Mental Health Effects of COVID-19

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525 B Street, Suite 1650, San Diego, CA 92101, United States
50 Hampshire Street, 5th Floor, Cambridge, MA 02139, United States
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Library of Congress Cataloging-in-Publication Data
A catalog record for this book is available from the Library of Congress

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library

ISBN 978-0-12-824289-6

For information on all Academic Press publications
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Publisher: Nikki Levy
Acquisitions Editor: Joslyn Chaiprasert-Paguio
Editorial Project Manager: Barbara Makinster
Production Project Manager: Omer Mukthar
Cover Designer: Mark Rogers

Typeset by SPi Global, India

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Chapter 8

Social isolation as a laboratory model of depression

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Introduction: Social isolation as a laboratory model of depression

Chronic social isolation in humans, whether self-imposed or enforced, appears as a striking environmental condition that can be compared to the absence of basic physiological needs such as water, food, or sleep. Social isolation refers to a significantly diminished number of interpersonal interactions or a complete lack of any interaction. An adult person goes through an average of 12 social interactions per day according to a 2018 study on a comprehensive American sample (Zhaoyang, Sliwinski, Martire, & Smyth, 2018). These refer to in-person interactions that may take place in the household, workplace, or public space. Modern life contains several elaborate types of interpersonal interaction (Goffman, 1990). Social interactions are not only central to human life, but constitute the daily routine for several other species.

This chapter starts with a global definition of sociality, the tendency to engage in social interactions. I discuss how the negative effects of social isolation for an animal depend on the degree of sociality of that species. After reviewing the species-specific responses to isolation, I differentiate self-imposed isolation from enforced social isolation. The latter has been experienced by millions of people across the globe during the COVID-19 pandemic. It has also been utilized as a laboratory model of chronic stress for nonhuman primates and rodents. I review the behavioral and physiological effects of social isolation, and discuss the wide-range use of isolation as a laboratory model of depression.

In Maslow's famous model of human motivation, the five-stage hierarchy of needs, social needs such as love and belongingness occupy the middle (third) level (Maslow, 1943, 1954). According to this theory, the absence of social interaction cannot to be compared to the deficiency of physiological needs such as water, food, and sleep in terms of its immediate effects. The long-term effects of chronic social isolation, in contrast, can be devastating. Interpersonal

Mental Health Effects of COVID-19. https://doi.org/10.1016/B978-0-12-824289-6.00005-2

interaction occupies a core part in the human sociality as detailed later. Hence, the complete lack of it for a long period of time, as in solitary confinement, is associated with cognitive decline and several psychopathologies.

In order to appreciate the psychobiological significance of social interaction in humans, one does not need to observe the severe consequences of chronic (total) social isolation, as the early monkey studies revealed with precision (Harlow, Dodsworth, & Harlow, 1965). Irrespective of the actual level of isolation an individual experiences, the perception of social isolation is sufficient to produce serious negative results (Cacioppo & Hawkley, 2009). The relationship between loneliness, defined as the distress emerging from lack of a desired level of social interaction or connection, and health is well established in the literature (Heinrich & Gullone, 2006; House, Landis, & Umberson, 1988). Meta-analyses indicate a strong correlation between loneliness and cancer (Deckx, van den Akker, & Buntinx, 2014), cardiovascular disease (Valtorta, Kanaan, Gilbody, Ronzi, & Hanratty, 2016), dementia (Kuiper et al., 2015), psychosis (Michalska da Rocha, Rhodes, Vasilopoulou, & Hutton, 2018), and of course, depression (Erzen & Çikrikci, 2018). Recent work focused on loneliness as a major outcome of the COVID-19 pandemic and associated psychopathologies (Giallonardo et al., 2020; Killgore, Cloonan, Taylor, & Dailey, 2020; Tull et al., 2020). With these data at hand, loneliness, that is mere perception of social isolation, emerges as a risk factor for mortality (Holt-Lunstad, Smith, Baker, Harris, & Stephenson, 2015; Holt-Lunstad, Smith, & Layton, 2010).

