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The psychoneuroendocrine response of aggression due to COVID-19 social isolation

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Abstract

The pandemic caused by the SARS-COV-2 virus in the years 2020-2022 altered the emotional behavior of humans. The restrictive feeling caused by the isolation and the change of life habits that demanded a social separation promoted anxiety, distress, apathy, domestic violence, educational problems, and economic instability, among other aspects. Erroneous statistics, and social media information about the number of people infected by the coronavirus SARS-COV-2, aggravated human anxiety and depression. This review compares the main psychological effects caused by pandemic isolation compared to other isolated social contexts. We studied the primary central nervous system areas involved in human reactive aggressiveness behavior. We examine this behavior in relationship with catecholamines and hormones during social isolation. We do not measure or analyze any hormone in our laboratory and only describe the circuits involved in the neuroendocrine response to the aggressive behavior.

Keywords: *COVID-19. Isolation. Aggression. Stress.*

La respuesta psiconeuroendocrina de la agresión debido al aislamiento social por Covid 19

Resumen

La pandemia causada por el virus Sars-Cov-2 durante los años 2020 a 2022, alteró la conducta emocional de los humanos. El sentimiento de restricción causado por el aislamiento y el cambio de hábitos de vida que demandaron una separación social promovieron: ansiedad, estrés, apatía, violencia doméstica, problemas educativos e inestabilidad económica, entre otros aspectos. Estadísticas erróneas y de los medios de información acerca del número de personas infectadas por el Coronavirus Sars-Cov-2 agravaron la ansiedad y la depresión humana. Esta revisión compara los principales efectos psicológicos causados por el aislamiento durante la pandemia comparado con otros contextos de aislamiento social. Nosotros estudiamos las áreas primarias involucradas en la conducta de agresión reactiva en los humanos y analizamos esta conducta en relación con las catecolaminas y hormonas durante el aislamiento social. No medimos ni analizamos ninguna hormona en nuestro laboratorio solo describimos los circuitos involucrados en la respuesta neuroendocrina a la conducta agresiva.

Palabras clave: *COVID19. Aislamiento. Agresión. Estrés.*

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Introduction

The term "social isolation" can be defined as a multidimensional construction that refers to the inadequate amount and quality of interactions with others. It occurs either in individual groups or at community levels[1]. The psychological impact on people subjected to enforced social isolation by COVID-19 during a long period induced anxiety, depression, distress, anger, apathy, sleep problems, loneliness, boredom, or aggressiveness[2-4]. Nonetheless, mental health significantly impacts life quality, as it influences interpersonal and intrapersonal interaction. Few studies are related to the negative psychological impact on human emotions due to prolonged periods of isolation. Different factors involve the emotional response to the pandemic state in people, such as socioeconomic status, education, age, knowledge, or uncertainty about the disease.

Anxiety, depression, insomnia, and stress are common effects in individuals during centralized and home quarantine periods[5-7]. The scenario shown by the evidence suggests a psychological and hormonal influence provoked by the pathophysiological processes involved in response to social isolation. This review presents a synergy among hormonal factors, brain circuits, and social isolation derived from the COVID-19 pandemic on aggressive human behavior.

The social context in an aggressive reaction

Social isolation has been present in historical moments since the early records of human civilization, such as yellow fever and Spanish influenza. The SARS-CoV-2 virus outbreak has significantly impacted the world's population since its declaration as a sanitary emergency in 2020 and current times. An important risk factor for aggressive behavior due to COVID-19 is how each individual copes with the different restrictive recommendations. They function to keep the virus from spreading and living with uncertainty during a pandemic. The main one is home quarantine to prevent infection for themselves and others. An examination of Turkish people's experience during this type of isolation revealed that most of the population experiences bad feelings (anxiety, distress, and depression), which increases when there is a diagnosed case of SARS-COV-2 infection in their household[8].

In the case of children, UNICEF reported that the closure of schools increased abuse and physical violence against children during the Ebola epidemic from 2014 to 2016[9].

A similar situation has presented for women in the COVID-19 pandemic. A study in Tunez, Africa, showed a higher number of women experiencing violence (78% of the patients were de novo) during social isolation. Women who suffer from domestic abuse have more propensity to develop mental conditions, one of which is depression[10].

