Pontifícia Universidade Católica
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Exploring the effect of social isolation on anxiety and depression: A comparative analysis of depressive behaviors in carioca rats high and low levels of conditioned freezing and their implications in humans

Dissertação de Mestrado

Dissertation presented to the Programa de Pós-Graduação em Psicologia of PUC-RIO in partial fulfillment of the requirements for the degree of Master em Psicologia.

Advisor: Jesus Landeira-Fernandez
Co-advisor: Thomas Eichenberg Krahe

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Dedico esta dissertação às mais de 300 milhões de pessoas que
são impactadas pelos transtornos de ansiedade e a depressão,
cujos desafios interferem em suas interações sociais,
Aos meus colegas psicólogos, que se dedicam em acolher e
oferecer suporte adequado,
Às/os cientistas, que por meio de incessantes buscas por novos
conhecimentos, contribuem significativamente para a prática
clínica e o bem-estar de tantos

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Abstract

Peçanha, Amanda Felix Lima Araujo; Fernandez, Jesus Landeira (Advisor). **Exploring the effect of social isolation on anxiety and depression: A comparative analysis of depressive behaviors in carioca rats with high and low levels of conditioned freezing and their implications in humans.** Rio de Janeiro, 2024. 89p. Dissertação de Mestrado - Departamento de Psicologia, Pontifícia Universidade Católica do Rio de Janeiro.

Anxiety disorders are among the most prevalent psychiatric disorders worldwide, and clinical findings indicate significant comorbidity between anxiety disorders and depression in the same individual. Specifically concerning generalized anxiety disorder (GAD), comorbidity with depression is often present. A major concern is the impact of these disorders on social interactions. The state of tension and excessive worry exhibited by these individuals can be transmitted to those in their social circles, while social interactions can also serve as an anxiety-provoking factor for them. There are still gaps in understanding the behavioral, neurobiological, and genetic mechanisms involved in these disorders, and these aspects need to be investigated. Concerns about the rising prevalence of anxiety and depression disorders underscore the necessity of understanding the dual nature of social interactions in mental health, highlighting their role as sources of well-being as well as potential stressors. Our aim is to examine the relationship between anxiety disorders and depression with social isolation. Through empirical research using Carioca rats, a bidirectionally selected animal model of anxiety with high and low conditioned freezing responses, we intend to quantitatively analyze the impact of social isolation on depression-like behavior in these strains (Article 1). Subsequently, through a comprehensive review of existing literature, we will investigate whether social isolation alleviates symptoms associated with these disorders, taking into account the emotional and cognitive mechanisms involved in social interactions among humans (Article 2). To this end, 72 animals were divided into three strains: Carioca with high conditioned freezing (CAC), Carioca with low conditioned freezing (CBC), and control animals (CTR) with intermediate freezing levels. Half of the animals were maintained in groups according to their respective lineage, while the other half were kept in socially isolated conditions within smaller

cages. Subsequently, all animals were subjected to the forced swim test, where their behaviors were analyzed. Following the findings, we expanded our studies through a narrative review to understand how these psychiatric disorders interact with interpersonal relationships.

Keywords

Carioca high- and low-conditioned freezing rats; generalized anxiety disorder; anxiety and depression comorbidity; social contagion stress.

Resumo

Peçanha, Amanda Felix Lima Araujo; Fernandez, Jesus Landeira. **Explorando o efeito do isolamento social na ansiedade e depressão: uma análise comparativa dos comportamentos depressivos em ratos cariocas com alto e baixo nível de congelamento condicionado e suas implicações em humanos.** Rio de Janeiro, 2024. 89p. Dissertação de Mestrado - Departamento de Psicologia, Pontifícia Universidade Católica do Rio de Janeiro.

Os transtornos de ansiedade estão entre os transtornos psiquiátricos mais prevalentes em todo o mundo, e achados clínicos apontam para significativa comorbidade entre transtornos de ansiedade e depressão no mesmo indivíduo. Especificamente em relação ao transtorno de ansiedade generalizada (GAD), a comorbidade com depressão em muitos casos está presente. Uma questão de grande preocupação é o impacto desses transtornos nas interações sociais. O estado de tensão e excessivas preocupações exibidas por esses indivíduos podem ser transmitidas para as pessoas de seu convívio social, assim como as interações sociais podem funcionar como um fator ansiogênico para essas pessoas. Ainda existem lacunas a respeito dos mecanismos comportamentais, neurobiológicos e genéticos envolvidos nesses transtornos, e esses aspectos precisam ser investigados. Preocupações com o aumento da prevalência dos transtornos de ansiedade e depressão ressaltam a necessidade de compreender a natureza dual das interações sociais na saúde mental, enfatizando o seu papel como fontes de bem-estar quanto como potenciais estressores. Nosso objetivo é examinar a relação dos transtornos de ansiedade e depressão com o isolamento social. Por meio de uma pesquisa empírica utilizando os ratos Cariocas, um modelo animal de ansiedade selecionado bidirecionalmente para alta e baixa resposta de congelamento condicionado, pretendemos analisar quantitativamente o impacto do isolamento social no comportamento semelhante ao depressivo nessas linhagens (artigo 1). Posteriormente, através de uma análise abrangente da literatura existente, investigamos se o isolamento social alivia os sintomas comuns a esses transtornos, considerando os mecanismos emocionais e cognitivos envolvidos nas interações

sociais entre humanos (artigo 2). Para tanto, 72 animais foram divididos nas três linhagens Carioca com alto congelamento condicionado (CAC), Carioca com baixo congelamento condicionado (CBC) e os animais controle (CTR) com níveis intermediários de congelamento. Metade dos animais foram mantidos agrupados de acordo com a respectiva linhagem e a outra metade foi mantida isolada socialmente em gaiolas menores. Posteriormente todos os animais foram submetidos ao teste do nado forçado, tendo seus comportamentos analisados. Na sequência, conforme os dados encontrados, ampliamos nossos estudos através de uma revisão narrativa para compreendermos como esses transtornos psiquiátricos interagem com as relações interpessoais.

Palavras-chave

Ratos Cariocas de alto e baixo congelamento condicionado; transtorno de ansiedade generalizada; comorbidade ansiedade e depressão; contágio social por estresse.

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Article 01

1. Theoretical background

1.1 The Impact of Anxiety and Depression Disorders on Social Interactions

From an evolutionary perspective, belonging to groups is essential for the survival and continuity of the species (Axelrod et al., 1981; Šimić et al., 2021). Through socialization, individuals develop the perceptions, emotions, and behaviors that are essential for their relationships (Heinrich et al., 2006; Cacioppo et al., 2014). The innate ability to experience empathy and emotional contagion facilitates connections between individuals and enhances survival in adverse situations (Eslinger et al., 2021; Engert et al., 2019). In this context, not only humans but also rodents and other species possess the ability to share emotions, whereby the behavior of one can influence the behavior of another (Carnevali et al., 2020; Lages, et al, 2023; Debiec & Olsson, 2017). Given the significant importance of social interactions, the stress induced by social isolation elevates the risk of illness and the development of mental disorders across various species (Popa E. 2023; Cacioppo et al., 2014). However, when interactions are accompanied by neuroendocrine and behavioral alterations present in anxiety and depression disorders, they can significantly affect the relational well-being of these individuals (Czerwińska & Pawłowski 2020; Saris et al., 2017; Keller et al., 2017).

Anxiety and depression disorders are characterized by alterations in brain structure and function that play a crucial role in emotional and cognitive processing (Wang et al., 2016; Keller et al., 2017). These alterations are readily observable through pronounced anhedonia, a negative self-perception and worldview, and an increased state of hypervigilance (Porcelli et al., 2019; Knyazev et al., 2016). Psychiatric symptoms associated with the disruption of functional homeostasis and social factors, such as the perception and interpretation of others' emotional states (Fiksdal et al., 2019; Lee et al., 2015; Min et al., 2012).

The high comorbidity between anxiety disorders and depression results in significant impairments, particularly in relationships, which are profoundly affected (Czerwińska & Pawłowski, 2020; Zhou et al., 2023). Individuals affected by these disorders exhibit reduced gratification from social interactions, a phenomenon that

may be linked to an overall increased tendency toward negativism (Czerwińska & Pawłowski, 2020; Keller et al., 2017). Additionally, brain regions associated with reward from social activities exhibit reduced activity in individuals with depression, suggesting a diminished capacity for social pleasure (Kupferberg et al., 2016; Triscoli et al., 2019).

Studies using animal models of anxiety enhance our understanding of this phenomenon, revealing that animals exhibiting a heightened freezing response show reduced engagement in social interactions (Dias et al., 2009). Similarly, studies on alcohol consumption have been associated with reduced anxiety and increased sociability in both humans and animals (Blanchard et al., 1993; Brook & Willoughby, 2016; Caumiant et al., 2023; Pohorecky, 1991; Varlinskaya & Spear, 2015; Bezerra-Karounis et al., 2020).