The aforementioned research on humans, whether utilizing a longitudinal design, clinical correlations, or meta-analysis, reveals little about the physiological and neurological consequences of social isolation. These often require laboratory work with animal models. Then the question is species specificity of the versatile negative effects of actual or perceived social isolation. Species specificity refers to characteristic biological properties or behaviors of a species. These include any kind of feature that distinguishes one species from another. Different animals can show different types or levels of response to social isolation as part of their species-specific properties. Sociality, the biological tendency to associate with conspecifics, defines the species-specific meaning and outcomes of social isolation (Eisenberg, 1966). For this reason, how depressed an individual organism will be following a long period of social isolation depends on the *normal* social behavior of that organism. Linking the detailed biological findings of animal isolation studies to the correlational data from clinical research depends on the cross-species commonalities of social isolation as well as the distinctive features of human sociality.

Sociality and the meaning of isolation

The COVID-19 pandemic forced millions of people across the globe to self-isolate for the first time in their lives, creating a novel and devastating feeling of boredom. This global experience reminded us the centrality of social interaction in our lives. Being a key notion for human beings, we often consider other animals to share our strong need for social interaction. As such, we have an anthropomorphic tendency (Epley, Waytz, & Cacioppo, 2007) with regards to the sociality and isolation of other animals. How terrible must it be for all those animals that are kept in social isolation by humans either as pets or zoo residents? This question, naïve as it may seem, constitutes a key subject in ethology. Human beings are *social animals* that possess a strong need for social interaction and, thus, a high level of sociality. Still, the highest degree of sociality, known as eusociality (Wilson, 1971), is often observed in certain types of insects like the termites, ants, bees, and wasps (Sherman, Lacey, Reeve, & Keller, 1995). The criteria to be considered eusocial include living in large groups, having a collective care for babies, and possessing a division of labor in reproduction (i.e., not allowing every member to reproduce) (Wilson, 1971). Other insects, and yet other animals, would be categorized as presocial, quasisocial, subsocial, or parasocial based on how much an individual organism tends to associate with conspecifics (Costa, 2018). This rather complex scientific terminology of sociality emerges as a result of the variability of social behavior and different degrees of sociality in the animal kingdom (Costa & Fitzgerald, 1996; Dew, Tierney, & Schwarz, 2016).

Careful observation of other animals indicates that not all animals are as gregarious as humans (Alcock, 2001). The aforementioned question on pitying a caged animal may be flawed, that is irrelevant, depending on the species (Lorenz, 2002). For human beings, the answer is obvious and would not require a global trend in self-isolation due to a pandemic. Solitary confinement is a substantially severe type of imprisonment with several psychopathological effects in the long term (Grassian, 1983; Grassian & Friedman, 1986). While the highly social nature of human beings is well established, there is still a debate on the exact degree of their sociality and whether they can be considered eusocial, possessing the highest level of social organization observed in nature (Foster & Ratnieks, 2005; Wilson & Hölldobler, 2005).

The degree of sociality of a species is assessed by observation of social behavior under normal conditions and is a reflection of the evolutionary, that is *biological*, need for sociality. Social behaviors, by definition, have evolved to provide a better chance for survival, just like other forms of animal behavior, emotions, and instincts (Bailey & Moore, 2018; Nowak, 2006; Rubenstein & Abbot, 2017). The *psychological* need for sociality, however, may not easily be understood under normal conditions within the habitat of a species. Social isolation constitutes the paradigm for testing this kind of mental need for sociality. The metabolic, physiological, and psychological effects of long-term enforced social isolation vary between different species, and these negative effects do not show a simple, linear correlation between the degree of sociality (Bailey & Moore, 2018).