Elderly adults have been one of the most studied social groups due to the relationship between loneliness and vulnerability present in their lives. Furthermore, associated with one or more comorbidities, their behavior becomes more aggravated depending on their surroundings. Living alone and having a low income of money can have a considerable impact on their well-being. These factors can lead to a depletion in the immune system, inducing more harm than smoking, obesity, cardiovascular conditions, and cancer[11,12].

Young adults, women, people who lived alone, individuals with a low level of school education, low incomes, urban residents, and limited ethnic groups presented high levels of loneliness before and during the pandemic in the United Kingdom[13]. Furthermore, people with constant social isolation present a higher level of dissatisfaction with their home, nutrition, work, government, and other institutions. They can also show less connection to the people surrounding them and an increase in the consumption of illicit substances[14,15].

A study on inmates in social confinement (defined as an individual placed in social isolation in a cell for 24 h) had various physical problems such as gastrointestinal, urinary, insomnia, diaphoresis, migraines, and weakness. They also had psychological symptoms, and the most recurring was mental rumination. Inmates presented too revenge acts, hostile behavior, irritability, rage, physical and verbal violence toward another individual, objects, or even themselves. In the long run, the effects can be damaging because the inmate can get familiarized with social isolation. It can complicate their reintegration into society because they can bring the manners they had while in social confinement[14]. Poor mental health conditions increased the incidence of violence against women, children, seniors, and vulnerable groups during the lockdown. It suggests having a relation with the stress a person suffers as a consequence of the situations presented in the global emergency. People losing their job or family member experimented constant exposure to frustration. It increases alcohol abuse or any other illicit substance. It promoted more consumption inside their home, increasing mental diseases[8].

Neuroendocrine mechanisms and reactive aggression due to social isolation

Reactive aggression refers to acts committed in negative affective states, such as anger, frustration, or in response to provocation[16]. The frustration-aggression model postulates that an obstacle to goal attainment leads to frustration and may lead to an attack. It is a defensive response to perceived or actual provocation characterized as anger, affective instability, disinhibition, and impulsive behavior named "hot-blooded"[17]. In reactive aggressiveness, several axes were studied. We describe the specific neuronal regions and their connectivity to nuclei to detect a stimulus or a process of hostility[18]. The different circuits in this section are the core aggression circuit (CAC), the hypothalamus-pituitary-adrenal (HPA) axis, the locus coeruleus system, and the mesolimbic dopamine pathway (MDP). We hypothesize that these circuits conform a system that induces, contrasts, and exhibits reactive aggression.

CAC

Multisensory stimuli must overpass the CAC to produce a chemical imbalance that leads to aggression[19]. It can be unleashed and blocked through this circuit from the following brain regions: the medial amygdala (MeA), the bed nucleus of the stria terminalis (BNST), the ventrolateral portion of the ventromedial hypothalamus (VMHvl), and the ventral premammillary nucleus (PMv) by sending multiple catecholamines to generate a positive or negative feedback stimulus, depending on the reactive-aggression cue that is present in the environment[20].

The CAC controls the reaction by capturing serotonin; this stimulates the hippocampus-lateral striatum pathway and the medial prefrontal cortex (mPFC)[21,22]. Low levels of serotonin generated by isolation by the COVID-19 pandemic inhibit the connectivity between CAC and mPFC and the limbic system pathway, inducing uncontrolled reactive aggression.

HPA axis and distress

The hypothalamus induces the adrenocorticotropic hormone released by the pituitary. This gland sends the signal to the adrenal cortex to produce cortisol.

The HPA axis has intrinsic activity by maintaining an underlying 24-h cortisol rhythm stress-dependent mechanism linked to an activity level as positive feedback. In humans, this circadian rhythm consists of high cortisol levels during the start of the wake cycle (morning). It decreases through the afternoon and reaches the lowest level at night-time, at the beginning of the sleep cycle[23].

Glucocorticoids have different affinities for mineralocorticoid receptors and glucocorticoid receptors. The physiological feedback response to circulating glucocorticoids induces homeostasis. Maintaining an adequate cortisol rhythm could prevent some affective disorders[24].

The HPA axis reaction to stress reflects the organism's response to distress: intense reactions are versatile, but intemperate ones can lead to destructive impacts. Drawn-out cortisol harmful effects, which may not be clinically evident, have the potential to serve as biomarkers of disease susceptibility and aggressive reactivity[21,22].

