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nbmeditor@gmail.com

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COVID-19, Social Isolation and Human Stress

Comparative Behavior & Welfare

Oliveira, G. M[1] and Rossi, M. I. D.[2]

1.Laboratório de Biologia Celular – Instituto Oswaldo Cruz/FIOCRUZ – Rio de Janeiro, Brasil; gmoliveira@ioc.fiocruz.br. 2. Instituo de Ciência e Tecnologia em Biomodelos (ICTB/FIOCRUZ), Rio de Janeiro – RJ, Brasil. ines.doria@fiocruz.br. Telephone: 55 21 25621366.

Abstract: In late 2019, a novel coronavirus (COVID-19) was identified in Wuhan, a city in the Hubei province of China. COVID-19 rapidly spread and led to an outbreak in China and then became a global health emergency. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2 or COVID-19), showed high transmission capacity and morbidity. To date, despite intensive research, an effective drug, therapy or vaccine against COVID-19 has yet to be confirmed. In this way, WHO suggests that the most efficient method for controlling transmission is social isolation/quarantine to the population. The human being and the laboratory mouse (Mouse Lab) are highly social species with a high capacity to adapt to new routines, as long as they are carried out gradually and the resilience/susceptibility individual's characteristics. The COVID-19 pandemic promoted a rapid and necessary imposition of social isolation on the population. Swiss Webster Outbred stock, although adapted to the situation of restricted space, during their maintenance are also subject to abrupt changes in their routine (strong stressor factor). On the hand, in both species we can define a distress intersection point: abrupt break in routine and compromise in social relationships in both species. For this reason, we can observe in the Swiss Webster ethology various behavioral disturbances, such as family violence, aggression exacerbated and violence. In this review, we hope, through comparative behavioral analysis, to avoid, mitigate and alleviate social stress in humans, mainly through procedures for raising animal welfare. The suggest possibilities as increase of activities virtual social interaction, environment comfort, intellectual and physical activities, in other words elevated adaptation capacity. In conclusion, we believed that our knowledge of Mouse Lab ethology can be useful in this dramatic moment to which all countries are subjected, since, by minimizing stress, the most rudimentary emotions, similar between humans and mice, can be rationalized in the human being and promote the improvement of the human being's quality of life, even in social isolation/quarantine.
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Keywords: COVID-19, social isolation, comparative behavior, Swiss Webster and stress.

CONTEXT OF THE STUDY PROPOSAL

I. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2):

1. COVID-19 Pandemic:

In late 2019, a novel coronavirus (first: 2019-nCov, then: SARS-CoV-2) was identified as the cause of a cluster of pneumonia cases, which infected a lot of people in Wuhan, a city in the Hubei province of China (Tan *et al.*, 2020). SARS-CoV-2 (COVID-19) rapidly spread and led to an outbreak in China and then became a global health emergency. Despite the control measures and isolations have been applied for prevention, the infection has increased and caused a pandemic (Chen *et al.*, 2020). Although this virus belongs to a relatively well-known viral family, Coronaviridae, and is similar to viruses that caused severe acute respiratory syndrome (SARS), which had an outbreak in 2002, and Middle East respiratory syndrome (MERS), which had an outbreak in 2012. The COVID-19 in some characteristics, there are a lot of uncertainties and unknown specifications about this virus such as its origin and source of infection, its emergence, and its mechanism of action and transmission (Chen *et al.*, 2020).

2. COVID-19 and social isolation:

The total number of COVID-19 cases reached 156.622 with 5.845 subsequent deaths (Khachfe *et al.*, 2020). China, Italy, and Iran have the highest number of cases worldwide. During the first 22 days, the incidence rate of COVID-19 increased significantly to reach 1.81 cases per million persons. In the present

moment, United States of America showed 999. 237 cases and 56.037 deaths. The high infectivity of the disease led many governments to adopt strict regulations and measures with the aim of containing its spread. That was followed by a significant decrease over the next 11 days to reach 0.071 cases per million persons (Khachfe *et al.,* 2020). A steady rise then followed, which saw a significant increase in incidence rate to 1.429 cases per million persons. Percentages of death and cured cases varied across the different countries; nevertheless, death percentages have generally been decreasing since the start of the crisis (Khachfe *et al.,* 2020). In conclusion, only adopting precautionary regulations such as social isolation, increasing sanitation, and employing strict quarantine measures have proved to be beneficial in containing the virus (Gorbalenya, 2020).