1.2 Social Isolation as a source of relief for anxiety and depressive symptoms

Studies conducted with rats exhibiting heightened levels of anxiety show exaggerated activation of brain circuits responsible for regulating neuroendocrine responses to aversive stimuli (A. León et al., 2013; L. A. León et al., 2020; Mousovich-Neto et al., 2015; Salviano et al., 2014). In this context, research indicates that the physiological and behavioral alterations commonly observed in these more anxious animals can affect the interactions among rats of the same lineage through stress contagion (Chun et al., 2022; Debiec & Olsson, 2017; Dimitroff et al., 2017; Peen et al., 2021). Contagion may occur through the sensory pathways of these animals, manifesting in a manner congruent with their constant state of alertness (Carnevali et al. 2020). Interestingly, in our study, following a period of isolation, these animals exhibited a prolonged latency to cease swimming in the Forced Swim Test, indicating a reduction in depressive-like behavior. This psychological impact underscores the dual nature of interactions in mental health, highlighting their role as both sources of well-being and stress. Although social isolation is not a healthy alternative for most individuals, for those affected by anxiety and depression disorders, a reduction in social interactions may serve as a source of relief (Heinrich et al., 2006; Porcelli et al., 2019; Saris et al., 2020). The impaired interpretation of social cues, along with the perception of self, interacts with functional deficits that affect socialization (Porcelli et al., 2019; Czerwińska et. al 2020).

The hypoactivation of brain regions essential for cognitive reappraisal may explain why individuals with anxiety and depression are more susceptible to resorting to avoidance as a strategy for managing their emotional vulnerabilities (Porcelli et al., 2019; Saris et al., 2020; Kalokerinos et al., 2017; Cludius et al., 2020; Aldao et al., 2010).

2. Objectives

This thesis comprises two articles. The first article aims to investigate the impact of social isolation on CHF, CLF, and CTL rats, with the model exhibiting the highest level of anxiety serving as a reliable animal model for Generalized Anxiety Disorder (GAD). The second article, through a comprehensive literature review, explores the dual nature of social interactions in mental health, emphasizing their role as both a source of well-being and stress. Focusing on anxiety and depression, it examines how these disorders disrupt social dynamics. Both studies have the following main objectives:

- Investigate the relationship between anxiety and depression disorders with social isolation.

- Discuss the hypothesis that social isolation alleviates symptoms of anxiety and depression.

3. Article section

3.1 ARTICLE 01

The impact of social isolation on depression-like behavior in carioca high- and low-conditioned freezing rats

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Amanda Peçanha, Silvia Maisonnette, Antonio Pedro M.Cruz, Claudio C. Filgueiras, Thomas E.Krahe & J. Landeira-Fernandez*

Abstract

This study investigated the impact of social isolation in Carioca High-Conditioned Freezing (CHF) rats, an animal model of generalized anxiety disorder (GAD). Animals selected for high (CHF), low trait anxiety (Carioca Low-Conditioned Freezing, CLF), and control rats from randomly bred populations (CTL) were housed in groups or kept isolated in their cages for 14 consecutive days. On the fifteenth day, all animals underwent the Forced Swimming Test (FST), where the latency to immobility was assessed as a depressive-like measure. Under standard grouping conditions, CHF rats showed a shorter latency to immobility in the FST compared to CTL and CLF animals, indicating depressive-like characteristics and possible GAD comorbidity. Social isolation decreased the latency to immobility in CLF and CTL animals, while it paradoxically increased this measure in CHF animals. Therefore, social isolation exerted a depressive-like action in CTL and CLF rats, but had a protective or "antidepressant-like" effect in CHF animals. Since, CHF rats are housed with other animals with high trait anxiety, such protective action induced by social isolation might have been due to the mitigation of what has been referred to as "social stress contagion". These results are discussed regarding the association between depressive-like behaviors and reduced social engagement.

Keywords: Carioca high- and low- conditioned freezing rats; generalized anxiety disorder; anxiety and depression comorbidity; social contagion stress.

1. Introduction

Social isolation is directly related to mental disorders, given the significance of socialization for the development of various species (Grigoryan et al., 2022). The stress induced by social isolation, aside from increasing the risks of death and cardiovascular diseases, is associated with symptoms of anxiety and depression, as well as a state of anhedonia experienced by depressed patients (Andreatini Bacellar, 1999; Grigoryan et al., 2022). Frequent stress from social factors can disrupt homeostasis, leading to dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and increased cortisol levels in humans (Fiksdal et al., 2019; Lee et al., 2015; Min et al., 2012). These changes may affect metabolism, social behavior, mood, and cognitive functions (Knezevic et al., 2023). Previous studies indicate that such neuroendocrine alterations can increase the like-lihood of developing depressive disorders (Dienes et al., 2013). Furthermore, depressed patients show structural and functional abnormalities in brain regions that play a crucial role in emotional processing, motivated behavior, and cognitive control (Keller et al., 2017; Wang et al., 2016). Understanding how these effects can differen-tially impact the behavior of individuals with high and low levels of anxiety is crucial for developing interventions that can prevent potential amplifying effects of mental disorders, as well as minimize existing ones.

Anxiety disorders are among the most prevalent psychiatric disorders worldwide (Bandelow & Michaelis, 2015; Combs & Markman, 2014), and clinical findings point to a significant comorbidity between anxiety disorders and depression in the same individual (Goodwin, 2021; Gorman, 1996; Lamers et al., 2011). However, the behavioral, neurobiological, and genetic mechanisms underlying this comorbidity remain unclear. Specifically, in relation to generalized anxiety disorder (GAD), the rate of comorbidity with depression ranges from 40 to 60% (Brawman-Mintzer et al., 1993; Carter et al., 2001; DeMartini et al., 2019; Moffitt et al., 2007; Ruscio et al., 2017), with in many cases. Studies show that individuals experiencing both anxiety and depression often exhibit greater challenges and obstacles in their interpersonal connections compared to those without mental health issues (Czerwińska & Pawłowski, 2020; Zhou et al., 2023).

In addition to linking the lack of social interaction with mental disorders, studies indicate humans' ability to be influenced by the emotional state of others through social interaction (Dimitroff et al., 2017). Thus, individuals who frequently exhibit tension and stress-related emotions can transmit their heightened state to others within their social circle, creating a form of social transmission (Debiec & Olsson, 2017).

Models of social isolation using rats provide insights into the effects of this condition compared to standard group housing, considering the nuances of each type of social interaction and the characteristics of the animals. Indeed, rodents are frequently utilized in the study of mental disorders due to their close evolutionary relationship with humans (Andersen & Winter, 2019). These animals display strong sociability, thrive in communal settings, and demonstrate the capacity a throve of emotions, akin to humans (Carnevali et al., 2020). Frequent stress caused by social factors can disrupt homeostasis, resulting in dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and corticosterone concentrations in rodents (Kinlein et al., 2019; Mumtaz et al., 2018).

It's noteworthy that animal models based on fight or flight fear responses, such as freezing behavior to cued or contextual fear conditioning, have been effectively utilized to explore the underlying physiopathological mechanisms of anxiety disorders (Castro-Goes et al., 2009; Castro-Gomes & Landeira-Fernandez, 2008; Raber et al., 2019; Santos et al., 2006). In this regard, over the past 15 years, our laboratory has established the Carioca rat lines through bidirectional selective breeding, chosen for their ability to freeze in response to footshock-associated contextual cues – named the Carioca High-conditioned Freezing (CHF) and the Carioca Low-conditioned Freezing (CLF) lines (Castro-Gomes & Landeira-Fernandez, 2008). Previous findings, both from our lab and others, have established the CHF rats as an animal model for generalized anxiety disorder GAD (Castro-Gomes et al., 2011; Macêdo-Souza et al., 2020). For instance, CHF rats exhibit higher plasma corticosterone concentrations and engage in fewer social contacts than CLF and normal animals (Cavaliere et al., 2020; Dias et al., 2009; Mousovich-Neto et al., 2015; Salviano et al., 2014). Furthermore, CHF rats exhibit more anxious-like behaviors than CLF rats in the elevated plus maze and cue fear conditioning tests (Macêdo- Dias et al., 2009, 2014; Souza et al., 2020).

Interestingly, similar freezing behavior has also been observed in humans (Brandão, 2004; Brandão et al., 2008; Hashemi et al., 2021).

It can be argued that the fear response of rats to perceived environmental sensitivity is differently influenced by housing type: whether they are grouped with other animals of the same freezing trait lineage or socially isolated (Chun et al., 2022; Debiec & Olsson, 2017; Peen et al., 2021). Although studies indicate that social isolation increases levels of stress and anxiety (Mann et al., 2022), the lack of social interaction can also induce depressive-like behaviors in these animals (Grigoryan et al., 2022; Takatsu-Coleman et al., 2013). Consequently, it is necessary to investigate how the absence of social interaction affects depressive-like behaviors in animals with varying conditioned freezing traits. In this study, the behavior of CHF and CLF rats from different breeding lines related to anxiety like behavior, named Carioca High- and Low-Freezing (CHF, CLF), was evaluated in the Forced Swim Test (FST). The FST, developed by Porsolt and colleagues in 1977, was designed as a pharmacological screening tool for depressive disorders, proving effective for studying this type of intervention (Porsolt et al., 1977). The duration of immobility and the latency time, which is the time it takes for the animal to stop swimming after being put into the water, are measured to assess the extent of the animal's depression-like behavior. The sooner the animal ceases swimming and the longer the period of immobility, the more it resembles depressive behavior, indicating resignation to escaping from a threatening situation (Grigoryan et al., 2022; Takatsu-Coleman et al., 2013).

Building upon these findings, we sought to investigate the impact of social isolation on CHF, CLF, and CTL rats, with the former serving as an animal model of GAD (Castro-Cruz et al., 2024; Castro-Gomes et al., 2011). Individuals affected by this disorder suffer from a persistent, intense, and disproportionate fear across different life contexts, including social experiences and behaviors (DeMartini et al., 2019; Hamm, 2020).