With regards to interspecies differences in social behavior and the need for sociality, it must be remembered that *social stress*, the type of stress emerging in the presence of an unfamiliar conspecific, can be as distressing as social isolation. This phenomenon, also observed/assessed in humans (Kirschbaum, Pirke, & Hellhammer, 1993), develops with the opposite environmental conditions. The presence, as opposed to absence, of social interaction may also be a source of significant distress (Masis-Calvo et al., 2018; Tamashiro, Nguyen, & Sakai, 2005). Confrontation studies that introduce an animal to a new cage with unknown same-sex conspecifics to induce social stress have documented the versatile negative effects in guinea pigs (Sachser & Lick, 1989) as well as rats and mice (Koolhaas, de Boer, Buwalda, & Meerlo, 2016; Koolhaas, De Boer, De Rutter, Meerlo, & Sgoifo, 1997). Like the distress created by chronic social isolation, social stress can induce pathological alterations in several biological processes including immune functions (Bartolomucci, 2007; Takahashi, Flanigan, McEwen, & Russo, 2018).

Laboratory rodents and humans share numerous common features in relation to sociality. In both species, a relatively long-term isolation period is associated with cognitive decline and different health problems (Kappeler, Cremer, & Nunn, 2015). This chapter reviews the validity and reliability of social isolation as a laboratory model of depression in relation to its effects in humans, a subject of study which attracted substantial attention with the COVID-19 pandemic.

Defining social isolation

The classical definition of social isolation refers to the absence of sensory stimuli from conspecifics. These could include visual stimuli such as one's image, auditory or acoustic cues such as spoken language or species-specific alarm signals, tactile, and olfactory stimuli (Kim & Kirkpatrick, 1996). This objective definition is sufficient when there is no external social stimulus. It does not, however, incorporate the interspecies differences in the degree of sociality. As described before, certain animals show, and require, substantially more social interaction than others.

For some species, a complete absence of social stimuli is not needed to create (the perception of) social isolation. Differences in social behavior and the differential stress responses to isolation across the animal kingdom require an overarching definition that can account for all species. As an alternative to the classical definition based on the mere frequency of socially relevant sensory stimuli, social isolation was proposed to be calculated with an index of social interaction incorporating the population parameters (Bailey & Moore, 2018). According to this functional theory, social isolation must be assessed by comparing an individual's social interaction to an ideal, that is optimal, level of social interaction within a population (Bailey & Moore, 2018). This framework defines social interaction in relation to the evolutionary or ecological *fitness* of the organism, describing how well an individual adapts to its environment (Hawkley & Capitanio, 2015).

It is known that the same idea holds true for human beings. Social isolation cannot be defined merely based on how much time an individual spends avoiding conspecifics, that is the deviation from mean frequency of interaction within the population. Social isolation, as a by-product of evolution, has an impact on fitness traits, which leads to the interindividual variation in seeking isolation (Hawkley & Capitanio, 2015). The psychological effects of isolation vary across people even following long-term solitary confinement (Grassian, 1983; Grassian & Friedman, 1986).

Social isolation can be enforced by an external force or self-imposed by the organism. The former constitutes a potent laboratory model of despair for several animals. In the lab, isolation of an animal is enforced by the experimenter, as governments or local authorities enforced people to self-isolate during the COVID-19 pandemic. Self-imposed isolation, in which the organism isolates itself without any external order or force, is also designated as social isolation. Why would an organism, human, or other animal would want to self-isolate? The answer, once again, relies in our evolutionary heritage.

Social isolation is a natural process emerging as a consequence of evolutionary needs. It has been inherited, like many other physiological and psychological features, through generations of interaction with conspecifics as well the surrounding environment (Bailey & Moore, 2018; Nowak, 2006). Social isolation is not only a product, but also a determinant of evolutionary dynamics via natural selection. Animals that are isolated from their conspecifics influence evolution in several ways. Social isolation inhibits evolution by decreasing the chances for sexual selection (see Judge, 2010). It may also lead to cryptic genetic variation, a latent form of genetic variation that is expressed under abnormal conditions (Paaby & Rockman, 2014). This, in contrast, would potentiate evolution by providing a rapid evolutionary change (Bailey & Moore, 2018). The strong desire for solitude and self-imposed long-term isolation in humans, as observed in certain hermits and other recluses, should be evaluated with this evolutionary perspective (see Boyd, Rubin, & Wessely, 2012).