3. Human stress and social isolation:

Imposed quarantine or isolation is an unfamiliar and unpleasant experience that involves separation from friends and family, and a departure from usual, everyday routines (Onyeaka e*t al.,* 2020). Isolation is known to cause psychosocial problems, especially for those recognised as vulnerable (Yahya *et al.,* 2020). While all humans are at risk of psychological harm when kept in isolation, the most vulnerable in these situations are children and adolescents, older adults, minority groups, those from lower socio-economic groups, females, and people with preexisting mental health conditions (Shuja *et al*., 2020; Marčinko *et al*., 2020);

The social isolation it´s strong stress factor in humans (Marčinko *et al*., 2020). Observed elevated intensity of the family violence during pandemics is associated with a range of factors including economic stress, disaster-related instability, increased exposure to exploitative relationships, and reduced options for support (Wang *et al.,* 2020). Due to the social isolation measures implemented across the globe to help reduce the spread of COVID-19, people living in volatile situations of family violence are restricted to their homes (Vieira *et al*., 2020). Social isolation exacerbates personal and collective vulnerabilities while limiting accessible and familiar support options (Usher *et al.,* 2020). In many countries, including Australia, we have already seen an increase in demand for domestic violence services and reports of increased risk for children not attending schools; a pattern similar to previous episodes of social isolation associated with epidemics and pandemics (Humphreys, *et. al.,* 2020).

II. Ethology of the Swiss Webster:

1. Phylogenic and natural behavior:

Despite a detailed study of the genus *Mus*, or *Mus musculus* species, from their genealogy, phylogeny, and all historical aspects of the origin of lineages currently used in the laboratory. We can say that they were animals captured in the wild, from different subspecies of *Mus musculus* (from different geographical regions) and genetically engineered hundreds of years ago (da Costa, *et al*., 2019). This genetic manipulation is perhaps the most interesting issue the great possibility that we are manipulating in house facilities a new subspecies of *Mus musculus laboratorius*, due to the artificial selection we make and the choice and control of mating. Finally, the supposed *M. m. laboratorius*, both inbred and outbred stocks have a strong genetic background of wild mice of different subspecies, demonstrating that hybridization occurred naturally and artificially among *M. musculus* species (Evangelista *et al.,* 2019). However, it also suffered selective pressures and its evolution and natural behavior did not stop, tending to adapt to space restriction when kept in a laboratory environment. Facility of the feed access, territorialism, social interaction, commensal human-related, reproduction and aggression are mainly natural behavior of the mouse and also observed in house facilities (Oliveira, 2018).

The Swiss Webster origin, documented in 1926, by Clara J. Lynch, a genetics-interested cancer researcher who worked at the Rockefeller Institute for Medical Research in New York. Lynch imported two male and seven female mice from André de Coulon's non-endogenous albino stock, and all animals derived from these mice were known as 'swiss' as a nickname used by Lynch in his laboratory. Lynch also collaborated and gave his 'swiss' mice to other researchers, both inside and outside the Rockefeller Institute. In 1932, one of these researchers was Leslie Webster, who carried out susceptibility experiments for viral infection and distributed the mice to academic and commercial breeders, including Carworth Farms in the United Kingdom, which produced what is now called Swiss Webster (Evangelista *et al*., 2019).