2. Material and methods

2.1. Animals

The study involved 72 male Wistar rats (240–300 g), all bred and housed in the animal facilities of the Psychology Department at the Pontifical Catholic University of Rio de Janeiro, PUC-Rio, Brazil. These animals were descendants of the 42nd and 43rd generations selectively bred over the past 15 years for either high (CHF) or low trait anxiety (CLF), as indicated in the contextual fear conditioning paradigm. Strong phenotypic divergence regarding their respective anxiety-related traits was achieved from the third generation onward. Further details of the phenotyping protocol are available elsewhere (Castro-Gomes & Landeira-Fernandez, 2008). Age-, weight-, and sex-matched Wistar rats formed an additional control group (CTL) and consisted of off-springs from randomly bred populations.

All animals were housed under controlled room temperature conditions (24°C ± 1°C) with a 12-hour light/12-hour dark cycle (lights on 7:00 AM–7:00 PM). Animals were grouped in sets of six according to their respective lines in polycarbonate home cages measuring (18 cm x 31 cm x 38 cm). Animals from each breeding line (CHF, CTL and CLF) were assigned to social or isolation procedures. Experimental manipulations were carried out during the light phase of the light/dark cycle. Food and water were available ad libitum throughout the study. The experimental protocol, approved by the Local Committee for Animal Care and Use (PUC- Rio, protocol no. 234/2012), adhered to guidelines for experimental animal research established by the Brazilian Society of Neuroscience and Behavior (SBNeC) and the National Institutes of Health Guide for the Care and Use of Laboratory Animals. A detailed timeline from birth through behavioral testing can be found in Figure 1.

2.2. Contextual fear conditioning

The contextual fear conditioning took place simultaneously in four identical transparent conditioning chambers (25 cm × 20 cm × 20 cm), each enclosed in a sound-attenuating box illuminated by a 25 W red-light bulb and constantly stimulated by a 76 dB white noise. The floor consisted of 15 stainless steel rods through which electrical footshocks (0.6 mA, 1 s) could be delivered via a stimulator (Insight, São Paulo, Brazil, model x), connected to a computer interface. Ammonium hydroxide solution (5%) was used to clean the chamber before and after each subject.

The contextual fear conditioning spanned two consecutive days. On the first day, the animals underwent an 8-minute baseline period (pre-shock period) in the conditioning chamber. Following this, they experienced three unavoidable electric footshocks at fixed 20-second intervals, followed by an additional 2-minute period (post-shock period) without any aversive stimulation. Subsequently, they were returned to their home cages. The next day, each animal underwent an 8-minute session (test session) in the same experimental context without receiving electric footshocks. Freezing behavior, defined as the total absence of movement except for respiratory movements, was observed during the test session. A trained observer recorded freezing behavior according to a time-sampling schedule, noting its presence or absence at 2-second intervals.

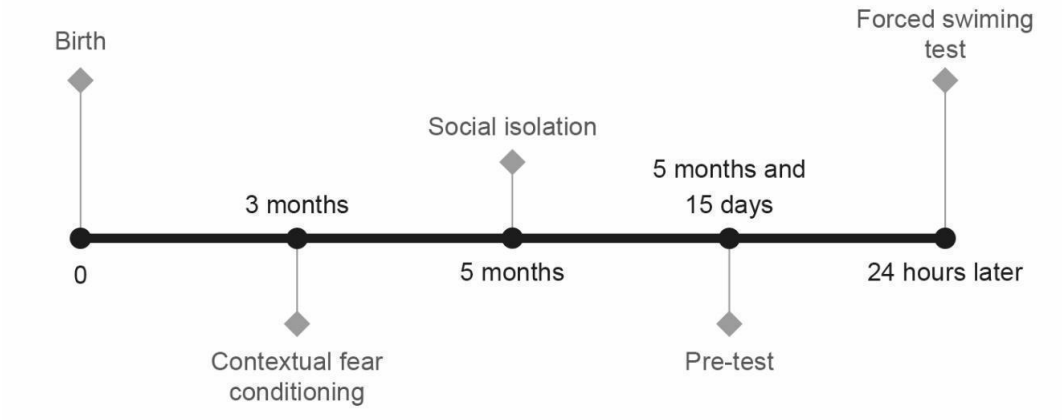

Figure 1. Timeline from animal birth, indicating the timing of behavioral tests.

2.3. Social isolation

Approximately two months after contextual fear conditioning, the isolated animals, comprising 12 CHF, 12 CLF, and 12 CTL, were housed individually in cages measuring 13 × 17.5 × 28 cm for 14 days. Aside from routine handling for cage changes, the animals remained isolated and undisturbed throughout this period. The lids of the isolated enclosures were inverted to facilitate greater movement for the animals and to prevent injuries. Consequently, food and wood shavings were placed inside, and the water bottle was affixed to the lid.

2.4. Forced swimming test (FST)

For the FST, we utilized the adaptation of the standard protocol described in Goulart et al. (2021), 72 animals were tested in the FST. Daily handling of grouped animals was conducted over a period of two weeks (2 minutes per day) prior to the FST. Handling of isolated animals was limited to cleaning their home cages. Rats were transferred to the room were the FST was conducted 30 minutes prior to the test for acclimation and stress reduction. Each rat was then individually placed in a cylindrical tank (67 cm high and 31 cm in diameter) filled with approximately 27 liters of water (25°C). The Forced Swimming test comprised two stages: a 15-minute pretest for acclimation and a subsequent 5-minute test phase 24 hours later, under the same test conditions. Latency was defined as the interval from when the animal enters the water until it ceases swimming. By the end of each FST session the water of the cylindrical tank was changed, and each animal was dried before returned to their cages.

4. Results

As can be observed in Figure 2, the CHF line exhibited the highest conditioned freezing, and the CLF line exhibited the lowest conditioned freezing. The CTL line exhibited an intermediate level of freezing. This interpretation was confirmed by a one-way ANOVA. Freezing results depicted a main effect of the breeding line ($F(72,2) = 249.9$; $p < 0.0001$), but no main effect of isolation ($F(72,2) = 0.24$; $p > 0.6$) or interaction between breeding line and isolation ($F(72,2) = 0.29$; $p > 0.7$).

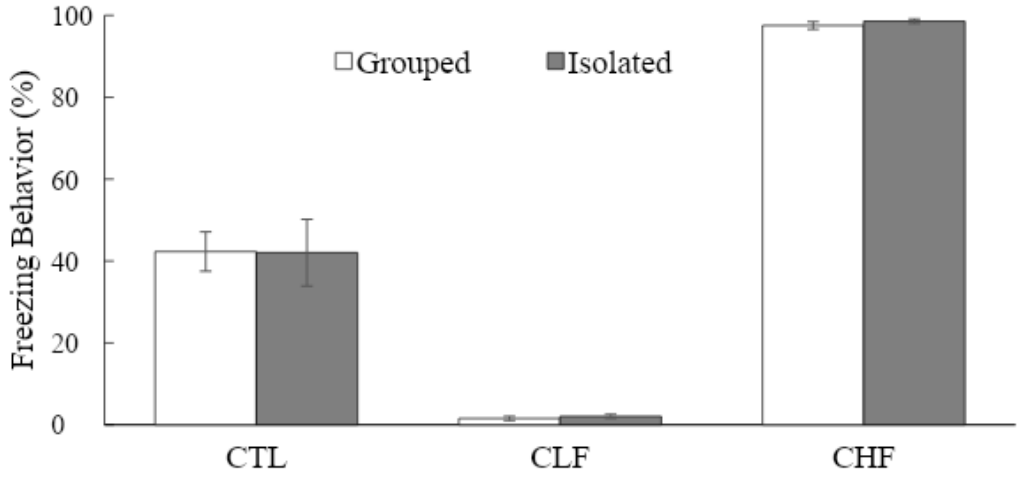

Figure 2. Mean ± SEM percentage of the time spent freezing among control (CTL), Carioca Low conditioned freezing (CLF) and Carioca high conditioned freezing (CHF) rats according to grouped or isolated conditions.

Figure 3 presents latency results of the animals exposed to the FST. Two-way ANOVA of the FST results indicated an interaction between breeding line and isolation ($F(72,2) = 5.83$; $p < 0.05$) as well as a main effect of breeding line ($F(72,2) = 3.72$; $p < 0.05$) but no main effect of isolation ($F(72,1) = 1.27$; $p > 0.05$). Pairwise post hoc comparisons indicated that CHF animal in the standard housing procedure showed a lower latency to stop swimming (i.e., higher depressive-like behavior) when compared to CTL or CLF animals exposed to the same housing procedure (both $p < 0.05$). Isolation was able to produce a depressive-like behavior among CTL and CLF animals when compared to the same line animals exposed to the standard housing procedure (both $p < 0.05$). An opposite effect was found among CHF animals, indicating that these animals exposed to the isolation

procedure presented higher latency to stop swimming when compared to CHF animals in the standard housing procedure group ($p < 0.05$).