Self-imposed/voluntary vs. enforced isolation

Doing something voluntarily and being forced to do the same thing often lead to different psychological effects, even when the action is highly desirable (Lewes, 1877). This difference between voluntary and involuntary activity is well studied in the laboratory for motor actions by using running wheels. Voluntary and forced treadmill running in rodents have different physiological effects especially in relation to the recovery after hemorrhagic stroke (Auriat, Grams, Yan, & Colbourne, 2006; Hayes et al., 2008; Ke, Yip, Li, Zheng, & Tong, 2011; Sato et al., 2020). This does not mean that forced exercise does no good or is always less effective than voluntary locomotor activity. While both were reported to be equally effective in attenuating cognitive impairment in an animal model of vascular dementia (Lin et al., 2015), forced, but not voluntary, exercise was found to reduce infarct volume in another study (Hayes et al., 2008). These results do not directly translate to other forms of activity or state. Locomotor activity has substantial ameliorative effects on health (Dunn, Trivedi, Kampert, Clark, & Chambliss, 2005; Niemann, Godde, Staudinger, & Voelcker-Rehage, 2014), which can merely shadow the potential negative effects rising from the forced nature of an involuntary task. Studies that identify the negative effects of forced running, however, can reflect the physiological outcome of the involuntariness component. The different physiological outcomes of voluntary and involuntary forms of a seemingly mechanical activity, that is exercise, can be useful to understand the differential effects of enforced vs. voluntary isolation.

To my knowledge, there is no laboratory model to test the specific physiological effects of the "voluntary" dimension of self-isolation in terms of its physiological effects, as typical laboratory rodents would not normally choose to be isolated like most humans. The differential psychological effects of voluntary vs. involuntary isolation cannot be revealed either. It is important to remember that voluntary self-isolation is very rare in human beings, as compared to other mammals (Eisenberg, 1966).

The Novel Coronavirus Disease (COVID-19), declared a pandemic by the World Health Organization in March 2020, constitutes the most novel and recent example of enforced human isolation. The so-called self-isolation during this worldwide incident would not occur without the official warnings and emergency regulations of the involved authorities. Self-isolation as a personal precaution may appear as an autonomous decision if not enforced by a ruling authority. However, these decisions are still enforced by the environment, the pandemic, and cannot be compared to the aforementioned forms of monastic living that constitute self-chosen social isolation (Boyd et al., 2012). Social isolation of humans can not only be categorized as enforced as in solitary confinement or self-chosen, but observed with different levels of intention, as it became clear during COVID-19 (Farooq, Laato, & Islam, 2020). Furthermore, perceived social isolation, that is a strong feeling of loneliness, also leads to varying levels of hormonal and neuronal alterations (Cacioppo, Cacioppo, Capitanio, & Cole, 2015; Cacioppo, Capitanio, & Cacioppo, 2014). The motivation for reclusion can be medical (i.e., quarantine) as observed in 2020, political or religious with varying degree of intentionality (Boyd et al., 2012).

The behavioral effects of social isolation

The classical monkey social isolation study by Harlow et al. (1965) showed that 3 months of total social isolation or a prolonged period of semi-isolation in newborn monkeys is sufficient to produce highly fearful or aggressive behaviors, which were termed by the authors as "social damage." These animals were isolated during the *critical period* for developing social behavior (Scott, 1958). Strikingly, two out of six monkeys in the 3-month total isolation group developed anorexia, a severe loss of appetite, following termination of isolation, and one animal died for refusing to eat. Early social isolation studies in monkeys revealed several other negative consequences, including emergence of severe psychopathologies, including abnormal fear responses, hyperaggression (Mitchell, 1968; Suomi, Harlow, & Kimball, 1971). Similar observations of abnormal affective behavior, described as *isolation syndrome*, were also observed in rats (Hatch et al., 1965; Hatch, Wiberg, Balazs, & Grice, 1963).