2. Swiss Webster behavior and social stress:

The most important point that we must highlight in the science of laboratory animals and that can converge with the proposal of our study is the fact that these animals are under, permanent, space restriction. Another important factor is that the stress factor in mice is relative. The *Mus* genus (*Mus m laboratororius*, also) naturally are observed under stress state (eustress) and physiologically and neoroendocrinologically considered a homeostatic state. However, it should be noted that severe individual and social stress factors compromise welfare animal: i) Maintenance and procedures inadequate to

animal; ii) abrupt routine alteration and handling awkward; iii) feed supply lack, especially water; iv) regrouping of adult male individuals (da Costa *et al*., 2019).

The adaptability is key point (evolutive characteristic) of the success of the mouse lab and the maintenance of its relationship as a human being for so long (including in space restriction in house facilities). Then, can be affirm that stress state in mouse lab is closely related to the animal's inability to adapt to a (new) maintenance situation or procedure in the house facilities (da Costa *et al*., 2019). The stress can be observed in your behavior through: presence of high aggressive behavior, motor and exploratory activity decreased in subordinated mouse and isolation social individual. Furthermore, this behavior is compatible with depressive behavior described in the literature for experimental models (depression-like). Concluded, the Swiss Webster ethology is diverse and complex. However, in stress state (distress) we were able to observe that social disturbance and aggressive behavior during social and individual interaction promoted discomfort and stress in Mouse Lab and depression-like state (de Oliveira and Brito, 2019).

STRESS FACTORS: SIMILARITY BETWEEN HUMAN AND ANIMAL BEHAVIOR RESPONSE:

I. Stress factor and familiar behavior disturbance:

Table 1:

1. Stress Factors and Behavior				
Mice	Behavior Type	Convergence Point	Behavior Type	Humans
present	Familiar Violence	x	Familiar Violence	present
present	Infant abuse	x	Infant abuse	present
present	Intimate partner violence	x	Intimate partner violence	present
absent	Infanticide* / Femicide	x	Infanticide / Femicide	present

Figure 1:

Table and Figure 1: Family violence in Swiss Webster monogamous couples. The female can showed due to factors not yet elucidated, infanticide (*), however, the maternal behavior is more stable and reproducible than the paternal. Males can exhibit a varied type of behavior, from collaborative and affective (A) to highly aggressive behavior with their partner and their pups, generating family violence (B).

1. Human Being:

A very recent article published in The Guardian (2020) reported, in isolation social, on how the surge of domestic violence cases is a pattern being repeated Reporting from several different countries, the article highlighted alarming figures, for example a rise of 40% or 50% in Brazil. In one region of Spain, the government claimed that calls to its helpline had risen by 20% in the first few days of the confinement period and in Cyprus, calls to a similar hotline rose 30% in the week after the country confirmed its first case of coronavirus. In the UK, Refuge, one of the leading domestic abuse organizations reported that calls to the UK Domestic Violence Helpline increased by 25% in the seven days following the announcement of tighter social distancing and lockdown measures by the government. During the same period, there was a 150% increase in visits to the Refuge website (Bradbury-Jones, 2020; COVID-19 & Violence, 2020).

2. Swiss Webster mice:

Monogamous couples of Swiss Webster mice may exhibit behaviors similar to family violence in humans in approximately 10% of couples. This perceptual depending on the animals' population and poor adaptability to stress factors. Space restriction in house

facilities, the mice are more susceptible to the influence of stress factors such as: postpartum depression in primiparous females (infanticides); paternal aggression without apparent external cause, abrupt changes in the macro and microenvironment such as temperature, humidity and light. Moreover, the main stressors factors that mouse´s family violence is the inability and erratic human manipulation (puppies and parents), lack, substitution or intermittently feed supply and finally the quality of the floor/bed and, also, the abrupt or irregular substitution of the material or procedure (Campos *et al.*, 2018).