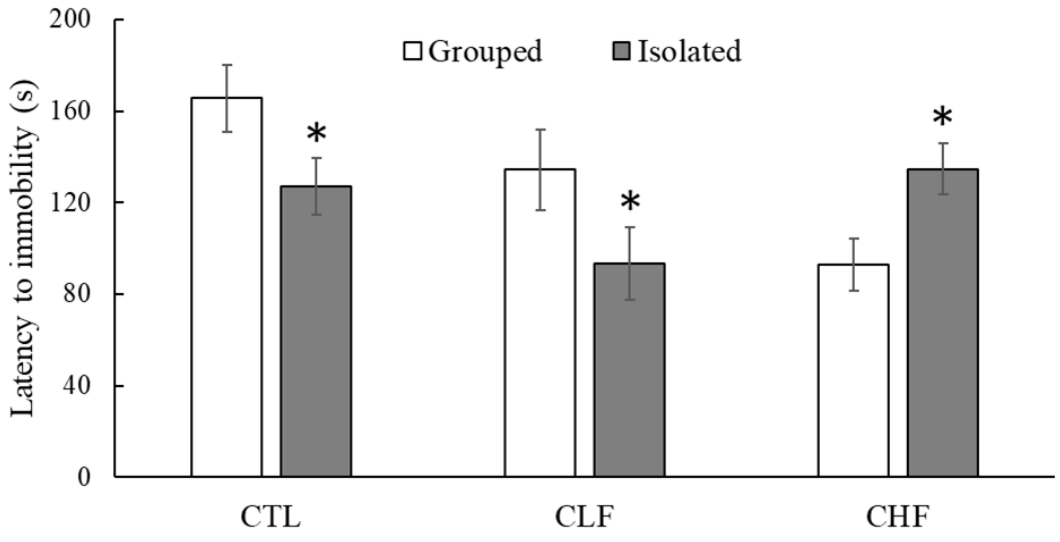

Figure 3. Mean ± SEM percentage of latency to immobility in to the forced swimming test among control (CTL), Carioca Low conditioned freezing (CLF) and Carioca high conditioned freezing (CHF) rats according to grouped or isolated conditions. * $p < 0.05$.

5. Discussion

In the present study, we investigated the impact of social isolation on CHF, CLF and control animals. Multiple studies using with CHF rats have consistently shown higher levels of freezing compared to CTL and CLF animals (Castro-Gomes & Landeira-Fernandez, 2008; Castro-Gomes et al., 2011; Cruz et al., 2024; Lages et al., 2023). As expected, our findings revealed that CHF animals exhibited a higher percentage of freezing compared to CTL and CLF rats, whereas the latter exhibited a significantly lower percentage of freezing compared to CTL and CHF animals (Castro-Gomes & Landeira-Fernandez, 2008; Castro-Gomes et al., 2011).

Regarding the latency to display immobility in the FST, grouped CHF rats showed smaller latency-times compared to CLF and CTL groups in the same housing condition, suggesting that grouped animals CHF exhibit a depression-like behavior which is consistent with studies from our laboratory that had used the same bidirectional line (Goulart et al., 2021). These results also converge with the fact

that there is a high level of comorbidity between anxiety disorders and depression, with a co-occurrence rate of 90% (Gorman, 1996).

The 14-day social isolation procedure induced depression-like behavior, as evidenced by the shorter latency times of the CLF and CTL isolated groups compared to their non-isolated counterparts. Surprisingly, isolation had the opposite effect on CHF rats, as isolated CHF rats showed longer latency times to stop swimming compared to those housed under standard conditions –immobility time was not measured. This result may be explained by the reduction of stress caused by isolating CHF animals from others with the same high anxiety trait. Given that, we have previously demonstrated that CHF rats also exhibit increased activation of the HPA axis and elevated corticosterone concentrations, indicating an exaggerated activation of brain circuits responsible for regulating the neuroendocrine response to aversive stimuli (A. León et al., 2013; L. A. León et al., 2020; Mousovich-Neto et al., 2015; Salviano et al., 2014). Indeed, isolation might paradoxically counteract stress associated with social interactions, potentially protecting against social stress (Carnevali et al., 2017; Chun et al., 2022; Peen et al., 2021). Supporting this hypothesis, previous studies from our laboratory showed that CHF animals display reduced engagement in social interactions (Dias et al., 2009). CHF animals demonstrated more anxiety-like behaviors when interacting with another rat from the same lineage, showing fewer social interacting behaviors toward one another such as sniffing, following, grooming, kicking, mounting, jumping on, wrestling, and boxing with, crawling under (Dias et al., 2009). Moreover, it was recently demonstrated that alcohol consumption is higher in CHF rats compared to CLF and controls (Bezerra-Karounis et al., 2020). The association between alcohol ingestion with reduced anxiety and increased socialization is well supported in the literature in both humans and animals (Blanchard et al., 1993; Brook & Willoughby, 2016; Caumiant et al., 2023; Pohorecky, 1991; Varlinskaya & Spear, 2015). In the sucrose test used by Lages et al. (2022) to investigate depressive-like behaviors, such as anhedonia, CHF rats on a high-sugar diet exhibited a dampening effect on the stress response compared to those fed only the standard diet. This finding suggests a link between the dopaminergic system and the HPA axis (Lages et al.,2022). Similarly, the Roman high- (RHA) and low- (RLA) avoidance strains demonstrate different coping mechanisms for stressors, influenced by genetic and environmental factors

(Fernández-Teruel, 2021). RHA rats are less fearful and exhibit a more impulsive profile, with a greater tendency to seek rewards, such as substance use (Fernández-Teruel, 2021; Giorgi et al., 2019). In contrast, RLA rats, which are more reactive to stressors, show heightened sensitivity to environmental changes and exhibit more pronounced behavioral inhibition, evidenced by freezing behavior, higher corticosterone levels, and increased HPA axis activation (Giorgi et al., 2019). These behavioral and neuroendocrine responses are linked to depressive-like behavior in the FST, as observed by Piras et al. (2003, 2014). However, the underlying mechanisms and brain regions associated with these phenomena remain largely unknown.

Studies in humans demonstrate that individuals suffering from depression show heightened amygdala activity, hyperactivity of the hypothalamic-pituitary-adrenal axis, and elevated cortisol levels (Czerwińska & Pawłowski, 2020; Keller et al., 2017). Interestingly, the same patients also display maladaptive social attitudes, pessimistic thoughts, and increased vigilance toward social dangers (Czerwińska & Pawłowski, 2020; Keller et al., 2017). Moreover, challenges in social relationships are common in individuals with anxiety or depression, particularly when these conditions coexist (Saris et al., 2017). Impoverished social connections could be linked to anhedonia, which includes the inclination to perceive not only adverse facial expressions but also negative physical cues overall (Pan et al., 2019). These negative social expectations contribute to favoring isolation, especially in patients with generalized anxiety disorder (Evans et al., 2019; Saris et al., 2017). Additionally, regions of the brain associated with social reward show reduced activity in individuals experiencing depression, leading to diminished enjoyment of social situations and a dislike for physical contact, which is crucial in social interactions (Kupferberg et al., 2016; Triscoli et al., 2019).

Many studies show that humans, rodents, and other animal species Share emotions, with consequences for social interactions (Carnevali et al., 2020; Lages et al., 2023). The behavior of one can influence the behavior of another, including for adaptive reasons, such as survival (Debiec & Olsson, 2017). Therefore, stress contagion may have influenced CHF animals in group conditions to exhibit a lower latency time for immobility. Since an animal can exert a kind of emotional cushioning on its cage partner, it also suffers from contagion by a certain level of stress, which can

compromise its health (Chun et al., 2022; Debiec & Olsson, 2017; Dimitroff et al., 2017; Peen et al., 2021). In order for stress contagion to occur, it is not necessarily required that one has participated in a particular stressful event. The sharing of emotional states among grouped CHF animals may have occurred due to exposure to behaviors and physiological changes among cage partners (Peen et al., 2021). In this sense, in a cage with six CHF animals, as in our study, the physiological and behavioral responses of these animals are consistent with a state of alertness most of the time without the occurrence of an apparent risk (Carnevali et al., 2017, 2020). The transfer of fear-related emotional states during social interactions among CHF animals can occur through sensory path-ways such as smell, hearing, and observation of behaviors, as described by Carnevali et al. (2020). The high corticosterone concentrations in these animals (Dias et al., 2009; Mousovich-Neto et al., 2015) may indicate heightened sensitivity in sensory pathways and avoidant behaviors associated with fear responses. In line with this, studies also highlight the impact of vicarious social learning among rodents on neurobiological and behavioral changes (Iñiguez et al., 2018; Sial et al., 2016). Therefore, a shorter latency time for immobility in grouped CHF animals suggests that they are less prone to cope with a stressful environment – i.e., CHF rats give up more quickly on attempting to escape from the water tank (Castagné et al., 2009; Espejo & Miñano, 1999; Grigoryan et al., 2022). This observation may indicate that these animals, when coexisting with others with the same high anxiety trait, are more affected by the prevailing emotional state in the environment, resorting to passive coping strategies compared to CHF animals living in isolation. Nonetheless, overall our results highlight and support the connection between stress contagion and the ability to handle stress (Carnevali et al., 2017; Chun et al., 2022; Debiec & Olsson, 2017). To fully understand the different approaches to managing social stress, further experiments are essential, particularly given the complexity of depressive disorders.

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3.2 ARTICLE 02

Can social isolation alleviate symptoms of anxiety and depression?

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Abstract

This study examines the complex interplay between social behavior and mental health, focusing on the neurobiological mechanisms underlying human interactions and their alterations associated with anxiety and depression disorders. These conditions are characterized by heightened threat perception, pervasive worry, physiological responses, emotional dysregulation, and maladaptive behaviors. Through narrative review, this study examines both aspects, addressing social isolation as both a risk factor and an avoidance behavior that may provide temporary relief but ultimately perpetuate the clinical condition in the long term. The findings offer valuable insights for clinical practice, emphasizing interventions that enhance cognitive flexibility to foster stable and supportive interpersonal relationships.