This research gave rise to utilization of social isolation as a general psychopathology model. In different studies, the effects of various social isolation paradigms have been associated with schizophrenia (Geyer, Wilkinson, Humby, & Robbins, 1993; Wilkinson et al., 1994), hyperactivity and attention deficit hyperactive disorder (ADHD) (Einon & Morgan, 1978; Gentsch, Lichtsteiner, Frischknecht, Feer, & Siegfried, 1988; Matsumoto, Fujiwara, Araki, & Yabe, 2019), autism (Burrows et al., 2017; Matsumoto et al., 2019), alcoholism (Roske, Baeger, Frenzel, & Oehme, 1994), drug abuse (Jones, Marsden, & Robbins, 1990), and anxiety (Weiss, Pryce, Jongen-Rêlo, Nanz-Bahr, & Feldon, 2004; Zorzo, Méndez-López, Méndez, & Arias, 2019). Rodent isolation was then proposed as a model for anxiety (Parker & Morinan, 1986).

Another particular psychopathology, depression, also attracted significant scientific attention in relation to social isolation. With its versatile behavioral outcomes on various cognitive and affective tasks, social isolation became a widespread laboratory model of depression (Jesberger & Richardson, 1985). Its consequences were found to be comparable to the behavioral despair induced in the forced swim test (Jaffe, De Frias, & Ibarra, 1993), the gold standard rodent model of clinical depression (Unal & Canbeyli, 2019). Unlike the majority of neuroscientific research, the relationship between social isolation and depression-like behavior in rodents was also tested and confirmed in female animals (Martin & Brown, 2010). Furthermore, in a mouse study, even a 12-h isolation paradigm led to behavioral despair in the forced swim test (Takatsu-Coleman et al., 2013), indicating acute social isolation as a separate despair model emerging via distinct neuronal and hormonal mechanisms (Shahar-Gold, Gur, & Wagner, 2013).

In addition to its affective outcomes, social isolation in the laboratory led to observable cognitive consequences. Isolated rearing in monkeys leads to diminished performance in learning tasks that involve object recognition and discrimination (Sánchez, Hearn, Do, Rilling, & Herndon, 1998). Later research in rodents revealed impaired spatial working memory (Zorzo et al., 2019) and reversal learning performance, indicating cognitive rigidity and deficits in rule learning (Jones, Marsden, & Robbins, 1991). Similar results were observed in humans with substantially fewer social connections, even when they are not in a state of total isolation. Gerontological studies revealed that elderly people with few social contacts are more likely to display global cognitive decline (Ellwardt, Van Tilburg, & Aartsen, 2015; Lee & Kim, 2016). In line with the laboratory findings, social isolation in elderly people was correlated with impairments in working memory (McGue & Christensen, 2007). Hippocampus-dependent episodic memory performance was also impaired in socially isolated seniors (Klaming, Annese, Veltman, & Comijs, 2017; Mousavi-Nasab, Kormi-Nouri, & Nilsson, 2014). These results are not surprising as the strong association between cognitive competence, which refers to creative thinking and problem solving skills, and depression is well established by clinical (Channon, Baker, & Robertson, 1993), correlational (Burt, Zembar, & Niederehe, 1995), functional imaging (Eugène, Joormann, Cooney, Atlas, & Gotlib, 2010), and animal studies (Atesyakar, Canbeyli, & Unal, 2020). Indeed, a cognitive model of depression has been developed by Beck (1967) more than 50 years ago (also see Beck, 2008).

Reversing the devastating effects of social isolation, especially the apparent depressed state, emerged as the next major research question since the early monkey isolation studies. Imipramine, a tricyclic antidepressant (TCA), was proved useful (Suomi, Seaman, Lewis, DeLizio, & McKinney Jr, 1978). Interestingly, the most successful attempt was to use other (healthy) monkeys, designated therapist monkeys as a form of rehabilitation (Suomi, Harlow, & McKinney, 1972). Later research in rodents found several other antidepressants, including fluoxetine, to be effective in isolation-induced despair (Martin & Brown, 2010). The therapeutic effects of antidepressants on the isolation-led behavioral despair in animals strengthen the face validity of social isolation as a laboratory model of clinical depression.

