., Ren, L., Guo, L., Guo, R., Chen, T., Hu, J., Xiang, Z., Mu, Z., Chen, X., Chen, J., Hu, K., Jin, Q., Wang, J., Qian, Z., 2020. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. *Nat. Commun.* 11, 1620. <https://doi.org/10.1038/s41467-020-15562-9>.
- Oxman, T.E., Berkman, L.F., Kasl, S., Freeman, D.H., Barrett, J., 1992. Social support and depressive symptoms in the elderly. *Am. J. Epidemiol.* 135, 356–368. <https://doi.org/10.1093/oxfordjournals.aje.a116297>.
- Padgett, D.A., Glaser, R., 2003. How stress influences the immune response. *Trends Immunol.* 24, 444–448. [https://doi.org/10.1016/S1471-4906\(03\)00173-X](https://doi.org/10.1016/S1471-4906(03)00173-X).
- Paloyelis, Y., Doyle, O.M., Zelaya, F.O., Maltezos, S., Williams, S.C., Fotopoulou, A., Howard, M.A., 2016. A spatiotemporal profile of in vivo cerebral blood flow changes following intranasal oxytocin in humans. *Biol. Psychiatry* 79, 693–705. <https://doi.org/10.1016/j.biopsych.2014.10.005>.
- Pan, Y., Liu, Y., Young, K.A., Zhang, Z., Wang, Z., 2009. Post-weaning social isolation alters anxiety-related behavior and neurochemical gene expression in the brain of male prairie voles. *Neurosci. Lett.* 454, 67–71. <https://doi.org/10.1016/j.neulet.2009.02.064>.
- Patel, A.P., Paranjpe, M.D., Kathiresan, N.P., Rivas, M.A., Khera, A.V., 2020. Race, socioeconomic deprivation, and hospitalization for COVID-19 in English participants of a national biobank. *Int. J. Equity Health* 19, 114. <https://doi.org/10.1186/s12939-020-01227-y>.
- Penninx, B.W.J.H., Beekman, A.T.F., Bandinelli, S., Corsi, A.M., Bremmer, M., Hoogendijk, W.J., Guralnik, J.M., Ferrucci, L., 2007. Late-life depressive symptoms are associated with both hyperactivity and hypoactivity of the hypothalamic-pituitary-adrenal axis. *Am. J. Geriatr. Psychiatry* 15, 522–529. <https://doi.org/10.1097/JGP.0b013e318033ed80>.
- Pereda-Pérez, I., Popović, N., Otalora, B.B., Popović, M., Madrid, J.A., Rol, M.A., Venero, C., 2013. Long-term social isolation in the adulthood results in CA1 shrinkage and cognitive impairment. *Neurobiol. Learn. Mem.* 106, 31–39. <https://doi.org/10.1016/j.nlm.2013.07.004>.
- Peters, S., Slattery, D.A., Uschold-Schmidt, N., Reber, S.O., Neumann, I.D., 2014. Dose-dependent effects of chronic central infusion of oxytocin on anxiety, oxytocin receptor binding and stress-related parameters in mice. *Psychoneuroendocrinology* 42, 225–236. <https://doi.org/10.1016/j.psycheneu.2014.01.021>.
- Pfeiffer, P.N., Ganoczy, D., Ilgen, M., Zivin, K., Valenstein, M., 2009. Comorbid anxiety as a suicide risk factor among depressed veterans. *Depress Anxiety* 26, 752–757. <https://doi.org/10.1002/da.20583>.
- Pickett, C.L., Gardner, W.L., Knowles, M., 2004. Getting a cue: the need to belong and enhanced sensitivity to social cues. *Personal. Soc. Psychol. Bull.* 30, 1095–1107. <https://doi.org/10.1177/0146167203262085>.
- Pierrehumbert, B., Torrisi, R., Laufer, D., Halfon, O., Ansermet, F., Beck Popovic, M., 2010. Oxytocin response to an experimental psychosocial challenge in adults exposed to traumatic experiences during childhood or adolescence. *Neuroscience* 166, 168–177. <https://doi.org/10.1016/j.neuroscience.2009.12.016>.