Keywords: Social isolation; Social behaviors; Anxiety and depression disorders; Emotional dysregulations; Avoidance

Introduction

Humans, like other animal species, develop primarily through social interactions through social interactions across their lifespan (Holt-Lunstad, 2018; Cacioppo et al., 2014). Within this framework, the absence of socialization can lead to stress, exerting a profound impact on both physical and mental health (Popa E. 2023; Cacioppo et al., 2014). Research suggests that the tendency toward isolation can arise from a combination of social, psychological, and neurobiological factors (Luhmann et al., 2023; Reinhard et al., 2022; Zhang & Dong (2022); Nguyen et al., 2024). While social interactions shape individuals' self-perceptions and influence their motivation to engage with others, intrinsic characteristics such as personality traits, emotional regulation, and stress responses also play a significant role in determining social withdrawal (Monferrer et al., 2021; Heinrich et al., 2006). In this process, the interpretations and perceptions individuals form about themselves through their social interactions directly influence their desire to connect with others, reinforcing patterns of either engagement or avoidance (Monferrer et al., 2021).

The dynamics of social interactions are particularly complex for individuals with mental disorders, as these conditions often amplify distortions in reality perception (Holt-Lunstad J. 2018; Hogenelst et al., 2015). Anxiety disorders, among the most common mental health conditions worldwide, are characterized by excessive fear, worry, and avoidance behaviors triggered by perceived threats (World Health Organization, 2025; American Psychiatric Association, 2022; Bandelow & Michaelis, 2015; Combs & Markman, 2014;). These disorders often lead to hypervigilance, impaired emotional regulation, catastrophic thinking, physical symptoms such as muscle tension and gastrointestinal disturbances, as well as difficulty concentrating and sleep problems (Russo et al., 2013; Czerwińska et al., 2020; Penninx et al., 2021). Similarly, depressive disorders are marked by a persistent sad, empty, or irritable mood lasting at least two weeks, often accompanied by anhedonia, or the loss of interest and pleasure in previously enjoyable activities (American Psychiatric Association, 2022). Both conditions

result in emotional and cognitive impairments that affect daily functioning, with symptoms influenced by genetic predisposition and social factors such as loss, trauma, and chronic stress (Goodwin et al., 2021; World Health Organization, 2025; van Kleef et al., 2022; Pellicano et al., 2023). Notably, these disorders frequently co-occur, with approximately 50–60% of individuals diagnosed with an anxiety disorder, particularly generalized anxiety disorder (GAD), also meeting the criteria for depression (Goodwin et al., 2021; Gorman, 1996; Lamers et al., 2011; Brawman-Mintzer et al., 1993; Carter et al., 2001; Moffitt et al., 2007). This overlap is attributed to shared genetic vulnerabilities, though anxiety disorders are more influenced by environmental factors, while depression disorders are more closely linked to genetic predisposition (Goodwin et al., 2021). Their co-occurrence leads to greater symptom severity, increased functional impairment, and a more chronic and treatment-resistant course (Penninx et al., 2021; (Zhou et al., 2023; Czerwińska et al., 2020). Anxiety disorders, like depressive disorders, also induce changes in cognitive processing (Nguyen et al., 2024). With that said, when these two disorders are comorbid, they can amplify subjective social isolation and the perception of emotional disconnection in relationships, which is one of the dimensions most associated with mental disorders, particularly depression (Nguyen et al., 2024; Taylor et al., 2018). Due to the inherent complexity of mental disorders and social isolation, establishing a causal and sequential relationship between them presents a significant challenge.

Social isolation and mental disorders, such as anxiety and depression disorders, exhibit a complex bidirectional relationship. In some cases, a lack of social interactions may serve as a predisposing factor for the development of these disorders, exacerbating stress responses and impairing emotional regulation. Conversely, individuals with anxiety and depression disorders often struggle to maintain interpersonal relationships, which can lead to a progressive pattern of social withdrawal. This review examines both aspects, addressing social isolation as both a risk factor and an avoidance behavior that may provide temporary relief but ultimately perpetuate the clinical condition in the long term.

Methods

This narrative review was conducted to integrate findings on the relationship between social isolation and anxiety and depressive disorders, with a particular emphasis on the underlying neurobiological mechanisms of social interactions and their alterations in affected individuals. The literature selection included empirical studies, systematic reviews, and meta-analyses, drawing from widely recognized databases such as PubMed, Scopus, PsycINFO, and Web of Science. References published between 1965 and 2024 were analyzed, using key search terms such as “social isolation,” “social behavior,” “social brain,” “anxiety and depression disorders,” “emotional dysregulation,” and “avoidance.”The selection process focused on studies that provide relevant insights into social behavior and the impact of anxiety and depressive disorders on social interactions**.** Conversely, studies not directly related to the research theme were excluded. This review was structured into distinct thematic sections to provide a comprehensive and integrative perspective. First, the importance of social interactions is discussed, highlighting their role in emotional well-being and physiological stress regulation. The review then explores the neurobiological foundations of social behavior and social isolation, focusing on brain circuits involved in social processing. A dedicated section further examines the role of key neurotransmitters serotonin, dopamine, and oxytocin in modulating social behavior. Following this, the review outlines the impact of anxiety and depression disorders on the neurobiology of social behavior, emphasizing how these conditions alter emotional processing and social perception. Additionally, it explores the interaction between serotonin, dopamine, and oxytocin within the context of anxiety and depressive disorders. Finally, the review addresses the intersections between emotion, social cognition, and emotional regulation, emphasizing their significance in understanding interpersonal difficulties associated with these disorders.

The Influence of Social Interactions on Anxiety and Depression Disorders

Humans are inherently social, driven by a fundamental need for belonging that influences their thoughts, emotions, and behaviors (Heinrich et al., 2006). While cultural variations exist, humans generally seek stable, lasting relationships over fleeting connections (Baumeister et al., 1995). From an evolutionary perspective, forming enduring bonds is vital for survival and reproductive success, contributing to species preservation (Axelrod et al., 1981; Šimić et al., 2021). Adults within groups have a higher likelihood of survival due to access to support in risky situations and care during illness (Axelrod et al., 1981; Baumeister et al., 1995).

Beyond survival, social connections foster health and resilience within communities (Baumeister et al., 1995). Individuals who build relationships often experience positive emotions such as happiness, empathy, and connection, which enhance their quality of life and support long-term emotional well-being (Hogenelst et al., 2015; Faraji et al., 2023).

Emotional experiences, being deeply personal, play a fundamental role in socialization by influencing group dynamics and signaling risks, belonging, or exclusion among peers (Eslinger et al., 2021). Although emotions are unique to each individual and may sometimes be suppressed, they remain a crucial motivating factor that is reflected in observable behaviors and is subject to the influence of interpersonal interactions (Eslinger et al., 2021; Kingsbury et al., 2020). Social interactions, in turn, amplify these emotions, uniting individuals in shared experiences—whether joyful or challenging, such as fear (Eslinger et al., 2021; Darwin, 1965). Innate skills, such as empathy and emotional contagion are essential for promoting a sense of belonging within groups, as they facilitate emotional connections between individuals (Eslinger et al., 2021; Engert et al., 2019).

At a cognitive level, adaptive thoughts are those linked to a sense of belonging and the pursuit of secure bonds within a group (Baumeister et al., 1995). Human cognition, characterized by its sophistication and unique capacity for socially contextualized learning and emotional sharing, underpins our sociability (Vieira & Oliva, 2017, p. 14-35). This intricate network of cognitive interactions, refined

through evolution, enables self-evaluation and peer assessment while also exposing us to both cognitive rigidity and flexibility (Vieira & Oliva, 2017, p. 14-35; Eslinger et al., 2021).

The ability to form interpersonal connections is essential for securing social support (Cohen et al., 1985). However, individuals lacking secure relationships are more vulnerable to developing psychological disorders, such as anxiety and depression disorders, which can severely affect mental and physical health (Cohen et al., 1985; Nguyen et al., 2020; Nguyen et al., 2024). Perceived loneliness, rooted in the psychological sensation of not belonging, significantly activates the alert system, triggering stress responses that can lead to physiological, cognitive, and immunological changes, thereby increasing risks to both physical and mental health (Cacioppo et al., 2009; Nguyen et al., 2020; Nguyen et al., 2024; Taylor et al., 2018). Furthermore, difficulties in interpreting, expressing, and experiencing emotions can hinder social interactions, resulting in reduced support and increased misunderstandings (Niedenthal et al., 2012).

As several studies indicate, a lack of socialization is strongly associated with an increased risk of developing anxiety and depression disorders (Cacioppo et al., 2009; Taylor et al., 2018; Nguyen et al., 2024). However, preexisting psychological factors may contribute to social isolation, while inadequate social support can further compromise mental health, creating a bidirectional cycle (Matthews et al., 2016; Hawkley & Cacioppo, 2010). Moreover, the development of psychological disorders is influenced by a complex interplay of factors, including genetic predisposition, traumatic experiences, chronic stress, neurobiological dysregulation, and environmental influences (Caspi et al., 2003; Kendler et al., 2011).