The physiological effects of social isolation

The versatile psychological effects of social isolation point to pathological alterations in several systems of the body. Research revealed long-term isolation to cause substantial changes in neuroendocrine and immune functions in addition to its neuroanatomical and neurophysiological effects, leading to dysfunction in different neuronal circuits/pathways. Not surprisingly, many of these systems that are summarized as follows are also involved in the pathophysiology of depression (Krishnan & Nestler, 2008; Nestler et al., 2002). In this regard, one particular correlation is noteworthy to mention: clinical depression has been associated with higher mortality rates by several studies (Machado et al., 2018). Similarly, increased mortality, derived from long-term correlation studies, do not only emerge as a result of social isolation, but also loneliness (Holt-Lunstad et al., 2010; Steptoe, Shankar, Demakakos, & Wardle, 2013).

Disrupted immune functions are well-documented consequences of social isolation (Bartolomucci, 2007). Human social isolation and loneliness lead to heightened inflammatory responses (Cole et al., 2007; Steptoe, Owen, Kunz-Ebrecht, & Brydon, 2004). These are accompanied with different metabolic, neuroendocrine, and cardiovascular problems (Caspi, Harrington, Moffitt, Milne, & Poulton, 2006; Steptoe et al., 2004). Postweaning isolation in rats leads to HPA axis hyperfunction, observed as substantially elevated levels of ACTH and corticosterone in response to stress in male rats (Weiss et al., 2004) and impairs glucocorticoid-mediated negative feedback in response to acute stress (Boero et al., 2018). Furthermore, altered glucocorticoid levels in social isolation are correlated with the coping strategy (see Unal & Canbeyli, 2019) in the forced swim test (Vargas, Junco, Gomez, & Lajud, 2016). The association between HPA axis reactivity and depression is also observed in humans: loneliness is positively correlated with increased HPA axis function (Doane & Adam, 2010; Nowland, Robinson, Bradley, Summers, & Qualter, 2018). Interestingly, similar to the aforementioned rodent study on the differential relationship between isolation-led glucocorticoid levels and coping strategy in the forced swim test (Vargas et al., 2016), HPA axis activation in humans is differentially correlated with different types of depression. Clinically high levels of CRH are observed in atypical depression, whereas a down-regulated HPA axis activity and a resultant deficiency in CRH underlie melancholic depression (Gold & Chrousos, 2002).

Dysfunction of the HPA axis is accompanied by disruptions in the oxidative/nitrosative stress pathway (Filipović, Todorović, Bernardi, & Gass, 2017; Gądek-Michalska, Tadeusz, Bugajski, & Bugajski, 2019). In addition to dysfunction in neuronal pathways, a number of region-specific neuroanatomical alterations were discovered in animal models of isolation. Studies that incorporate social deprivation in monkeys revealed decreased dendritic arborization in Layer IV neurons of the motor cortex (Struble & Riesen, 1978) and Purkinje cells of the cerebellum (Floeter & Greenough, 1979). These early results, however, may also reflect the neuronal consequences of decreased locomotor activity rather than a lack of social interaction. Subsequent research in rodents pinpointed to another cortical region, the prefrontal cortex, as the foremost neuroanatomical target of isolation. Mice placed in postweaning isolation for 2 to 8 weeks in different studies showed significantly decreased myelin thickness in the prefrontal cortex due to oligodendrocyte dysfunction (Liu et al., 2012; Makinodan, Rosen, Ito, & Corfas, 2012). Morphological and other cellular changes were also observed in astrocytes (Sun et al., 2017) and principal neurons (i.e., pyramidal cells) (Yamamuro et al., 2018) of the prefrontal cortex.