- Pohl, T.T., Young, L.J., Bosch, O.J., 2019. Lost connections: oxytocin and the neural, physiological, and behavioral consequences of disrupted relationships. *Int. J. Psychophysiol.* 136, 54–63. <https://doi.org/10.1016/j.ijpsycho.2017.12.011>.
- Pohl, T.T., Jung, O., Di Benedetto, B., Young, L.J., Bosch, O.J., 2021. Microglia react to partner loss in a sex- and brain site-specific manner in prairie voles. *Brain Behav. Immun.* <https://doi.org/10.1016/j.bbi.2021.05.026>.
- Pournajafi-Nazarloo, H., Partoo, L., Yee, J., Stevenson, J., Sanzenbacher, L., Kenkel, W., Mohsenpour, S.R., Hashimoto, K., Carter, C.S., 2011. Effects of social isolation on mRNA expression for corticotrophin-releasing hormone receptors in prairie voles. *Psychoneuroendocrinology* 36, 780–789. <https://doi.org/10.1016/j.psycheneu.2010.10.015>.
- Powell, N.D., Sloan, E.K., Bailey, M.T., Arevalo, J.M.G., Miller, G.E., Chen, E., Kobor, M.S., Reader, B.F., Sheridan, J.F., Cole, S.W., 2013. Social stress up-regulates inflammatory gene expression in the leukocyte transcriptome via  $\beta$ -adrenergic induction of myelopoiesis. *Proc. Natl. Acad. Sci. USA* 110, 16574–16579. <https://doi.org/10.1073/pnas.1310655110>.
- Pressman, S.D., Cohen, S., Miller, G.E., Barkin, A., Rabin, B.S., Treanor, J.J., 2005. Loneliness, social network size, and immune response to influenza vaccination in college freshmen. *Health Psychology: Official Journal of the Division of Health Psychology*. *Am. Psychol. Assoc.* 24, 297–306. <https://doi.org/10.1037/0278-6133.24.3.297>.
- Quinn, M.E., Stanton, C.H., Slavich, G.M., Joormann, J., 2020. Executive control, cytokine reactivity to social stress, and depressive symptoms: testing the social signal transduction theory of depression. *Stress* 23, 60–68. <https://doi.org/10.1080/10253890.2019.1641079>.
- Ravens-Sieberer, U., Kaman, A., Erhart, M., Devine, J., Schlack, R., Otto, C., 2021. Impact of the COVID-19 pandemic on quality of life and mental health in children and adolescents in Germany. *Eur. Child Adolesc. Psychiatry*. <https://doi.org/10.1007/s0087-021-01726-5>.
- Reber, S.O., Neumann, I.D., 2008. Defensive behavioral strategies and enhanced state anxiety during chronic subordinate colony housing are accompanied by reduced hypothalamic vasopressin, but not oxytocin, expression. *Ann. N. Y. Acad. Sci.* 1148, 184–195. <https://doi.org/10.1196/annals.1410.003>.
- Reber, S.O., Obermeier, F., Straub, R.H., Straub, H.R., Falk, W., Neumann, I.D., 2006. Chronic intermittent psychosocial stress (social defeat/overcrowding) in mice increases the severity of an acute DSS-induced colitis and impairs regeneration. *Endocrinology* 147, 4968–4976. <https://doi.org/10.1210/en.2006-0347>.
- Reber, S.O., Birkeneder, L., Veenema, A.H., Obermeier, F., Falk, W., Straub, R.H., Neumann, I.D., 2007. Adrenal insufficiency and colonic inflammation after a novel chronic psycho-social stress paradigm in mice: implications and mechanisms. *Endocrinology* 148, 670–682. <https://doi.org/10.1210/en.2006-0983>.
- Reber, S.O., Obermeier, F., Straub, R.H., Veenema, A.H., Neumann, I.D., 2008. Aggravation of DSS-induced colitis after chronic subordinate colony (CSC) housing is partially mediated by adrenal mechanisms. *Stress* 11, 225–234. <https://doi.org/10.1080/10253890701733351>.
- Reber, S.O., Langgartner, D., Foertsch, S., Postolache, T.T., Brenner, L.A., Guendel, H., Lowry, C.A., 2016a. Chronic subordinate colony housing paradigm: a mouse model for mechanisms of PTSD vulnerability, targeted prevention, and treatment-2016 Curt Richter Award Paper. *Psychoneuroendocrinology* 74, 221–230. <https://doi.org/10.1016/j.psycheneu.2016.08.031>.