Stressful occasions in the early life may have an etiologically critical part in the HPA anomalies as psychiatric disorders that include: depression, bipolar disorder, anxiety disorders, eating disorders, schizophrenia, substance abuse, dissociative disorder, and post-traumatic stress disorder, among other mental illnesses[25]. As a survival mechanism, cortisol produces an immediate systemic reaction, stressful situations such as social isolation cause chronic cortisol overproduction.

Lack of stimulus to the corticosterone receptors can alter the feedback of cortisol. Cortisol levels measured through saliva, the cortisol awakening response, or the diurnal cortisol slope (DCS) can identify any stress or suicidal behavior pattern. The DCS measures the fluctuation of cortisol levels throughout the day and registers if there is any abnormality in the cortisol levels. Any disorder caused by stressful situations, such as social isolation, can dull and plane the cortisol slope[26].

Social isolation is associated with loneliness by consequence, while loneliness refers to the self-perception of how somebody feels in their relationships. A study on adults between 25 and 75 during social isolation evaluated the association between salivary cortisol and items from psychological scales that determine loneliness. The hormone levels specifically define the differences between social isolation and loneliness. The results showed a relationship between a flattened DCS in social isolation cases, meaning higher late cortisol levels and dysfunctions in the HPA axis[27]. It has been found that subjects' response to an aggressive impulse shows a higher salivary cortisol level, which increases each time they keep this aggressive behavior[28].

As stress is a fundamental factor in how the COVID-19 virus impacts the body, it is natural to think about how

stress reduction helps prevent this disease by strengthening the immune system and avoiding other illnesses that can result in comorbidities. Physical activation, social interaction (including communication through virtual platforms), psychological therapy, hygiene habits, and healthy routines can help improve the body's situation and reduce distress[29]. We believe stress reduction might also benefit patient recovery after COVID-19 infection.

Locus coeruleus - Norepinephrine system (NE)

The locus coeruleus - NE has a significant role in arousal, attention, and stress response. Every time there is a stress response, a signal works in the hypothalamus and HPA axis. The basal forebrain induces wakefulness to make the body enter alertness and regulate the autonomous nervous system (fight or flight response). The thalamus also triggers sleeplessness, sensory processing, stress detection, and pain modulation. Whenever there is an intense secretion of norepinephrine with the inhibition of the thalamus, the reactive aggressor feels less pain while being in a fight situation. The amygdala and the hippocampus get stimulated to process episodic and emotional memories. In contrast, all areas work together with the spinal cord, which mediates the motor and sensory functions during the wakefulness impulse stimulated by the vagus nerve[30].

The amount of tyrosine hydroxylase neurons in the neocortex is markedly different across species. In dementia, there is no coexpression of GABA in the locus coeruleus as it was related to measures of aggressive behavior. Furthermore, in Alzheimer's disease, a decrease in norepinephrine in the temporal cortex was linked to cognitive impairment[31]. Dementia does not directly correlate to social isolation; we believe that its presence might aggravate confinement effects.

Reactive aggressiveness

Reactive aggressiveness can be caused by extrinsic factors and by multiple variables of the mental state. It affects aggressive expression in modulating the response and internal communication of the CAC in conjunction with the HPA axis as well as the Locus Coeruleus system[19].

Aggressive arousal occurs due to a preserved subcortical CAC. As a response to the COVID-19 pandemic, catecholamines decrease due to a lack of exposure to the social environment. This situation increases the basal level of cortisol and serotonin without controlling aggressive impulses (for this reason, it is called reactive aggressiveness) through the mPFC[16].

The specific axes that modulate and express aggression of each species direct the stimuli that generate aggressiveness inside the CAC. The output of these cues promotes reactive aggressive actions through projections in the premotor area of the midbrain. It simultaneously induces motor actions of aggressive nature during their lifespans. It happens due to the activation of the striatum through activation by dopaminergic cells[12].

The hypothalamus processes stimuli in and out of the central nervous system, working in conjunction with the CAC and the HPA axis (Fig. 1)[29,32].

In the HPA-axis response system, cortisol levels would, then, become maximally elevated due to the aggressive encounter. Therefore, during early childhood, if cortisol levels are measured in a familiar, non-stressful setting, and low levels of cortisol may be more likely to predict low levels of aggression[26]. However, if taken in a context where aggressive interactions are prevalent, high cortisol levels may better indicate high levels of aggression. According to the frustration-aggression theory typically applied to reactive aggression, this form of aggression arises predominantly among children with a strong orientation toward negative information during the initial stages of social interaction processing (SIP). There is a tendency to interpret this information as threatening or frustrating, and it can become emotionally aroused due to their interpretation of the incoming social information[33].