3. Intersections points (Human & Mouse Lab):

The difference between social isolation in humans and space restriction in the mouse lab differs in the mice evolution adaptability and abnormal situation to the social interactions in human. Other way, space restriction exposed mouse lab to the stress factors in the similar way isolation social human imposed situation. Then, in both cases, in general, the disruption from the regular routine, by itself, becomes a relevant stressor situation. As well as, the lack of subsidies for survival, such as the supply of food, the birth of infants or the need for permanent care for newborns, in the case of humans and mouse lab. In human, relevant yet the life costs and the economic perspective (Bradbury-Jones, 2020 and Vieira, *et al.*, 2020). All of these factors similarly act in the rudimentary brain regions (human & mouse lab) and higher stress reduces the ability to discern the prefrontal cortex, consequently, the appearance of the behavior disturbance as family violence episodes (Kaufling, 2019).

II. Individual and Social Violence:

Table 2:

Social Stress Factors and Behavior				
Mice	Behavior Type	Convergence Point	Behavior Type	Humans
present	Interindividuals Aggression	x	Interpessoal Aggression	present
present	Lesions Fight	x	Lesions Fight	present
absent	Muricide		Homicide	present
absent	Suicide		Suicide	present

Figure 2:

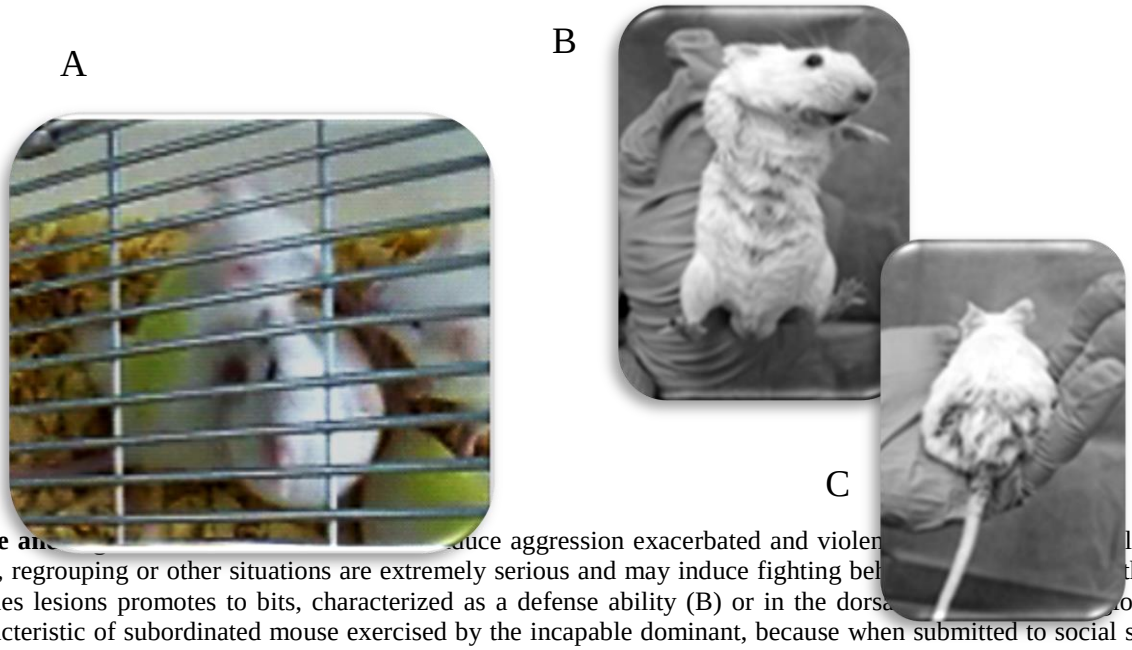

Table an duce aggression exacerbated and violen le and adult, regrouping or other situations are extremely serious and may induce fighting bel thorax injuries lesions promotes to bits, characterized as a defense ability (B) or in the dors on (C) characteristic of subordinated mouse exercised by the incapable dominant, because when submitted to social stress, demonstrated a highly aggressive behavior, or we can call it violent individual.