Emotional and cognitive adjustment difficulties commonly observed in anxiety and depression disorders impair individuals' adaptive capacity, significantly affecting their interpersonal relationships (Russo et al., 2013; Czerwińska et. al 2020; Porcelli et al., 2019). The subjective perception of being understood, respected, and emotionally supported plays a crucial role in determining the extent to which individuals believe their social support network can alleviate depressive symptoms (Wang et al., 2022). The literature highlights resilience as a key coping mechanism that integrates intrinsic and interpersonal factors, promoting adaptive capacity,

fostering more positive responses to adversity, and reducing symptoms of anxiety and depression (Zhou et al., 2024; Palacio et al., 2020). Relationships characterized by open communication, where individuals feel safe expressing difficulties and receiving support, are considered beneficial as they enhance adaptability to life challenges (Zhou et al., 2024; Palacio et al., 2020). Furthermore, relationships that encourage acceptance, flexibility, and self-care practices contribute to stress reduction, which is crucial for managing these disorders (Zhou et al., 2024). While social relationships can serve as a protective factor against anxiety and depression symptoms, negative social interactions have the potential to exacerbate psychological distress (Zhou et al., 2024; Farrer et al., 2024). Higher levels of negative social interactions are significantly associated with increased symptoms of depression and anxiety (Farrer et al., 2024). Interactions with friends and family that convey unavailability, excessive demands, harsh criticism, judgment, and persistent relational conflicts leading to distress and stress have a particularly detrimental impact on mental health (Farrer et al., 2024).

Neurobiological Bases of Social Behavior and Social Isolation

Social behavior is regulated by various brain regions and neural circuits, each contributing to different aspects of social and cognitive functioning (Lanooij et al., 2023). Research highlights the connectivity between structures involved in social cognition, such as the Default Mode Network (DMN), which supports psychological processes essential for attributing meaning to the mental states of oneself and others- critical during social interactions (Menon, 2023; Adolphs. 2009).

The regions comprising the Default Mode Network (DMN) operate in an integrated manner, continuously associating individual and environmental factors to construct shared meanings, thereby facilitating social communication (Yeshurun et al., 2021;

Moser et al., 2021). Several of these regions perform self-referential functions, including the medial prefrontal cortex (mPFC), the posterior cingulate cortex (PCC), and the temporoparietal junction (TPJ), which are involved in differentiating the self from others (Fareri et al., 2020; Menon, 2023). The precuneus is associated with the processing of personal information, while the angular gyrus plays a role in retrieving relevant memories (Fareri et al., 2020). Moreover, the DMN plays a central role in social cognition, anticipating future actions based on past experiences and exhibiting heightened responses to interactions with people compared to objects (Fareri et al., 2020; Menon, 2023). Evidence suggests that functional connectivity between the superior frontal gyrus and the superior parietal lobule is more pronounced during interactions with close individuals than with strangers (Fareri et al., 2020). Complementarily, studies indicate that the interaction between the DMN and the ventral striatum, mediated by the executive control network (ECN), enhances the value of social rewards derived from close interpersonal relationships, highlighting the role of these connections in modulating social behavior (Fareri et al., 2020; Moser et al., 2021). According to the literature, the activation of the (DMN) plays a crucial role in modulating prosocial responses, both behaviorally and emotionally. This process occurs as the DMN integrates internal cognitive states with external environmental cues, enabling the production of socially appropriate reactions (Oliveira et al., 2023).

Studies in social neuroscience highlight the role of cortical regions in analyzing complex social behaviors (Lanooij et al., 2023). For instance, the anterior insular cortex (AI) interacts with different brain regions depending on the social context, playing a significant role in affective states that range from positive feelings, such as compassion, admiration, and a sense of justice, to negative experiences like pain and disgust in social interactions (Lamm et al., 2010). Due to the adaptive value of social connection, the social pain triggered by perceived rejection or lack of belonging is often likened to physical pain in its ability to signal potential risks (Cacioppo. 2009). In line with this hypothesis, neuroimaging studies reveal the activation of similar brain structures in both physical and emotional pain, including the insula (IA), anterior cingulate cortex (ACC), and dorsal anterior cingulate cortex (dACC) (Eisenberger et al., 2003; Cacioppo, 2009; Kross et al., 2011).

Humans and other mammals exhibit strong social motivation, driven in part by their capacity for empathetic communication, which is widely considered genetically determined (Decety et al., 2004). The pro-social tendency to share emotional states and seek support during stress reduces activity in the anterior cingulate cortex (ACC), a region essential for emotional regulation. This process also downregulates activity in the amygdala and the hypothalamic-pituitary-adrenal (HPA) axis, aiding stress management (Walker et al., 2013).

Research suggests that the same neural networks are involved in both the identification and expression of emotions (Decety et al., 2004). Among these, the amygdala plays a central role in recognizing facial expressions, particularly those associated with fear. It integrates sensory information from environmental stimuli with behavioral, autonomic, and endocrine responses critical for emotional recognition (Decety et al., 2004; Raam et al., 2021; Walker et al., 2013; Gangopadhyay et al., 2021).

Neural systems that synchronize across individuals have been identified at the cortical level in processes such as understanding actions, processing pain, and recognizing emotions (Decety et al., 2004; Kingsbury et al., 2020). This phenomenon forms the neurophysiological foundation of social cognition through the automatic activation of motor or emotional representations (Decety et al., 2004). Moreover, patterns of activation and deactivation vary depending on factors such as context and the specific emotions involved (Decety et al., 2004).

A key component of socialization is the ability to perform executive functions, particularly understanding the mental states of oneself and others (Decety et al., 2004; Faraji et al., 2023). The prefrontal cortex (PFC) plays a vital role in regulating social behavior, including inhibitory control, self-regulation, and cognitive flexibility (Decety et al., 2004; Gunaydin et al., 2014; Faraji et al., 2023). Additionally, the right inferior parietal cortex contributes to the ability to assertively adopt another's perspective, allowing for the understanding of their experiences without one's own perceptions interfering in this process (Decety et al., 2004). These capabilities are essential for developing empathy and social well-being, which are deeply connected to the individual’s interactions and environment (Decety et al., 2004). Interactions among the medial prefrontal cortex, amygdala, and orbitofrontal cortex facilitate the processing of information critical for

socialization (Gangopadhyay et al., 2021). Similarly, the hippocampus (HPC) plays a key role in social memory, aiding in the discrimination between familiar and unfamiliar individuals, as well as in less complex social behaviors, such as sexual behavior (Xu et al., 2021; Lanooij et al., 2023).

Oxytocin, a neuropeptide produced in the hypothalamus, is released into both the bloodstream and brain in response to reproduction-related stimuli, such as childbirth, breastfeeding, and sexual activity, as well as during social interactions and stressful situations (Rappeneau et al., 2024). Its release highlights humans' ultrasocial nature, demonstrating an intrinsic motivation to connect with others from an early age (Tomasello. 2014). Moreover, it is well accepted that oxytocin plays a critical role in regulating amygdala activity by reducing hypothalamus and hypothalamic-pituitary-adrenal (HPA) axis activation in stressful situations (Heinrichs et al., 2009). This regulation promotes more adaptive social behaviors (Heinrichs et al., 2009; Rappeneau et al., 2024). Therefore, oxytocin integrates cognitive processes that favor social interactions in healthy individuals (Rappeneau et al., 2024). However, its dysregulation has been linked to mental disorders associated with difficulties in forming and maintaining social relationships (van Kleef et al., 2022).

In contrast to the neural activations associated with pro-social behaviors, social isolation is linked to the dysregulation of key neural circuits involved in emotional regulation, stress response, and social cognition. Studies indicate that social isolation leads to reduced connectivity between the medial prefrontal cortex (mPFC) and limbic structures, impairing emotional regulation and increasing vulnerability to anxiety and depression disorders (Xiong et al., 2023; Cacioppo et al., 2015). This weakened mPFC-limbic connectivity disrupts top-down inhibitory control over amygdala activity, leading to heightened threat perception, increased fear responses, and exaggerated stress reactivity (Hawkley et al., 2010; Vitale et al., 2022). Concurrently, hippocampal dysfunction impairs stress contextualization and cognitive flexibility, which are essential for adaptive coping mechanisms (Vitale et al., 2022). Moreover, hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis further exacerbates neuroinflammatory responses and cortisol dysregulation, contributing to long-term impairments (Vitale et al., 2022; Cacioppo et al., 2015).

Serotonin, Dopamine and Oxytocin Modulation of Social Behavior

The serotonergic system (5-HT) plays a relevant role in fundamental processes vital for survival and species preservation, including mood regulation, reproduction, feeding, sleep, pain perception, temperature control, learning, memory, and social behaviors (Kiser et al., 2012). Social interactions are strongly influenced by serotonergic activity, which is highly responsive to environmental stimuli and context-dependent factors (Kiser et al., 2012; Young S. N. 2013). Emotionally secure and socially enriched environments tend to promote more adaptive, sociable, and resilient behaviors in the face of challenges (Kiser et al., 2012; Young S. N. 2013). Conversely, stressful environments can disrupt the serotonergic system, reducing mood and impairing social behaviors (Kiser et al., 2012; Young S. N. 2013). The role of serotonin is essential in the maintenance of emotional well-being, promoting more reflective and less impulsive behaviors that are conducive to social contexts (Niederkofler et al., 2015).

Dopamine, another neurotransmitter of significant importance, not only facilitates but is essential for motivation and gratification in positive social interactions (Walker et al., 2013; Gunaydin et al., 2014). This neurotransmitter plays a critical role in the modulation of social behaviors by systematically processing information and valences that enhance social learning (Faure et al., 2022). In this manner, social experiences can alter dopaminergic activity, which may subsequently lead to either social cohesion or social withdrawal (Faure et al., 2022). Furthermore, the functional interaction between serotonin and dopamine also encompasses cognitive functions, and alterations in their levels are associated with mental disorders that impact social relationships (Niederkofler et al., 2015; Faure et al., 2022).