Children experience many situations as frustrating due to insufficient information-processing capacities, making them react aggressively. Rheumatoid arthritis is related explicitly to deviations during the earlier stages of SIP. Reactive aggression was associated with an overactive HPA-axis response to two different stressors, while the proactive attack was unrelated to stress reactivity[33]. It is relevant to avoid social isolation in children and adults to avoid stressful situations affecting their behavior and wellbeing.

Control mechanisms of reactive aggressiveness

Serotonergic mediation

Human aggression presents diverse behaviors and psychiatric disorders categorized in the fifth edition of the diagnostical and statistical manual of mental disorders[34]. Aggressiveness plays a significant role in virtually all living beings as a part of their survival instincts;

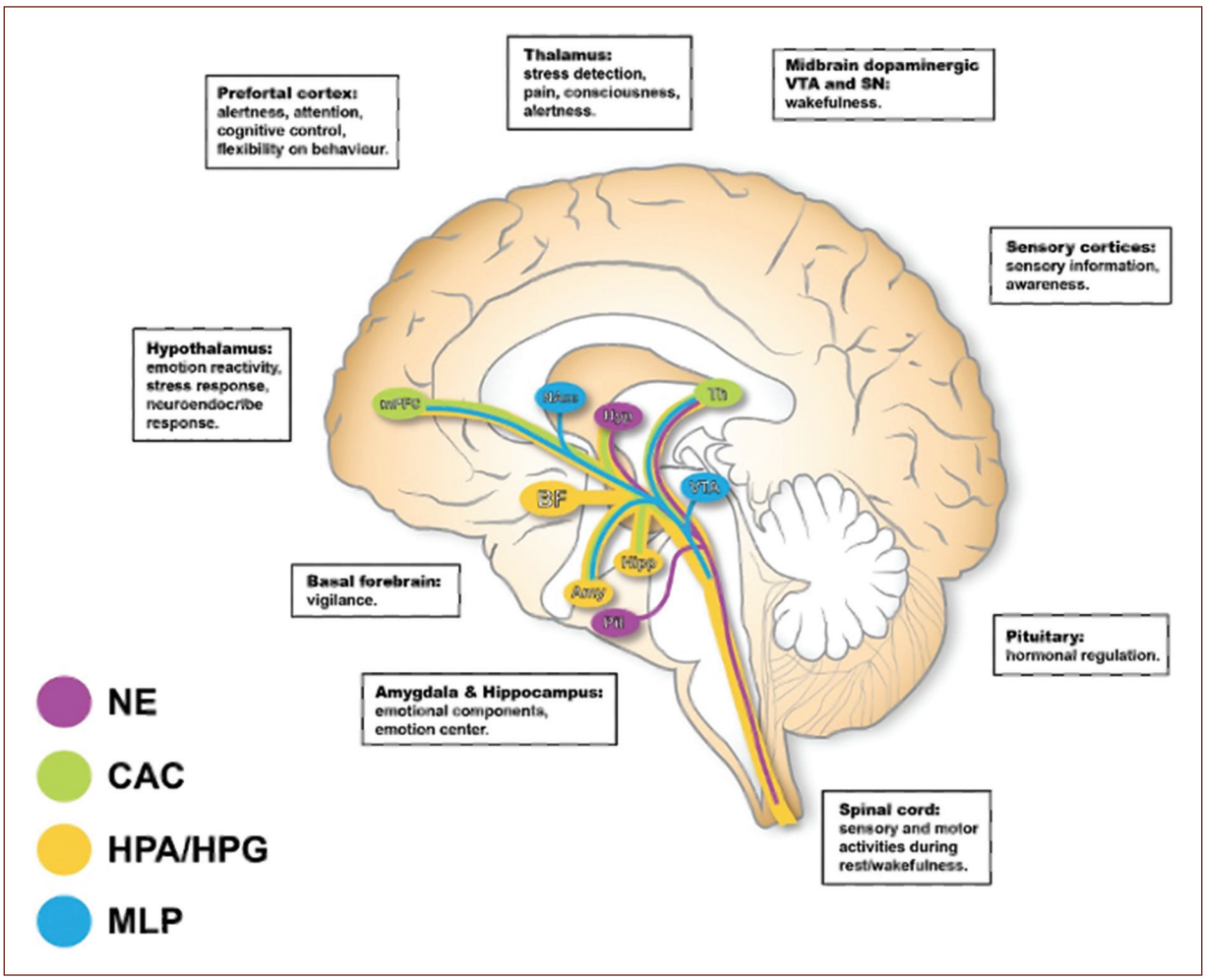

Figure 1. The neuroendocrine pathways involved in reactive aggression.
The Locus Coeruleus - Norepinephrine system (NE); the Core Aggression Circuit (CAC); the Hypothalamus-Pituitary-Adrenal axis (HPA/HPG); and the Mesolimbic-Dopamine pathway (MLP) interact in conjunction to dispatch and regulate reactive aggression.

however, it can be harmful when it manifests in excessive ways[35].

The serotonin system could be responsible for inhibiting aggression, whereas the dopaminergic system initiates it, and the GABA system modulates the intensity[34]. Serotonin hypofunction in the anterior cortex and the anterior cingulate gyrus is related to aggressive behavior[36]. This malfunction reduces control of the dopamine system leading to hyperactivity[37]. Neurons that produce serotonin are found in the mid and hindbrain projecting to the rostral and caudal brain areas[35].

Serotonin is synthesized by 5-hydroxytryptophan; it works as a modulator of the central nervous system. Multiple aspects, such as cellular differentiation, proliferation, and migration synaptogenesis, are involved in the behavioral processes. Serotonin system disorders can be related to impulsiveness and aggression. The serotonin axis is related to anxiety, attention deficit, hyperactivity disorders, and autism spectrum, among others[35].

Mutations and polymorphisms of metabolic enzymes are present in the production and degradation of serotonin, carrier proteins in charge of releasing or internalizing it[34].