- Reber, S.O., Siebler, P.H., Donner, N.C., Morton, J.T., Smith, D.G., Kopelman, J.M., Lowe, K.R., Wheeler, K.J., Fox, J.H., Hassell, J.E., Greenwood, B.N., Jansch, C., Lechner, A., Schmidt, D., Uschold-Schmidt, N., Früchsl, A.M., Langgartner, D., Walker, F.R., Hale, M.W., Lopez Perez, G., van Treuren, W., González, A., Halweg-Edwards, A.L., Flesher, M., Raison, C.L., Rook, G.A., Peddada, S.D., Knight, R., Lowry, C.A., 2016b. Immunization with a heat-killed preparation of the environmental bacterium *Mycobacterium vaccae* promotes stress resilience in mice. *Proc. Natl. Acad. Sci. USA* 113, E3130–E3139. <https://doi.org/10.1073/pnas.1600324113>.
- Riem, M.M.E., Kunst, L.E., Bekker, M.H.J., Fallon, M., Kupper, N., 2020. Intranasal oxytocin enhances stress-protective effects of social support in women with negative childhood experiences during a virtual Trier Social Stress Test. *Psychoneuroendocrinology* 111, 104482. <https://doi.org/10.1016/j.psycheneu.2019.104482>.
- Ross, A.P., McCann, K.E., Larkin, T.E., Song, Z., Grieb, Z.A., Huhman, K.L., Albers, H.E., 2019. Sex-dependent effects of social isolation on the regulation of arginine-vasopressin (AVP) V1a, oxytocin (OT) and serotonin (5HT) 1a receptor binding and aggression. *Horm. Behav.* 116, 104578. <https://doi.org/10.1016/j.yhbeh.2019.104578>.
- Saavedra, J.M., Armando, I., Bregonzio, C., Juorio, A., Macova, M., Pavel, J., Sanchez-Lemus, E., 2006. A centrally acting, anxiolytic angiotensin II AT1 receptor antagonist prevents the isolation stress-induced decrease in cortical CRF1 receptor and benzodiazepine binding. *Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol.* 31, 1123–1134. <https://doi.org/10.1038/sj.npp.1300921>.
- Saavedra-Rodríguez, L., Feig, L.A., 2013. Chronic social instability induces anxiety and defective social interactions across generations. *Biol. Psychiatry* 73, 44–53. <https://doi.org/10.1016/j.biopsych.2012.06.035>.
- Sammarco, A., Konecny, L.M., 2008. Quality of life, social support, and uncertainty among Latina breast cancer survivors. *Oncol. Nurs. Forum* 35, 844–849. <https://doi.org/10.1188/08.ONF.844-849>.
- Schiavone, S., Sorce, S., Dubois-Dauphin, M., Jaquet, V., Colaianna, M., Zotti, M., Cuomo, V., Trabace, L., Krause, K.-H., 2009. Involvement of NOX2 in the development of behavioral and pathologic alterations in isolated rats. *Biol. Psychiatry* 66, 384–392. <https://doi.org/10.1016/j.biopsych.2009.04.033>.
- Schmidt, D., Reber, S.O., Botteron, C., Barth, T., Peterlik, D., Uschold, N., Männel, D.N., Lechner, A., 2010. Chronic psychosocial stress promotes systemic immune activation and the development of inflammatory Th cell responses. *Brain Behav. Immun.* 24, 1097–1104. <https://doi.org/10.1016/j.bbi.2010.04.014>.
- Schmidt, A.K., Slattery, D.A., Gläser, J., Hiergeist, A., Gryksa, K., Malik, V.A., Hellmann-Regen, J., Heuser, I., Baghai, T.C., Gessner, A., Rupprecht, R., Di Benedetto, B., Neumann, I.D., 2019. Minocycline alters behavior, microglia and the gut microbiome in a trait-anxiety-dependent manner. *Transl. Psychiatry* 9, 223. <https://doi.org/10.1038/s41398-019-0556-9>.
