

Abstract

1. I suggest that authors do not use the words: first, second...

Response: We have deleted these words.

2. The authors speak: "... models of stress-related psychiatric disorders (depression-and anxiety-like behavior, cognitive impairment and addiction-like symptoms)...", but these are behaviors of animals and not models.

Response: We have modified this sentence according to the suggestion of the reviewer.

"In the subsequent section, we describe the animal models commonly used in the study of resilience to social stress, and we focus on the effects of chronic social defeat (SD), a kind of stress induced by repeated experience of defeat in an agonistic encounter, on different animal behaviors (depression- and anxiety-like behavior, cognitive impairment and addiction-like symptoms)."

3. The authors need to define: 1. chronic social defeat or 2. Repeated social defeat. Look in the keywords.

We have defined chronic social defeat (see the previous point) and have deleted the word "repeated" in the keyword "social defeat".

Text

1. The concept of resilience in the field of drug addiction

- The authors explain other things in this topic, they could use: 1 and 1.1.

Response: Following the suggestion of the reviewer we have divided this section into two subsections: 1.1. The concept of resilience, and 1.2. Resilience to stress and drug addiction.

- I think that it is important to define PTSD and it is the first time of initials (second paragraph). Remove the words in the third paragraph.

Response: we have defined PTSD in the second paragraph and modified the third paragraph accordingly.

- There are lack of references, for example, the author"s write "Most research about resilience has....", but they cited only one reference. Please revise similar cases.

Response: In our opinion, this sentence *"Most research about resilience has focused on the biological and behavioral profile of individuals who are resilient to developing psychiatric illnesses such as depression and PTSD after exposure to stress."* and the next sentence *"However, studies on resilience to the effects of stress on the initiation, maintenance and relapse to addictive disorders are very limited."* do not require references, since it is a logical conclusion we have come to after a review of the literature on resilience. We consider that the references cited throughout the paper support this affirmation.

- The authors must revise the references, for example, Bruce S. McEwen, 2016, did not speak about substance use disorders. Morgan, 2002, speaks about scholar stress and not AUD.

Response: We agree with the reviewer about the reference of McEwen, 2016 [8] and have modified the sentence as follows: *"Stressful experiences have a profound impact*

on the brain [8]; for this reason, stress can increase vulnerability to addiction”.

Regarding the reference of Morgan, 2002 [12], thanks to the reviewer’s comment we have detected a mistake. The correct reference is Morgan et al., 2018, which we have included in the reference list. The reference of Morgan, 2002 corresponds with the sentence *“Higher levels of NPY in response to acute stress predict less psychological distress and fewer symptoms of dissociation”* (page 10). We have renumbered this reference [45] in the reference list.

- I did not understand the question, resilience and resiliency. Are there the same or different words to authors? Please, the authors need to explain better.

Response: Resilience and resiliency are different concepts. Resilience is a wider concept with multiple meanings: a personality trait, a dynamic process in the life of an individual, an outcome (the absence of illness after stress), etc. In contraposition, resiliency is a personality trait clearly defined as *“the ability to flexibly adapt impulse control relative to contextual demand”*. We have distinguished between the two concepts in the manuscript: *“In addition, it is important to distinguish between resilience (a concept with multiple meanings) and resiliency, which is a personality trait that has been linked to alcohol/drug problems and is defined as “the ability to flexibly adapt impulse control relative to contextual demand”.* (page 7, lines 2-6).

2. Behavioral traits and protective factors associated with resilience

- “Different protective (resilience) factors...” Why is resilience between ()? - The authors explain many times what resilience is, I think that is unnecessary.

Response: We have modified the sentence “Different protective (resilience) factors...” as follows: *“Different protective factors associated with resilience can be identified on biological, psychological, and social levels.”* In our opinion, the explanation of resilience in this section facilitates the understanding of the concept of stress inoculation.

3. Physiological response to stress and resilience

- “... and acute stress increases serotonin turnover in the amygdala, hypothalamus, PFC and NAcc [36] ”. In these cases there are many studies demonstrating the opposite effect, I believe that the authors can cite at least one reference. Furthermore, the reference is wrong.

Response: First of all, we have checked the reference used in the sentence *“acute stress increases serotonin turnover in the amygdala, hypothalamus, PFC and NAcc [36]”* and have confirmed that it is a review that states: *“Acute stress is associated with increased serotonin turnover in several brain regions, including the amygdala, the nucleus accumbens and the PFC”*. In any case, we have now included two references of experimental papers that demonstrate these effects and have changed the word hypothalamus to hippocampus (Miura et al., 2002; Culman et al., 2018) [37, 38]. In addition, in line with the suggestion of the reviewer, we have added two references of research that demonstrates the opposite effect: *“, although other studies have shown a lack of an effect of acute stress on serotonin turnover in the amygdala, NAcc, striatum (de la Garza and Mahoney, 2004) [39] and hypothalamic paraventricular nucleus [38] (Culman et al., 2018).”*(page 10, lines 13-15).