Frans de Waal, primatologist, in his excellent book "Our Inner Ape: The Best and Worst of Human Nature" (2005) speculate that human violence occurs through a depersonification and disqualification psychological process between individuals or different groups (De Waal, 2006). Human brain rudimentary regions, as amygdala and hippocampus, associated to emotions such as empathy, fear and hate are overlapping with rationality (De Waal, 2006). The complexity of violence and its study has a multidisciplinary character involving areas such as medicine, epidemiology, sociology, psychology, criminology, education and economics. In the mouse lab, violence can be considered as escalated, exacerbated or uncontrolled aggressive behavior during mice interactions, mainly males. Didactically, violence arises from aggression, when the individual intentionally starts to direct his aggressive energy. Therefore, it is an acquired behavior, where the individual can (or cannot) use instruments and prepares to attack the other or himself (Campos *et al.*, 2016).

If considered social isolation during COVID-19 pandemic as strong factor stressor can be observed the susceptibility of the human despersonification between population mainly because individuals are under negative emotions as: i) the permanent sensation of the danger and life risk, instinctive fear; ii) the high transmissibility of the virus, making the other individual a potential transmitter; iii) the necessary social isolation, which paradoxically removes the human being's ability to structure empathetic relationships with others (De Waal, 2016).

In many ways, the human in a stressful situation increases the possibility of violent episodes. In our situation, the pandemic promotes a situation of social stress, where on the one hand the propensity to violence increases, on the other hand, the interpersonal distance decreases the incidence of situations of violence (Moccia *et al.*, 2020).

In this case, we have to consider specific cases, such as homeless, addicts homeless, and, specific examples, extreme episodes such as the possibility of homicide in the Philippines, physical aggression in India and hostility to the old-aged in all the world when do not comply with social isolation (Lima *et al.*, 2020).

2. Swiss Webster Mice:

Our research group has been study the violence genesis or exacerbated aggression for four years. The Swiss Webster Outbred stock, male and adult, has a high susceptibility to social stress during regrouping of the different individuals in a new cage (space restriction). However, in 10 to 15% of groups, even under social stress, individuals coexist harmoniously, absent aggression or violence. Then we are research the neuroendocrine/neurobiological mechanisms of this process, the resilience and susceptibility of each individual to social stress and correlated to the presence of the exacerbated aggressive behavior (Van Loo et. al., 2003). Our preliminary theory is that severe emotional traumas occur during the animal's neurological development (mainly post-birth period) may not be evident when these animals are kept grouped between infants (3 and 4th weeks of life). However, in adulthood (≥ 8th week of life) the regrouping of adult male individuals promotes in the animal more susceptible to the action of stressors, some type of pre-existing trauma, demonstrating serious changes neuroendocrine/neurobiological alterations as corticosterone levels not elevated under social stress, dopamine levels increased, reactive oxygen species expression higher in the frontal cortex of the aggressive mouse brain. In resume, the regrouping of adult male mice would be this strong social stressful situation that would “trigger” the exacerbated aggressive behavior in the Swiss Webster (Campos *et al.*, 2016; Fragoso *et al.*, 2016; Miranda *et al.*, 2019).

3. Intersections points (Human & Mouse Lab):

The human aggression and violence resulting from social stress, at this moment, is mitigated by social isolation (Zhang *et al.*, 2020). However, we must be aware that essential work places and human social group such as hospital environments, and other essential services, mainly of male individuals in adulthood, are more probability aggressive episodes occurrence (Williamson *et al.*, 2020; Wu *et al.*, 2020). In addition, can be observed the violence and social stress during COVID-19 pandemic in minority and vulnerability population as homeless and addict homeless (Lima *et al.*, 2020).