- Scotti, M.-A.L., Carlton, E.D., Demas, G.E., Grippo, A.J., 2015. Social isolation disrupts innate immune responses in both male and female prairie voles and enhances agonistic behavior in female prairie voles (*Microtus ochrogaster*). *Horm. Behav.* 70, 7–13. <https://doi.org/10.1016/j.yhbeh.2015.01.004>.
- Seetharaman, S., Flesher, M., Park, C.R., Diamond, D.M., 2016. Influence of daily social stimulation on behavioral and physiological outcomes in an animal model of PTSD. *Brain Behav.* 6, e00458. <https://doi.org/10.1002/brb3.458>.
- Seltzer, L.J., Ziegler, T., Connolly, M.J., Prosski, A.R., Pollak, S.D., 2014. Stress-induced elevation of oxytocin in maltreated children: evolution, neurodevelopment, and social behavior. *Child Dev.* 85, 501–512. <https://doi.org/10.1111/cdev.12136>.
- Senst, L., Baimoukhametova, D., Sterley, T.-L., Bains, J.S., 2016. Sexually dimorphic neuronal responses to social isolation. *eLife* 5. <https://doi.org/10.7554/eLife.18726>.
- Serra, M., Pisu, M.G., Floris, I., Biggio, G., 2005. Social isolation-induced changes in the hypothalamic-pituitary-adrenal axis in the rat. *Stress (Amst., Neth.)* 8, 259–264. <https://doi.org/10.1080/10253890500495244>.
- Shah, S.G.S., Nogueiras, D., van Woerden, H.C., Kiparoglou, V., 2020. The COVID-19 pandemic: a pandemic of lockdown loneliness and the role of digital technology. *J. Med. Internet Res.* 22, e22287. <https://doi.org/10.2196/22287>.
- Sharhabani-Arzi, R., Amir, M., Kotler, M., Liran, R., 2003. The toll of domestic violence. PTSD among battered women in an Israeli sample. *J. Interpers. Violence* 18, 1335–1346. <https://doi.org/10.1177/0886260503256842>.
- Shigemura, J., Ursano, R.J., Morganstein, J.C., Kurosawa, M., Benedek, D.M., 2020. Public responses to the novel 2019 coronavirus (2019-nCoV) in Japan: Mental health consequences and target populations. *Psychiatry Clin. Neurosci.* 74, 281–282. <https://doi.org/10.1111/pcn.12988>.
- Simpson, J.S.A., Carlson, L.E., Beck, C.A., Patten, S., 2002. Effects of a brief intervention on social support and psychiatric morbidity in breast cancer patients. *Psycho-Oncol.* 11, 282–294. <https://doi.org/10.1002/pon.565>.



- Singewald, G.M., Nguyen, N.K., Neumann, I.D., Singewald, N., Reber, S.O., 2009. Effect of chronic psychosocial stress-induced by subordinate colony (CSC) housing on brain neuronal activity patterns in mice. *Stress* 12, 58–69. <https://doi.org/10.1080/10253890802042082>.
- Slattery, D.A., Uschold, N., Magoni, M., Bär, J., Popoli, M., Neumann, I.D., Reber, S.O., 2012. Behavioural consequences of two chronic psychosocial stress paradigms: anxiety without depression. *Psychoneuroendocrinology* 37, 702–714. <https://doi.org/10.1016/j.psyneuen.2011.09.002>.
- Smith, C.J., Bilbo, S.D., 2021. Sickness and the social brain: love in the time of COVID. *Front. Psychiatry* 12, 633664. <https://doi.org/10.3389/fpsy.2021.633664>.
- Sohrabi, C., Alsafi, Z., O'Neill, N., Khan, M., Kerwan, A., Al-Jabir, A., Iosifidis, C., Agha, R., 2020. World Health Organization declares global emergency: a review of the 2019 novel coronavirus (COVID-19). *Int. J. Surg. (Lond., Engl.)* 76, 71–76. <https://doi.org/10.1016/j.ijsu.2020.02.034>.
- Solomon, Z., Mikulincer, M., Hobfoll, S.E., 1987. Objective versus subjective measurement of stress and social support: combat-related reactions. *J. Consult. Clin. Psychol.* 55, 577–583. <https://doi.org/10.1037/0022-006X.55.4.577>.