- Duman, 2009, is the review, other authors demonstrated the effects cited.

Response: We have added two original works demonstrating the effects cited in the text (Tural et al., 2018; Kozlovsky et al., 2007) [41,42]. (Page 10, line 24).

- "Communication between neural, hormonal and immune systems is mediated by cytokines, small molecules that mediate inflammatory processes". This phrase is lacking to speak about other molecules involved or cite the reference that only cytokines mediate the tree systems.

Response: As suggested by the reviewer, we have added other molecules involved in the communication between neural, hormonal and immune systems: *"Communication between neural, hormonal and immune systems is mediated by cytokines and chemokines, small molecules that mediate inflammatory processes, corticosteroids, pituitary hormones, catecholamines and neuropeptides [40, 47]."* (page 11, lines 6-9).

- I suggest the authors explain more about gut microbiota or remove "These bidirectional relationships between resilience and immunity are modulated by the gut microbiota [45]."

Response: We have now explained more about the relationship between resilience, immunity and gut microbiota. *"There is an interaction between the gut and the brain that involves neural, endocrine, and immune pathways. It seems that the stress-induced activation of the HPA axis stimulates the immune system and causes changes in microbial diversity [53](Makris et al., 2021). The gut microbiota has been associated with a wide range of physiological processes, including the response to stress [54](Cathomas et al., 2019). Oral intake of Bifidobacterium was shown to significantly increase the number of mice that were resilient after repeated social defeat stress with respect to control animals not receiving treatment [55](Yang et al., 2017). Moreover, administration of Lactobacillus was found to decrease anxiety-like behavior induced by repeated social defeat stress and to improve the immune response [56] (Bharwani et al., 2017)."* (page 11).

4. Animal models to study resilience to social stress

- The authors need to explain the difference of depression/anxiety in the humans x rodents. I disagree with this following sentence: "As with humans, some animals exposed to chronic stress develop depression–, anxiety–like symptoms";

Response: We have explained the difference of depression/anxiety in humans and rodents. *"As mentioned before, after exposure to stress, some humans develop a psychopathological disorder, such as depression or anxiety, while others are resilient to such effects. These disorders are complex and multifactorial and affect many aspects of human life; thus, no animal model can mimic the complexity of human disorder. However, animal models are useful for simulating some of the psychiatric symptoms [57] (Harris, 1989) or behavioral dimensions that characterize a disorder [58] (Frazer et al, 2005)."* (page 12, lines 2-8). In addition, we have modified the sentence "As with humans, some animals exposed to chronic stress develop depression–, anxiety–like symptoms" as follows: *"After exposure to chronic stress, some animals develop depression– and anxiety–like symptoms and other behavioral alterations (susceptible or vulnerable animals), while others exhibit clear resistance to at least some of the maladaptive sequelae of stress (resilient animals)."* (page 12, lines 8-12).

- The introduction of his part of the review is confusing. What the authors really want shown in the section? This point needs references.

Response: The aim of this introduction is to stress the usefulness of animal models for the study of resilience. We have included references (Harris, 1989; Frazer & Morilak, 2005; Ayash et al., 2020) [57-59]. (page 12, first paragraph).

- The authors explain the FST in this point, but the FST and other behavioral tests are behavioral tests and not animal models. These behavioral tests are used to evaluate the animal models. "The forced swim test (FST) is a classic model of depression".

Response: We agree with the reviewer's comment and have modified the title of this section "*Behavioral tests of anxiety- and depression-like symptoms*" and the sentence "The forced swim test (FST) is a classic model of depression" as follows: "The forced swim test (FST) is a classic behavioral test of depression-like symptomatology..." (page 15, lines 12-13).

- The authors say in the introduction of this part "This is not an exhaustive review of these models...", but they use 8 pages to speak about behavioral tests. I suggest revising this part, if it is very necessary. The authors can make the table.

Response: As the reviewer notes we state: "This is not an exhaustive review of these models...", because we do not explain all the animal models used to induce stress nor all the behavioral paradigms used to evaluate the presence of depression-, anxiety-, cognitive-, or addiction-like symptoms, but only those used in studies about resilience. However, many behavioral paradigms have been used in the field, and we feel it necessary to provide a brief description of each one and a short reference to resilience. In accordance with the reviewer's comment we have considered the option of including a table, but, in our opinion, it would not improve the paper. For this reason, we have decided to reduce the referred to section.