Another important point that gradual return of the interaction social at the moment in the finish of the social isolation, during the evolution of the COVID-19 pandemic. I believe that the stress factors will still present during many time, especially in socioeconomic activities, political and cultural standards. Thus, as demonstrated by our experimental design, the possibility stress resilience/susceptibility to each individuals and trauma impact can be responsible for situations of violence and aggression among social interactions in humans (Thomas et. al., 2015; Roy *et. al*, 2020)

Suicide is a serious public health problem. It is a violent attitude against yourself. During our diary routine can be observe that mouse lab and human are animals extremely social species. The Swiss Webster

mice when placed in space restriction and social isolation, shows quickly hypoactivity motor and exploratory, similar to depression in the human being (depression-like) (de Oliveira and Brito, 2019). Thus, elevation care for individuals without family support, or for various reasons, has the need to be in social isolation without interaction with another individual is much more likely to develop a severe state of depression, and in some cases committing suicide (Dudek *at el.*, 2019).

FINAL RFLECTIONS: MOUSE LAB & HUMAN, SOCIAL ISOLAMENT AND STRESS

Recent COVID-19 research showed a pilot and cross-sectional study to identify the characteristics of psychological distress across populations affected by the coronavirus pandemic. An increased prevalence of depression (29.2%) was found predominately in patients who experienced COVID-19 infection. Trends for an increased prevalence of depression comorbid with anxiety were identified in both patients who experienced COVID-19 infection (21.1%) and the general public (22.4%) compared to those in quarantine. Both patients who experienced COVID-19 infection (19.3%) and the general public (14.3%) also had a greater proportion of severe depressive symptom (Zhang *et al.*, 2020).

The vulnerability to psychological distress across populations in the COVID-19 pandemic could be attributable to various factors, including gender, social support, specific experiences with COVID-19 infection, length of isolation, and amount of exposure to the media (Brooks *et al*., 2020; Li *et al*., 2020). The preliminary findings from our study suggest that timely identification of psychological distress and precise classifying of the mental health needs across populations will facilitate development of targeted psychological interventions for individuals in epidemics of emerging infectious diseases (Zhang *at al*., 2020).

The study of the behavior of space-constrained Swiss Webster mice in a house facilities intend contribute, at this moment, keeping its diverse peculiarities, for the comparative behavior human & mouse lab under social stress, mainly isolation social/quarantine. In summary, the main points observed in mouse lab and correlated the human behavioral dynamics is that the abrupt break routine and difficulty of accepting the social isolation can be developed behaviors disturbance (Berry *et al.*, 2020). Mainly in the family environment, aggravated by the stress of the coexistence, accessibility to consumers products, including feed supply and maintenance of material comfort. The important impact of social isolation on the human population with low or without family and few social interactions should be very well observe, as the risk factor for the depression state and the possibility of suicide incidence increases (Todoya, 2017, Solomon, 2017) .

Other aspect, it's the return to social life. I believe that can be promote an increase in social stress, especially in specific environments such as the work places, political activity and others, consequently, promoting the propensity to aggressiveness and violence (physical, verbal or psychological) (Cameron *et al.*, 2017; Carnevali *et al.*, 2020).

Using the science of laboratory animals as a support for behavioral studies in humans under social isolation, the laboratory animals currently have a series of procedures for elevating welfare under space restrictions such, example, as environment enriching in the maintenance cage animals. This fact can also be applied to human beings and the improvement of their quality of life. In mouse lab, ultrasonic and odor communication and physical contact are essential for your welfare (Simola & Granon, 2019). The non-human primate uses, in addition to vocalization and other more elaborate methods. The "grooming" as the main social activity between individuals in social group (De Waal, 2006). The human being uses physical and verbal contact as a primary and primordial social activity (De Waal, 2006).

Thus, with the advancement of communications technology, the enrichment remote and web communications, products and devices that provide distance interaction between individuals in social isolation will provide a better quality of life and welfare for human beings in this difficult social phase. Moreover, Limit media exposure since overexposure to broadcasts of stressful situations has been linked to negative mental health outcomes and avoids misinformation. In as much as possible, develop new routines that include leisure activities and physical exercise (Fonseca *et al*, 2020).