- Soumier, A., Sirigu, A., 2020. Oxytocin as a potential defence against Covid-19? *Med. Hypotheses* 140, 109785. <https://doi.org/10.1016/j.mehy.2020.109785>.
- Steinhardt, M.A., Smith Jaggars, S.E., Faulk, K.E., Gloria, C.T., 2011. Chronic work stress and depressive symptoms: assessing the mediating role of teacher burnout. *Stress Health* 27, 420–429. <https://doi.org/10.1002/smi.1394>.
- Suzuki, S., Fujisawa, T.X., Sakakibara, N., Fujioka, T., Takiguchi, S., Tomoda, A., 2020. Development of social attention and oxytocin levels in maltreated children. *Sci. Rep.* 10, 7407. <https://doi.org/10.1038/s41598-020-64297-6>.
- Szeto, A., Nation, D.A., Mendez, A.J., Dominguez-Bendala, J., Brooks, L.G., Schneiderman, N., McCabe, P.M., 2008. Oxytocin attenuates NADPH-dependent superoxide activity and IL-6 secretion in macrophages and vascular cells. *Am. J. Physiol. Endocrinol. Metab.* 295, E1495–E1501. <https://doi.org/10.1152/ajpendo.00718.2008>.
- Takatsu-Coleman, A.L., Patti, C.L., Zanin, K.A., Zager, A., Carvalho, R.C., Borçoi, A.R., Cecon, L.M., Berro, L.F., Tufik, S., Andersen, M.L., Frussa-Filho, R., 2013. Short-term social isolation induces depressive-like behaviour and reinstates the retrieval of an aversive task: Mood-congruent memory in male mice? *J. Psychiatry Neurosci.* 38, 259–268. <https://doi.org/10.1503/jpn.120050>.
- Tanaka, T., Okamoto, S., 2021. Increase in suicide following an initial decline during the COVID-19 pandemic in Japan. *Nat. Hum. Behav.* 5, 229–238. <https://doi.org/10.1038/s41562-020-01042-z>.
- Tang, K., Gaoshan, J., Ahonsi, B., Ali, M., Bonet, M., Broutet, N., Kara, E., Kim, C., Thorson, A., Thwin, S.S., 2020a. Sexual and reproductive health (SRH): a key issue in the emergency response to the coronavirus disease (COVID-19) outbreak. *Reprod. Health* 17, 59. <https://doi.org/10.1186/s12978-020-0900-9>.
- Tang, Y., Benusiglio, D., Lefevre, A., Hilfiger, L., Althammer, F., Bludau, A., Hagiwara, D., Baudon, A., Darbon, P., Schimmer, J., Kirchner, M.K., Roy, R.K., Wang, S., Eliava, M., Wagner, S., Oberhuber, M., Conzelmann, K.K., Schwarz, M., Stern, J.E., Leng, G., Neumann, I.D., Charlet, A., Grinevich, V., 2020b. Social touch promotes interfemale communication via activation of parvocellular oxytocin neurons. *Nat. Neurosci.* 23, 1125–1137. <https://doi.org/10.1038/s41593-020-0674-y>.
- Taub, A., 2020. A New Covid-19 Crisis: Domestic Abuse Rises Worldwide. The Interpreter.
- Thackeray, J.D., Hibbard, R., Dowd, M.D., 2010. Intimate partner violence: the role of the pediatrician. *Pediatrics* 125, 1094–1100. <https://doi.org/10.1542/peds.2010-0451>.
- Torner, L., Plotsky, P.M., Neumann, I.D., Jong, T.R. de, 2017. Forced swimming-induced oxytocin release into blood and brain: Effects of adrenalectomy and corticosterone treatment. *Psychoneuroendocrinology* 77, 165–174. <https://doi.org/10.1016/j.psyneuen.2016.12.006>.
- Toth, I., Neumann, I.D., Slattery, D.A., 2012. Social fear conditioning: a novel and specific animal model to study social anxiety disorder. *Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol.* 37, 1433–1443. <https://doi.org/10.1038/npp.2011.329>.