Cellular level alterations in the prefrontal cortex are accompanied by pathological changes in its synaptic inputs, especially the mesocortical dopaminergic pathway (Blanc et al., 1980). Dopaminergic neurons that constitute the so-called *reward pathway* of the mammalian brain respond to social isolation (Matthews et al., 2016). Significantly lower levels of dopamine immunoreactivity were revealed in the neocortex and striatum of monkeys reared in total isolation for 9 months. No such difference was observed in the amygdala, the bed nucleus of the stria terminalis and basal forebrain, pointing to a selective reduction in dopaminergic innervation of the cortico-striatal circuitry (Martin, Spicer, Lewis, Gluck, & Cork, 1991). Later microdialysis studies in rats showed that long-term social isolation following weaning (postnatal day 21) led to several synaptic alterations in the dopaminergic system of the striatum (Hall et al., 1998) and the medial prefrontal cortex (Leng, Feldon, & Ferger, 2004). A more recent electrophysiological study showed that isolated rearing in rats led to an heightened dopamine terminal function in ex vivo slice recordings (Yorgason et al., 2016). Psychostimulant potency in the striatum was enhanced by social isolation in the same study, pinpointing to the potential neuronal link between isolation-induced depression and drug abuse (Yorgason et al., 2016). Social isolation of rats during their adolescent transition period (postnatal day 23 to 77) was sufficient to decrease dopamine D2 receptor expression in the prefrontal cortex (Fitzgerald, Mackie, & Pickel, 2013).

Pathological alterations in the dopaminergic system were also discovered following acute social isolation. Dopaminergic neurons of the dorsal raphe nucleus were discovered to be sensitive to acute isolation in mice (Matthews et al., 2016). Not surprisingly, increased synaptic dopamine levels have been observed during introduction of conspecifics at the end of an isolation period (Robinson, Heien, & Wightman, 2002). These studies altogether identify disrupted dopaminergic innervation of the prefrontal cortex, as a major component of isolation pathophysiology. Since dysfunction of the dopaminergic system constitutes a key factor in the etiology of clinical depression and underlies psychomotor symptoms of the disease (Unal & Canbeyli, 2019), the mesocortical pathway emerges as a key link between social isolation and depression.

Conclusion: The uniquely human aspect of social isolation

This chapter reviewed the basic evolutionary, psychological, and physiological aspects of social isolation, and its wide-range use as a laboratory model of depression. Some of these features are shared by several species while others cannot be generalized. Some animals including giant pandas, polar bears, jaguars, and blue whales are generally solitary, displaying true self-isolation in their habitat. As such, social isolation would not constitute a despair model for them. Nobel laureate ethologist Konrad Lorenz spent a lifetime observing and comparing social interactions of different species, expressing that the "state of mind, common to human prisoners, called boredom" (p. 54, Lorenz, 2002) is not a common feature of the animal kingdom, but shared by some monkeys, apes, and parrots, against our anthropological tendency to attribute our own drives and emotions to other animals. Boredom is the key emotion and state behind the effects of social isolation. It is not unique to human beings, but appears to be a fundamental human experience, as much as depression is a complex human psychopathology.

As surveyed in this chapter, numerous equivalent findings from clinical and longitudinal human studies as well as the laboratory work on other animals revealed social isolation as a major cause of depression. The use of social isolation in other animals as a despair model would depend on their regular sociality, that is to say how much boredom isolation would create. Rhesus monkeys and common laboratory rodents that share several biological and psychological properties with humans suffer similarly from long-term isolation. Social isolation, in this respect, is a solid model of depression for animals that are similar to humans in terms of their need for interaction with conspecifics. The devastating psychological consequences of COVID-19 precautions affected millions of people across the globe, reminding us of our deep urge for social interaction. It is likely that many humans will develop, or already have developed, depression as a result of the enforced social isolation procedures. Several new lines of research are currently investigating the effects of COVID-19 on mood and anxiety disorders, and related psychological phenomena (see Castelli, Di Tella, Benfante, & Romeo, 2020; Fofana et al., 2020; Giallonardo et al., 2020; Killgore et al., 2020; Tang et al., 2020; Tu, He, & Zhou, 2020; Tull et al., 2020). Future research may differentiate the role of social isolation from other psychological effects of COVID-19 (i.e., pandemic stress/fear) in postpandemic psychopathologies. Considering the psychosocial (Barbalet, 1999; Vodanovich & Kass, 1990) and cultural factors (Brissett & Snow, 1993) linking sociality and boredom in human life, and the recent isolation experience of the COVID-19 pandemic, social isolation emerges as a *human* model of depression more than anything.

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