- The following sentence is confused: "... and a varied combination of physical stressors (chronic unpredictable stress). Another widely used animal model is the chronic "mild" stress (CMS) paradigm [58] , in which animals are exposed to varying physical and psychosocial stressors". Chronic unpredictable stress and CMS are the same animal model.

Response: We have modified this sentence according to the reviewer's comment: "*Some of them use pharmacological stressors, such as daily administration of corticosterone [48], or physical stressors, such as restraint or immobilization [135]. Another model is based on a combination of physical and psychosocial stressors (chronic unpredictable stress or the chronic "mild" stress (CMS) paradigm) [58].*" (page 12, last paragraph).

- Vidal, 2011 in your study comparing Wild-type Groningen rats x Wistar rats; Sprague Sprague Dawley rats are Wild-type Groningen rats? - In the middle of text have: „" [143, 144, 14, 145] (Ferrer-Pérez et al., 2018; Burke et al, 2011; Aguilar et al., 2013; Montagud-Romero et al., 2016)." Please, the authors must revise the text.

Response: Thanks to the reviewer, we have detected these mistakes and have corrected them.

- Please, revise the citation 148.

Response: We have checked citation 148 (now reference 81) and have confirmed it is correct, as the study in question used two models of stress: 1. early maternal deprivation (MD, age 7-14 days) alone and 2. early maternal deprivation (MD, age 7-14 days) combined with unpredictable chronic stress (UCS, age 28-84 days). We have changed the abbreviation CUS to UCS.

- The point 4 must be better organized.

Response: We have reorganized point 4. First, we have described animal models of stress exposure and have included the learned helplessness model. Then, we have explained the behavioral paradigms used to evaluate anxiety- and depression-like symptoms, the learning and memory paradigms used to evaluate cognitive impairment and the animal models of addiction-like symptoms.

5. Advances concerning the neurobiological substrates of resilience

- I did not understand why the authors cited the references 5 and 29 to "The study of the neurobiology of resilience is a relatively young area of scientific investigation".

We have modified the references in this sentence (24, 35) (Southwick et al., 2005; Charney, 2004) (page 25, line 5).

- Please, the authors could explain exNMDA receptors in the text.

Response: We have included the word "*extrasynaptic*" before "*NMDA receptors*" (page 26, line 13).

- I tried understanding the aim with this point, but I did not find a connection with addiction disorders. I think that the authors need more focus or change the aim. The revision in turn of resilience is very good, but the text lacks its connection with addiction disorders.

Response: We thank the reviewer for his/her comment about our review of resilience. We understand that the text may seem to lack a connection with addiction disorders, since the literature about resilience to the effects of stress on these disorders is very limited. In fact, our research group is one of the few groups currently using animal models to investigate the neurobehavioral mechanisms underlying resilience to the effects of stress on addiction disorders. In our opinion all the knowledge obtained in the works about resilience to the effects of stress on depression- and anxiety-symptoms can be of great help to guide future research in the field of resilience to addiction disorders. In the present manuscript we have added the following sentence: "*Advances in this field may guide ongoing research regarding the neurobiological substrates of resilience to the effects of SD on addiction disorders*". (page 25, lines 18-20).

- BDNF has antidepressant-like effects and enhances hippocampal neurogenesis [215, 216]. Why was this phrase used in the context?

Response: We have used this phrase because these effects of BDNF suggest a role for this factor in the potentiation of resilience. We have added this idea to the original sentence: "*BDNF has antidepressant-like effects and enhances hippocampal neurogenesis [215, 216], which suggests an important role of this factor in the potentiation of resilience*" (page 33, last paragraph).

- In rodents exposed to SD, activation of hippocampal BDNF/TRKB signaling (by means of branched-chain amino acids, exercise and high protein diets) induces resilience to social avoidance [221]. The authors cited one reference, there are other references.

Response: We have cited two additional references (Lagace, et al., 2010; Duclot & Kabbaj, 2013) [235, 236]. (page 34, line 12).

- Sometimes the authors use the HPA axis and other times HPA system. Please standardize it.

Response: We have changed HPA system to HPA axis.

- “but not in resilient, mice” Revise the commas in all text.

Response: We have changed the sentence to: SD stress induces hypercortisolemia and adrenal hypertrophy in susceptible mice, but not in resilient rodents [223, 41].

- What is LC? Revise the initials in all text. You can have fewer initials.

Response: We have changed LC to locus coeruleus (page 10, line 9).

6. Resilience to the effects of social defeat on the rewarding properties of drugs of abuse

- When I put the three words (social defeat; addiction; resilience) in the Pubmed I found 862 papers. Revise it, I can be mistaken.

Response: We have repeated the search of Pubmed with these keywords and have found only 18 results. In fact, we frequently consult the literature about this issue and are aware that only a very limited number of related papers have been published.