The monoamine oxidase enzyme degrades the serotonin into 5-hydroxy indole acetaldehyde (5-HIAL). Finally, it transforms into 5-hydroxy indole acetic acid (5-HIAA) by one aldehyde dehydrogenase[38]. This acquired importance when low monoamine oxidase levels were demonstrated in aggressive male criminals by

Stalenheim in 2004[34]. The serotonin neurotransmitter has been proven to have an essential role in the aggression mechanisms of animals and humans. Fourteen existing serotonin receptors are autoreceptors because they module their serotonergic cell[39].

The 5-hydroxytryptamine receptor 1B (5-HT1B) can be in the axons of serotonergic and non-serotonergic cells. Both cases work as a so-called heteroreceptor that regulates cell activity. Serotonin binds and activates its 5-HT1B receptors.

The serotonin cotransporter protein pumps the extracellular serotonin and avoids overstimulating the postsynaptic neuron[40]. This effect is substantial because, in rodents, the regulation of the 5-hydroxytryptamine cotransporter and serotonin receptors reduces the aggressive response to a stimulus. There is a relationship between suicidal behavior, negative emotions, poor control of impulsiveness, bold exploits, drug consumption, and decreased food intake with a decrease in serotonin levels[35].

Dorsal Raphe Nuclei lesions have decreased the threshold in impulsiveness behavior[35]. The 5-hydroxytryptamine 2A receptor increases the neuron's activity and has a prominent expression in impulsiveness[35]. Low levels of 5-HIAA are associated with aggression[41].

The theory of low serotonin metabolites in aggression is that the low 5-HT cotransporter activity fails to concentrate serotonin in the cell, so there is a secondary depletion. Another possible explanation is that the presynaptic 5-HTB1 receptor has a lower activation threshold and initiates recapture sooner than expected, thereby reducing serotonin concentrations.

The MDP

The MDP controls serotonin cotransporter's expression linked to aggressive conduct. Ventral tegmental nucleus signals from the BNST and hypothalamus are directed to dopaminergic neurons in the same nucleus. The posterior BNST is strongly interconnected with the medial amygdala and likely processes social information[42]. Uncontrolled signals sent to dopaminergic neurons in the ventral tegmental area can generate aggressive behavior. Aggressive impulses increase due to reduced social interactions among persons during the COVID-19 pandemic.