According to our review proposal, all the comparative situations described can be correlated with mouse ethology, environmental enrichment and animal welfare in the house facilities (Bayne, 2018). In this way, we conclude that, despite all our anthropological, sociological and psychological human complexity, on a rudimentary emotional level, when we are exposed to a situation of social stress similar to the mouse lab space restriction, our instinctive and primitive reaction it becomes evident (Daun *et.al*., 2020; Azevedo *et al*., 2020). Finally, the possibility of mitigating or soften human stress and discomfort, also has a strong connection with current knowledge of the science of laboratory animals (Jensen et al., 2013).

Figure 3:

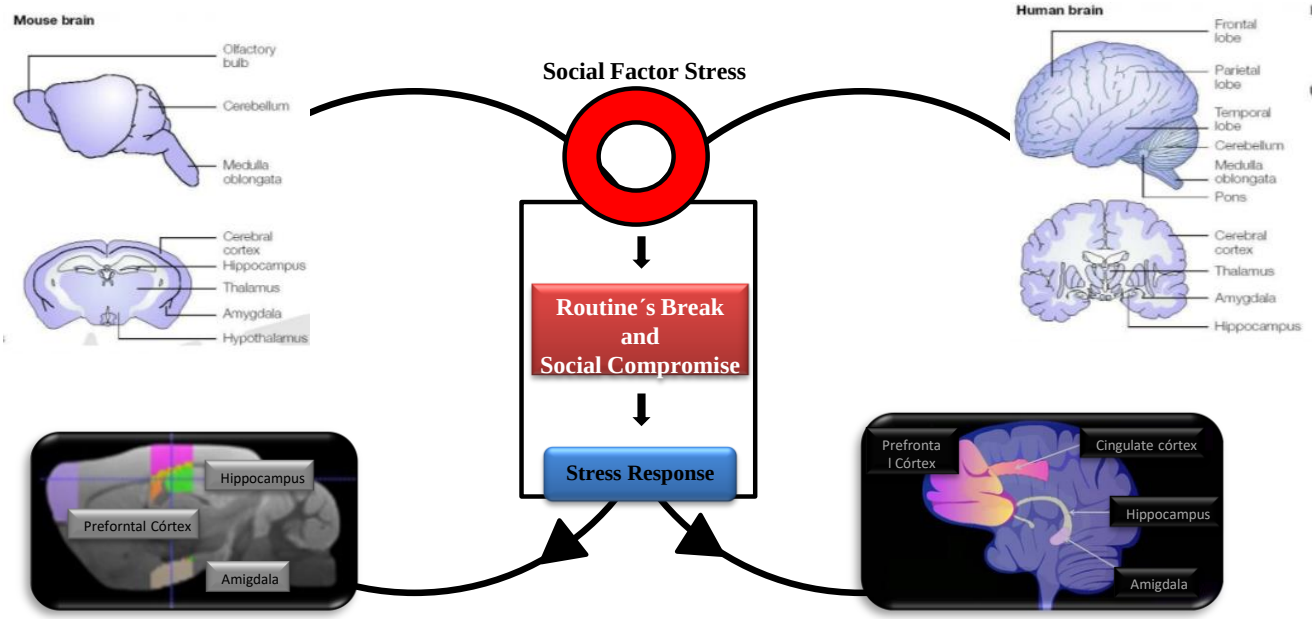

Figure 3: In summary, our review was based on two main points: comparative behavioral analysis and a stressful situation. During the COVID-19 pandemic, the human being was necessarily placed in social isolation. This human´s severe stressor factor because abruptly compromises the social routine of individuals, generating altered behaviors, especially in family nucleus relation. The first point of intersection (Human & Mouse Lab) is the demonstration of the similarity of the rudimentary brain structures in the Central Nervous System between humans and mouse, especially when related to the stress response. Swiss Webster mice in the house facilities are adapted to space constraints, but abrupt changes in their routine and an individual's social isolation promotes aggressive behavior and depression-like. Thus, similarities in behavior stress response our proposed related to alleviate the social stress of the human being in social isolation/quarantine. *Adaptated by Arnsten F. (2009) and Cryan J. (2003).*

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