- Tsai, T.-Y., Tseng, H.-H., Chi, M.H., Chang, H.H., Wu, C.-K., Yang, Y.K., Chen, P.S., 2019. The interaction of oxytocin and social support, loneliness, and cortisol level in major depression. *Clin. Psychopharmacol. Neurosci. Off. Sci. J. Korean Coll. Neuropsychopharmacol.* 17, 487–494. <https://doi.org/10.9758/cpn.2019.17.4.487>.
- Tuğtepe, H., Sener, G., Biyikli, N.K., Yüksel, M., Cetinel, S., Gedik, N., Yeğen, B.C., 2007. The protective effect of oxytocin on renal ischemia/reperfusion injury in rats. *Regul. Pept.* 140, 101–108. <https://doi.org/10.1016/j.regpep.2006.11.026>.
- Uchino, B.N., Cacioppo, J.T., Kiecolt-Glaser, J.K., 1996. The relationship between social support and physiological processes: a review with emphasis on underlying mechanisms and implications for health. *Psychol. Bull.* 119, 488–531. <https://doi.org/10.1037/0033-2909.119.3.488>.
- Usher, K., Bhullar, N., Durkin, J., Gyamfi, N., Jackson, D., 2020. Family violence and COVID-19: increased vulnerability and reduced options for support. *Int. J. Ment. Health Nurs.* 29, 549–552. <https://doi.org/10.1111/inm.12735>.
- Usta, Y.Y., 2012. Importance of social support in cancer patients. *Asian Pac. J. Cancer Prev. APJCP* 13, 3569–3572. <https://doi.org/10.7314/APJCP.2012.13.8.3569>.
- Vahratian, A., Blumberg, S.J., Terlizzi, E.P., Schiller, J.S., 2021. Symptoms of anxiety or depressive disorder and use of mental health care among adults during the COVID-19 pandemic - United States, August 2020-February 2021. *Morb. Mortal. Wkly. Rep.* 70, 490–494. <https://doi.org/10.15585/mmwr.mm7013e2>.
- van Os, J., Kenis, G., Rutten, B.P.F., 2010. The environment and schizophrenia. *Nature* 468, 203–212. <https://doi.org/10.1038/nature09563>.
- van Winkel, R., Stefanis, N.C., Myin-Germeys, I., 2008. Psychosocial stress and psychosis. A review of the neurobiological mechanisms and the evidence for gene-stress interaction. *Schizophr. Bull.* 34, 1095–1105. <https://doi.org/10.1093/schbul/sbn101>.
- Vanderschuren, L.J., Niesink, R.J., Spruijt, B.M., van Ree, J.M., 1995a. Mu- and kappa-opioid receptor-mediated effects on social play in juvenile rats. *Eur. J. Pharmacol.* 276, 257–266. [https://doi.org/10.1016/0014-2999\(95\)00040-r](https://doi.org/10.1016/0014-2999(95)00040-r).
- Vanderschuren, L.J., Stein, E.A., Wiegant, V.M., van Ree, J.M., 1995b. Social isolation and social interaction alter regional brain opioid receptor binding in rats. *Eur. Neuropsychopharmacol.* 5, 119–127. [https://doi.org/10.1016/0924-977X\(95\)00010-m](https://doi.org/10.1016/0924-977X(95)00010-m).
- Viana Borges, J., Souza de Freitas, B., Antoniazzi, V., Souza Dos Santos, C. de, Vedovelli, K., Naziaseno Pires, V., Paludo, L., Martins de Lima, M.N., Bromberg, E., 2019. Social isolation and social support at adulthood affect epigenetic mechanisms, brain-derived neurotrophic factor levels and behavior of chronically stressed rats. *Behav. Brain Res.* 366, 36–44. <https://doi.org/10.1016/j.bbr.2019.03.025>.
- Vindegaard, N., Benros, M.E., 2020. COVID-19 pandemic and mental health consequences: systematic review of the current evidence. *Brain Behav. Immun.* 89, 531–542. <https://doi.org/10.1016/j.bbi.2020.05.048>.
- Vingeliene, S., Hiyoshi, A., Lentjes, M., Fall, K., Montgomery, S., 2019. Longitudinal analysis of loneliness and inflammation at older ages: english longitudinal study of ageing. *Psychoneuroendocrinology* 110, 104421. <https://doi.org/10.1016/j.psyneuen.2019.104421>.