Conclusion

The alterations in human behavior during social isolation directly influence their social context and how people react to feeling lonely. COVID-19 quarantine in the first semester of 2020 promoted anxiety, aggressiveness, and stress in many communities surrounding the world. Important changes in basal cortisol, catecholamines, and serotonin levels induced this behavior. It promoted impulsiveness, reactive aggression, and frustration. The brain circuits involved in this negative emotional expression are possibly related to the CAC and an imbalance among the hormones and neurotransmitters mentioned before. Many studies are necessary to elucidate the aggressive reactions implied in human behavior in different social isolation contexts.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

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References

1. Clair R, Gordon M, Kroon M, Reilly C. The effects of social isolation on wellbeing and life satisfaction during pandemic. Humanit Soc Sci Commun. 2021;8:1-6.
2. Xiang M, Zhang Z, Kuwahara K. Impact of covid-19 pandemic on children and adolescents' lifestyle behavior larger than expected. Prog Cardiovasc Dis. 2020;63:531-2.
3. Shah SM, Mohammad D, Qureshi MF, Abbas MZ, Aleem S. Prevalence, psychological responses and associated correlates of depression, anxiety and stress in a global population, during the coronavirus disease (Covid-19) pandemic. Community Ment Health J. 2020;57:101-10.
4. Mukhtar S. Psychological health during the coronavirus disease 2019 pandemic outbreak. Int J Soc Psychiatry. 2020;66:512-6.
5. Özdin S, Özdin ŞB. Levels and predictors of anxiety, depression and health anxiety during COVID-19 pandemic in Turkish society: the importance of gender. Int J Soc Psychiatry. 2020;66:504-11.
6. Wang C, Pan R, Wan X, Tan Y, Xu L, Ho CS, et al. Immediate psychological responses and associated factors during the initial stage of the 2019 coronavirus disease (Covid-19) epidemic among the general population in China. Int J Environ Res Public Health. 2020;17:1729.