Oxytocin, a neuropeptide produced in the hypothalamus, is released into both the bloodstream and brain in response to reproduction-related stimuli, such as childbirth, breastfeeding, and sexual activity, as well as during social interactions and stressful situations (Rappeneau et al., 2024). Its release highlights humans' ultrasocial nature, demonstrating an intrinsic motivation to connect with others from an early age (Tomasello. 2014). Moreover, it is well accepted that oxytocin plays a critical role in regulating amygdala activity by reducing hypothalamus and

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Neurobiology of Anxiety and Depression Disorders

Integrating environmental stimuli with stored memories is a dynamic and essential cognitive process that enables individuals to interpret and respond to external inputs. This process is shaped not only by beliefs and emotions but also by the unique ways individuals perceive and process stimuli, resulting in highly personalized patterns of interpretation and reaction (Yeshurun et al., 2021). These patterns are further influenced by personal experiences, contextual factors, and prior knowledge, which collectively modulate cognitive and emotional responses to the environment (Yeshurun et al., 2021).

At the neural level, the Default Mode Network (DMN) serves as a central system for orchestrating this integration. The DMN enables seamless transitions between introspection and environmental engagement, supporting key cognitive processes such as self-referential thinking, episodic memory retrieval, and social cognition (Spreng & Andrews-Hanna, 2015; Menon, 2023). It helps individuals construct coherent internal narratives by integrating memory, language, and semantic representations, essential for imagining future scenarios and reflecting on past experiences (Buckner & Carroll, 2007; Menon, 2023). Furthermore, the DMN interacts dynamically with other brain networks, such as the salience and executive control networks, to balance attention between internal and external demands (Spreng & Andrews-Hanna, 2015; Menon, 2023). By harmonizing internal and

external information, the DMN plays a pivotal role in emotional regulation, adaptive decision-making, and resilience, highlighting its importance in mental health maintenance (Menon, 2023). In depressive and anxiety disorders, clinical complexity often stems from the interplay of genetic predispositions and environmental stressors, which contribute to their high comorbidity rates (Knyazev et al., 2016; Goodwin et al., 2021). The overlapping biological, psychological, and social factors associated with these disorders pose significant challenges for therapeutic interventions, requiring approaches that address both shared and disorder-specific features (Knyazev et al., 2016).

Research highlights the significant impact of depressive and anxiety disorders on the DMN, with alterations affecting not only psychiatric symptoms but also social processes, such as the perception and interpretation of emotional expressions (Saris et al., 2020; Yeshurun et al., 2021). These DMN modifications are not exclusive to depression and anxiety disorders, they are also observed in other conditions characterized by social dysfunctions (Knyazev et al., 2016; Saris et al., 2020; Yeshurun et al., 2021).

Regions of the prefrontal cortex (PFC), as key components of the DMN, play a vital role in functions such as self-referential thinking, belief evolution, and emotional identification (Saris et al., 2020). In individuals with depression disorder, functional deficits in these areas are closely linked to impaired emotional regulation and difficulties in establishing healthy social interactions. Numerous studies have highlighted that one of the key characteristics of depressive disorder is a decrease in motivation, which can lead to social isolation, often considered the primary cause of depression (Kiser et al., 2012; Faure et al., 2022). This alteration can be explained by anhedonia, a symptom commonly associated with depression, characterized by the loss of pleasure in activities previously perceived as enjoyable (Walker & McGlone, 2013; Liu et al., 2018). Neuroimaging studies have also revealed that reduced functional connectivity in brain structures involved in reward processing and social cognition, such as the default mode network (DMN), is associated with difficulties in forming social bonds and experiencing pleasure (Saris et al., 2020). These findings support the hypothesis that social isolation results from neural mechanism alterations related to motivation and reward rather than solely external factors (Saris et al., 2020). These difficulties can exacerbate social isolation,

perpetuating depressive states and reinforcing the cycle of emotional distress and diminished social engagement (Saris et al., 2020; Yeshurun et al., 2021). A decline in social interactions is a key feature of depression, reflected in reduced engagement with social rewards, heightened emotional suffering, and impaired interpretation of social cues (Porcelli et al., 2019; Knyazev et al., 2016). These challenges are often associated with reduced intrinsic motivation, increased vulnerability to rejection, diminished collaboration, and avoidance of competitive or demanding social scenarios. This impaired ability to navigate social contexts leads to maladaptive social decisions, perpetuating isolation and worsening depressive symptoms (Porcelli et al., 2019). Additionally, a strong vulnerability to social rejection is frequently tied to cognitive distortions in self-evaluation and negative interpretations of social interactions, which reinforce maladaptive emotional responses and sustain the depressive state (Porcelli et al., 2019; Czerwińska et. al 2020).

A central mechanism contributing to reduced socialization and heightened emotional suffering involves the insula, a brain region critical for integrating internal bodily states with external social and environmental information (Porcelli et al., 2019). The insula's role in creating a holistic emotional perception links it to the experience of emotional suffering in social contexts. Alongside the insula, the amygdala is hyperactivated in individuals with depression and anxiety, driving the heightened processing of negative emotions and reinforcing threat-related responses (Porcelli et al., 2019; Russo et al., 2013). This hyperactivity also extends to the nucleus accumbens (NAcc), a structure involved in reward processing, further disrupting the balance between emotional regulation and behavioral responses. Dysfunctional communication between subcortical and cortical regions, such as the orbitofrontal cortex (OFC) and medial prefrontal cortex (mPFC), impairs excitatory control, exacerbating emotional dysregulation, and contributing to feelings of disconnection and social withdrawal (Porcelli et al., 2019; Russo et al., 2013; Spreng et al., 2020).

Chronic stress, often fueled by negative social interpretations, induces significant physiological and cognitive changes, including mood alterations and impaired information processing (Knezevic et al., 2023; Cui et al., 2024). The hippocampus, which is closely connected to subcortical regions, plays a critical role in memory

encoding and contextualizing emotional experiences (Russo et al., 2013). In individuals with depression and anxiety disorders, disruptions in hippocampal function are associated with distorted information processing, favoring negative biases and ruminative thinking (Russo et al., 2013; Czerwińska et. al 2020). These dysfunctions are further exacerbated by chronic activation of the hypothalamic-pituitary-adrenal (HPA) axis, leading to prolonged norepinephrine and cortisol release, which undermines cognitive and emotional stability (Knezevic et al., 2023; Sandi et al., 2015; Czerwińska et al., 2020). Dysregulation of the HPA axis perpetuates a cycle of stress, emotional dysregulation, and cognitive impairments, commonly observed in anxiety and depression disorders (Knezevic et al., 2023; Craske et al., 2017).

An increased focus on processing negative emotions may stem from excessive rumination and impaired social cognition (Monferrer et al., 2021; Pan et al., 2019). Social cognition involves perceiving, interpreting, and responding to social information, and disruption of such cognitive ability often leads to withdrawal from social interactions (Monferrer et al., 2021). Although disruptions in brain activities related to negative emotions are particularly prominent in individuals with depression, those with anxiety disorders also show significant impairments in recognizing emotional stimuli, especially a heightened identification with expressions of fear (Knyazev et al., 2016).

Emotional tension, a hallmark feature of anxiety, is frequently linked to avoidant and inhibitory behaviors, as well as an increased tendency to perceive obstacles in social and environmental contexts (Knyazev et al., 2016). In depression, reduced social motivation primarily results in challenges with forming and maintaining intimate relationships (Czerwińska et al., 2020; Chen et al., 2019). Heightened sensitivity to negative evaluations—of both self and others - further impairs self-worth and decreases the willingness to participate in social interactions (McEvoy et al., 2013). However, despite a tendency toward social isolation, engaging in social activities often leads to symptom improvement in these individuals (Knyazev et al., 2016).

Dopamine, Serotonin and Oxytocin Interactions on Anxiety and Depression Disorder

Neurotransmitter-based studies have demonstrated that serotonin deficiency compromises dopamine release, suggesting an impairment in reward processing and anhedonia, both of which are core symptoms of depressive disorders (Liu et al., 2018; Kiser et al., 2012; Faure et al., 2022). Dysfunction in this interaction may impair the salience of social stimuli, contributing to reduced motivation for social engagement (Walker & McGlone, 2013; Liu et al., 2018).

In anxiety disorders**,** serotonergic hyperactivity disrupts dopaminergic mechanisms**,** reinforcing avoidant behaviors (Liu et al., 2018; Niederkofler et al., 2015). Key brain regions implicated in these dysregulations include the prefrontal cortex, nucleus accumbens (NAcc), and amygdala, all of which play a central role in emotional and cognitive regulation (Russo & Nestler, 2013).

Alterations in oxytocin levels in individuals with anxiety and depressive disorders driven by impairments in brain regions involved in threat perception and emotional regulation, have been linked to increased social withdrawal, social dysfunction and heightened sensitivity to social rejection (Neumann et al., 2016; Heinrichs et al., 2009; Dodhia et al., 2014).

Emotion and social cognition

Individuals respond emotionally based on their experiences and interpretations (van Kleef et al., 2022; Šimić et al., 2021). However, discrepancies frequently emerge between emotional states and their outward expressions, such as speech, behaviors,

or facial cues. These inconsistencies stem from the influence of social and clinical factors on the neural and psychological mechanisms that govern emotional processing (Karow et al., 2003; Heinrichs et al., 2009).