- Waldherr, M., Neumann, I.D., 2007. Centrally released oxytocin mediates mating-induced anxiolysis in male rats. *Proc. Natl. Acad. Sci. USA* 104, 16681–16684. <https://doi.org/10.1073/pnas.0705860104>.
- Wang, H.-T., Huang, F.-L., Hu, Z.-L., Zhang, W.-J., Qiao, X.-Q., Huang, Y.-Q., Dai, R.-P., Li, F., Li, C.-Q., 2017. Early-life social isolation-induced depressive-like behavior in rats results in microglial activation and neuronal histone methylation that are mitigated by minocycline. *Neurotox. Res.* 31, 505–520. <https://doi.org/10.1007/s12640-016-9696-3>.
- Wang, H.-X., Mittleman, M.A., Orth-Gomer, K., 2005. Influence of social support on progression of coronary artery disease in women. *Soc. Sci. Med.* (1982) 60, 599–607. <https://doi.org/10.1016/j.socscimed.2004.05.021>.
- Wang, P., Yang, H.-P., Tian, S., Wang, L., Wang, S.C., Zhang, F., Wang, Y.-F., 2015. Oxytocin-secreting system: a major part of the neuroendocrine center regulating immunologic activity. *J. Neuroimmunol.* 289, 152–161. <https://doi.org/10.1016/j.jneuroim.2015.11.001>.
- Wang, Z., Young, M.R.I., 2016. PTSD, a disorder with an immunological component. *Front. Immunol.* 7, 219. <https://doi.org/10.3389/fimmu.2016.00219>.
- Weigent, D.A., Blalock, J.E., 1995. Associations between the neuroendocrine and immune systems. *J. Leukoc. Biol.* 58, 137–150. <https://doi.org/10.1002/jlb.58.2.137>.
- Weintraub, A., Singaravelu, J., Bhatnagar, S., 2010. Enduring and sex-specific effects of adolescent social isolation in rats on adult stress reactivity. *Brain Res.* 1343, 83–92. <https://doi.org/10.1016/j.brainres.2010.04.068>.
- Weiss, I.C., Pryce, C.R., Jongen-Rélo, A.L., Nanz-Bahr, N.I., Feldon, J., 2004. Effect of social isolation on stress-related behavioural and neuroendocrine state in the rat. *Behav. Brain Res.* 152, 279–295. <https://doi.org/10.1016/j.bbr.2003.10.015>.
- Whiten, A., Byrne, R.W., 1988. The Machiavellian intelligence hypotheses: Editorial. In: Byrne, R.W., Whiten, A. (Eds.), *Machiavellian Intelligence: Social Expertise and the Evolution of Intellect in Monkeys, Apes, and Humans*. Clarendon Press/Oxford University Press, pp. 1–9.
- WHO, 2020a. Transmission of SARS-CoV-2: implications for infection prevention precautions: Scientific brief. ([https://apps.who.int/iris/bitstream/handle/10665/33314/WHO-2019-nCoV-Sci\\_Brief-Transmission\\_modes-2020.3-eng.pdf](https://apps.who.int/iris/bitstream/handle/10665/33314/WHO-2019-nCoV-Sci_Brief-Transmission_modes-2020.3-eng.pdf)).
- WHO, 2020b. Coronavirus disease 2019 (COVID-19): Situation Report - 51.
- WHO, 2021. Coronavirus disease (COVID-19): Weekly Epidemiological Update and Weekly Operational Update - Edition 65, published 9. November 2021.
- Wigger, A., Neumann, I.D., 2002. Endogenous opioid regulation of stress-induced oxytocin release within the hypothalamic paraventricular nucleus is reversed in late pregnancy: a microdialysis study. *Neuroscience* 112, 121–129. [https://doi.org/10.1016/s0306-4522\(02\)00068-4](https://doi.org/10.1016/s0306-4522(02)00068-4).
- Winter, J., Meyer, M., Berger, I., Royer, M., Bianchi, M., Kuffner, K., Peters, S., Stang, S., Langgartner, D., Hartmann, F., Schmidtner, A.K., Reber, S.O., Bosch, O.J., Bludau, A., Slattery, D.A., van den Burg, E.H., Jurek, B., Neumann, I.D., 2021. Chronic oxytocin-driven alternative splicing of Crfr2a induces anxiety. *Mol. Psychiatry*. <https://doi.org/10.1038/s41380-021-01141-x>.