7. Barros MB, Lima MG, Malta DC, Szwarcwald CL, Azevedo RC, Romero D, et al. Report on sadness/depression, nervousness/anxiety and sleep problems in the Brazilian adult population during the COVID-19 pandemic. Epidemiol Serv Saude. 2020;29:e2020427.
8. Gök, A. Examination of home quarantine experiences of individuals diagnosed with COVID-19 living in Turkey. Home Health Care Manage Pract. 2022;34:229-36.
9. Xue J, Chen J, Chen C, Hu R, Zhu T. The hidden pandemic of family violence during covid-19: unsupervised learning of tweets. J Med Internet Res. 2020;22:e24361.
10. Sediri S, Zgueb Y, Ouanes S, Ouali U, Bourgou S, Jomli R, et al. Women's mental health: acute impact of COVID-19 pandemic on domestic violence. Arch Womens Ment Health. 2020;23:749-56.
11. Malcolm M, Frost H, Cowie J. Loneliness and social isolation causal association with health-related lifestyle risk in older adults: a systematic review and meta-analysis protocol. Syst Rev. 2019;8:48.
12. Bzdok D, Dunbar RI. The neurobiology of social distance. Trends Cogn Sci. 2020;24:717-33.
13. Kalemi G, Michopoulos I, Efstathiou V, Tzeferakos G, Gkioka S, Gournellis R, et al. Self-esteem and aggression in women: differences between female prisoners and women without criminal records. Women Health. 2019;59:1199-211.
14. Shalev S. Solitary confinement as a prison health issue. In: Prisons and Health. Copenhagen, Denmark: WHO Regional Office for Europe; 2014. p. 27-35.
15. Bu F, Steptoe A, Fancourt D. Who is lonely in lockdown? Cross-cohort analyses of predictors of loneliness before and during the covid-19 pandemic. Public Health. 2020;186:31-4.
16. Miller JD, Lynam DR. Reactive and proactive aggression: similarities and differences. Pers Individ. 2006;41:1469-80.
17. Carré JM, McCormick CM, Hariri AR. The social neuroendocrinology of human aggression. Psychoneuroendocrinology. 2011;36:935-44.
18. Ross JA, Van Bockstaele EJ. The locus coeruleus- norepinephrine system in stress and arousal: unraveling historical, current, and future perspectives. Front Psychiatry. 2021;11:601519.
19. Lischinsky JE, Lin D. Neural mechanisms of aggression across species. Nat Neurosci. 2020;23:1317-28.
20. Rosell DR, Siever LJ. The neurobiology of aggression and violence. CNS Spectr. 2015;20:254-79.
21. Juruena MF, Cleare AJ, Bauer ME, Pariante CM. Molecular mechanisms of glucocorticoid receptor sensitivity and relevance to affective disorders. Acta Neuropsychiatr. 2003;15:354-67.
22. Mello AF, Juruena MF, Pariante CM, Tyrka AR, Price LH, Carpenter LL, et al. depression and stress: is there an endophenotype? Braz J Psychiatry. 2007;29:13-8.
23. Zelikowsky M, Hui M, Karigo T, Choe A, Yang B, Blanco MR, et al. The neuropeptide TAC2 controls a distributed brain state induced by chronic social isolation stress. Cell. 2018;173:1265-79.e19.
24. Ieraci A, Mallei A, Popoli M. Social isolation stress induces anxious-depressive-like behavior and alterations of neuroplasticity-related genes in adult male mice. Neural Plast. 2016;2016:6212983.
25. de Carvalho Tofoli SM, Von Werne Baes C, Martins CM, Juruena M. Early life stress, HPA axis, and depression. Psychol Neurosci. 2011;4:229-34.
26. Lopez-Duran NL, Olson SL, Hajal NJ, Felt BT, Vazquez DM. Hypothalamic pituitary adrenal axis functioning in reactive and proactive aggression in children. J Abnorm Child Psychol. 2008;37:169-82.
27. O'Connor DB, Gartland N, O'Connor RC. Stress, cortisol, and suicide risk. Int Rev Neurobiol. 2020;152:101-30.
28. Zilioli S, Jiang Y. Endocrine and immunomodulatory effects of social isolation and loneliness across adulthood. Psychoneuroendocrinology. 2021;128:105194.
29. Böhnke R, Bertsch K, Kruk MR, Naumann E. The relationship between basal and acute HPA axis activity and aggressive behavior in adults. J Neural Transm (Vienna). 2010;117:629-37.
30. Terbeck S, Savulescu J, Chesterman LP, Cowen PJ. Noradrenaline effects on social behaviour, intergroup relations, and moral decisions. Neurosci Biobehav Rev. 2016;66:54-60.
31. Matthews KL, Chen CP, Esiri MM, Keene J, Minger SL, Francis PT. Noradrenergic changes, aggressive behavior, and cognition in patients with dementia. Biol Psychiatry. 2002;51:407-16.
32. Brown CH, Bains JS, Ludwig M, Stern JE. Physiological regulation of magnocellular neurosecretory cell activity: integration of intrinsic, local and afferent mechanisms. J Neuroendocrinol. 2013;25:678-710.
33. Merk W, de Castro BO, Koops W, Matthys W. The distinction between reactive and proactive aggression: utility for theory, diagnosis and treatment? Eur J Dev Psychol. 2005;2:197-220.
34. Hagenbeek FA, Kluft C, Hankemeier T, Bartels M, Draisma HH, Middeldorp CM, et al. Discovery of biochemical biomarkers for aggression: a role for metabolomics in psychiatry. Am J Med Genet B Neuropsychiatr Genet. 2016;171:719-32.
35. Çetin FH, Torun YT, Güney E. The role of serotonin in aggression and impulsiveness. In: Serotonin-a Chemical Messenger Between all Types of Living Cells. Rijeka, Croatia: InTech; 2017. p. 241-51.
36. de Almeida RM, Ferrari PF, Parmigiani S, Miczek KA. Escalated aggressive behavior: dopamine, serotonin and GABA. Eur J Pharmacol. 2005;526:51-64.
37. Soderstrom H, Forsman A, Sjodin AK, Blennow K. New evidence for an association between the CSF HVA: 5-HIAA ratio and psychopathic traits. J Neurol Neurosurg Psychiatry. 2003;74:918-21.
38. Wong DT, Perry KW, Bymaster FP. The discovery of fluoxetine hydrochloride (Prozac). Nat Rev Drug Discov. 2005;4:764-74.
39. Hamon M, Blier P. Monoamine neurocircuitry in depression and strategies for new treatments. Prog Neuropsychopharmacol Biol Psychiatry. 2013;45:54-63.
40. Olivier B. Serotonin and aggression. Ann N Y Acad Sci. 2004;1036:382-92.
41. Coccaro EF, Lee R, Vezina P. Cerebrospinal fluid glutamate concentration correlates with impulsive aggression in human subjects. J Psychiatr Res. 2013;47:1247-53.
42. Yamaguchi T, Lin D. Functions of medial hypothalamic and mesolimbic dopamine circuitries in aggression. Curr Opin Behav Sci. 2018;24:104-12.