- Wolffgramm, J., 1990. Free choice ethanol intake of laboratory rats under different social conditions. *Psychopharmacology* 101, 233–239. <https://doi.org/10.1007/BF02244132>.
- Wolke, D., Lereya, S.T., 2015. Long-term effects of bullying. *Arch. Dis. Child.* 100, 879–885. <https://doi.org/10.1136/archdischild-2014-306667>.
- Wolke, D., Tippet, N., Dantchev, S., 2015. Bullying in the family: sibling bullying. *Lancet Psychiatry* 2, 917–929. [https://doi.org/10.1016/S2215-0366\(15\)00262-X](https://doi.org/10.1016/S2215-0366(15)00262-X).
- Wu, C., Liu, Y., Yang, Y., Zhang, P., Zhong, W., Wang, Y., Wang, Q., Xu, Y., Li, M., Li, X., Zheng, M., Chen, L., Li, H., 2020. Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. *Acta Pharm. Sin. B*. <https://doi.org/10.1016/j.apsb.2020.02.008>.
- Wu, K.K., Chan, S.K., Ma, T.M., 2005. Posttraumatic stress, anxiety, and depression in survivors of severe acute respiratory syndrome (SARS). *J. Trauma. Stress* 18, 39–42. <https://doi.org/10.1002/jts.20004>.
- Xia, N., Li, H., 2018. Loneliness, social isolation, and cardiovascular health. *Antioxid. Redox Signal.* 28, 837–851. <https://doi.org/10.1089/ars.2017.7312>.
- Yang, X., Yang, X., Kumar, P., Cao, B., Ma, X., Li, T., 2020. Social support and clinical improvement in COVID-19 positive patients in China. *Nurs. Outlook* 68, 830–837. <https://doi.org/10.1016/j.outlook.2020.08.008>.

- Yoshida, M., Takayanagi, Y., Inoue, K., Kimura, T., Young, L.J., Onaka, T., Nishimori, K., 2009. Evidence that oxytocin exerts anxiolytic effects via oxytocin receptor expressed in serotonergic neurons in mice. *J. Neurosci.* 29, 2259–2271. <https://doi.org/10.1523/JNEUROSCI.5593-08.2009>.
- Zandifar, A., Badrfam, R., 2020. Iranian mental health during the COVID-19 epidemic. *Asian J. Psychiatry* 51, 101990. <https://doi.org/10.1016/j.ajp.2020.101990>.
- Zelikowsky, M., Hui, M., Karigo, T., Choe, A., Yang, B., Blanco, M.R., Beadle, K., Gradinaru, V., Deverman, B.E., Anderson, D.J., 2018. The Neuropeptide Tac2 Controls a Distributed Brain State Induced by Chronic Social Isolation Stress. *e19 Cell* 173, 1265–1279. <https://doi.org/10.1016/j.cell.2018.03.037>.
- Zhang, H., Penninger, J.M., Li, Y., Zhong, N., Slutsky, A.S., 2020. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. *Intensive Care Med.* 46, 586–590. <https://doi.org/10.1007/s00134-020-05985-9>.
- Zhonghua Liu, Xing Bing, Xue Za Zhi, 2020. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. 41, (2): 145–151. <https://doi.org/10.3760/cma.j.issn.0254-6450.2020.02.003>.
- Zoicas, I., Slattery, D.A., Neumann, I.D., 2014. Brain oxytocin in social fear conditioning and its extinction: involvement of the lateral septum. *Neuropsychopharmacol.: Off. Publ. Am. Coll. Neuropsychopharmacol.* 39, 3027–3035. <https://doi.org/10.1038/npp.2014.156>.
- Zyrianova, Y., Kelly, B.D., Gallagher, C., McCarthy, C., Molloy, M.G., Sheehan, J., Dinan, T.G., 2006. Depression and anxiety in rheumatoid arthritis: the role of perceived social support. *Ir. J. Med. Sci.* 175, 32–36. <https://doi.org/10.1007/BF03167946>.