Non-verbal emotional expressions, such as facial and bodily cues, are essential for universal communication and group cohesion, enabling adaptation to dynamic environments (van Kleef et al., 2022; Šimić et al., 2021). Verbal communication, meanwhile, plays a crucial role in articulating emotional experiences, minimizing misunderstandings, and fostering closeness between individuals (van Kleef et al., 2022; Šimić et al., 2021). This is particularly important given that subjective interpretations often lead to miscommunication (van Kleef et al., 2022; Šimić et al., 2021).

Expressing emotions, such as sadness, can elicit empathetic responses from others and reinforce a sense of belonging, even without physical proximity, particularly when driven by affection and care (van Kleef et al., 2022). The ability to assertively express emotions—whether positive or negative—generally strengthens relationships, in contrast to suppression or indifference, which can weaken connections (van Kleef et al., 2022; Gross J, 2002). However, when emotional expressions are misaligned with the social context, they may lead to relational challenges. Therefore, regulating the intensity, duration, and timing of emotional expressions is essential (Gross J, 2002; Karow et al., 2003). Conversely, some individuals heavily rely on others' emotional expressions to evaluate their own value or abilities (van Kleef et al., 2022). During social interactions, people form self-judgments influenced by the emotions they experience, which in turn shape their social behaviors—whether authentically expressed or modified to seek social acceptance (Müller-Pinzler et al., 2017).

The ability to manage emotions and behaviors in response to social demands is associated with frustration tolerance, the capacity to cope with fear and anxiety, acceptance of solitude, and enjoyment of social interactions (Cole et al., 1994). Recent studies suggest that emotional intelligence and social problem-solving skills are governed by a network of shared brain regions (Oesch. 2024). These studies also explore the hypothesis that individual differences influence social cognition (Oesch, 2024). Dysregulation in these areas is often linked to cognitive dysfunctions, including rigid belief systems and subjective perceptions, which are

commonly observed in psychiatric disorders such as anxiety and depression (Cole et al., 1994; Messina et al., 2021; Oesch, 2024). Promoting cognitive flexibility can help alleviate negative emotional experiences, such as anger, sadness, anxiety, and hopelessness (Cole et al., 1994; Messina et al., 2021).

Emotions significantly influence cognitive processes, with individual approaches to environmental interaction and information interpretation directly shaping social interactions and group dynamics (Storbeck et al., 2007; Wascher et al., 2018). For effective group cohesion, flexibility in action selection is crucial for balancing individual needs with those of the group, facilitating harmonious relationships (Dunbar et al., 2007). As social interactions become increasingly complex, this flexibility requires the development of cognitive skills that enhance information processing, memory retention, and the recognition of signals that improve one's reputation within a group. These skills are also essential for avoiding harmful interactions, further strengthening social cohesion (Frith, 2007).

The interaction between cognition and emotional responses involves dynamic processes in which contextual, emotional, and individual characteristics modulate emotion regulation (Allegretta et al., 2024). Evidence suggests that essential skills for well-being, such as empathy, can influence this interaction in distinct ways, depending on their nature (Thompson et al., 2022). In the study conducted by Thompson et al. (2022), cognitive empathy, characterized by the ability to understand others' emotions without sharing their emotional state, is associated with greater emotional self-regulation. In contrast, affective empathy, which involves sharing another person's emotional state, tends to elicit more automatic emotional responses, making emotion regulation more challenging. This interaction does not occur in a static manner, demonstrating that in contexts of psychosocial stress and in real-time situations, individuals exhibit cognitive or automatic flexibility when regulating their emotions (Yang et al., 2020). To achieve this, different strategies, such as cognitive reappraisal, interoceptive awareness, and mindfulness, are employed to adapt to challenging social situations (Allegretta et al., 2024). Therefore, this dynamic regulation plays a crucial role in social cognitive processing, particularly in emotion recognition and expression. In this context, cognitive reappraisal facilitates a more accurate interpretation of emotional cues, while interoceptive awareness and mindfulness modulate emotional responses,

promoting more adaptive social interactions (Allegretta et al., 2024; Thompson et al., 2022; Yang et al., 2020).

Emotional and Cognitive Regulation

Anxiety and depressive disorders are often marked by changes in emotional and cognitive processes, including heightened emotional suffering, self-criticism, and negative social interpretations (Knyazev et al., 2016; Cisler et al., 2010; Porcelli et al., 2019). These changes are evidenced by avoidant behaviors, as individuals with high emotional sensitivity often evade discomfort, such as anxiety (Feldner et al., 2006). Thus, the way an individual experiences and expresses emotions can profoundly affect their mental health and ability to meet social demands (McRae et al., 2020; Saris et al., 2020; Hu et al., 2014).

Emotional dysregulations commonly observed in anxiety and depression disorders may be linked to alterations in neural networks, as outlined in a comprehensive review of the literature (Saris et al., 2020; Yeshurun et al., 2021; Porcelli et al., 2019; Russo et al., 2013). These dysregulations manifest as self-referential criticisms, increased vulnerability to rejection, and avoidance of social demands, such as the motivation to cooperate or compete (Porcelli et al., 2019; Czerwińska et. al 2020). Psychological suffering, exacerbated by diminished cognitive self-control, ineffective coping strategies, and difficulties in cognitive reappraisal—especially in social situations—often leads to hypervigilance and a sense of alienation in individuals with anxiety and depression (Cacioppo et al., 2009; McRae et al., 2020). Hypoactivation of brain regions essential for cognitive reappraisal may explain why these individuals are more likely to resort to suppression, rumination, and avoidance as strategies to reduce the intensity and expression of negative emotions (Porcelli et al., 2019; Saris et al., 2020; Kalokerinos et al., 2017; Cludius et al., 2020; Aldao et al., 2010). Rumination can lead individuals to engage in avoidance behaviors concerning their disturbed mental states. Similarly, suppression does not alter the subjective experience of emotions but rather inhibits

their outward expression (Aldao et al., 2010; Cludius et al., 2020; Kalokerinos et al., 2017). Such coping strategies for managing emotional vulnerabilities are frequently linked to isolation and temporary relief from the perceived demands of social interactions experienced by individuals with anxiety and depression (Saris et al., 2020; Yeshurun et al., 2021). In this regard, the studies conducted by Cacioppo et al. (2009) highlight the interplay between the sensation of disconnection associated with the quality of social interactions and cognitive alterations. This suggests that a temporary relief may occur when individuals, as a defensive mechanism, avoid what they perceive as social demands (Heinrich et al., 2006; Porcelli et al., 2019; Saris et al., 2020)

Discussion

Empirical evidence suggests that social isolation may heighten vulnerability to anxiety and depressive disorders, as the absence of social interactions is associated with increased stress reactivity and impaired emotional regulation (Cacioppo & Hawkley, 2009). Prolonged isolation can induce dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, leading to elevated cortisol levels and an exaggerated response to aversive stimuli (Sandi & Haller, 2015). Furthermore, the lack of social reinforcement may attenuate dopaminergic system activity, thereby compromising motivation and diminishing the hedonic value of social interactions (Russo & Nestler, 2013; Nguyen et al., 2020).

Another important aspect is that the predominance of negative emotions in anxiety and depressive disorders is associated with increased threat perception, emotional dysregulation, and social withdrawal (Cisler et al., 2010; Porcelli et al., 2019; Nguyen et al., 2024). Preclinical studies using high-anxiety rat models have also demonstrated reduced social interest and increased freezing behavior**,** further reinforcing the link between anxiety-related traits and social avoidance ((Bezerra-Karounis et al., 2020). Notably, when these animals are subjected to social isolation,

depressive-like behaviors tend to diminish**,** suggesting a potential protective effect of isolation in certain contexts (Peçanha et al., 2024). Moreover, neuroimaging studies in humans highlight structural and functional alterations in the medial prefrontal cortex (mPFC), amygdala, and orbitofrontal cortex (OFC)**,** supporting the notion that impairments in social signal processing may contribute to social withdrawal (Saris et al., 2020; Yeshurun et al., 2021; Porcelli et al., 2019; Russo et al., 2013). From a cognitive perspective**,** increased rumination and heightened attentional bias toward negative stimuli further reinforce subjective social isolation exacerbating avoidant behaviors (Knyazev et al., 2016; Pan et al., 2019; Porcelli et al., 2019; Nguyen et al., 2024; Taylor et al., 2018; Nguyen et al., 2020). This paradox may be partially explained by the role of chronic stress in modulating neural circuits involved in social motivation. Persistent hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis, often observed in individuals with anxiety and depression, can contribute to heightened vigilance and increased avoidance behaviors (Sandi & Haller, 2015; Knezevic et al., 2023).

Social isolation, when adopted as an avoidance strategy by individuals with anxiety and depressive disorders, may serve as a coping mechanism to mitigate the emotional burden associated with social interactions (Porcelli et al., 2019). An alternative hypothesis suggests that dysfunction within the dopaminergic reward system may contribute to reduced motivation for social engagement (Saris et al., 2020).

Although withdrawal from social interactions may temporarily alleviate the emotional burden in these individuals, clinical interventions should prioritize the promotion of high-quality social engagement, addressing both vulnerability to isolation and the challenges individuals face in social contexts. Cognitive Behavioral Therapy (CBT) has long demonstrated efficacy in cognitive restructuring and the modulation of adaptive responses for various mental disorders (Hofmann et al., 2012). With advancements in research, studies such as those by McRae & Gross (2020) emphasize the integration of cognitive reappraisal and emotional regulation strategies, as utilized in CBT, to enhance social resilience in individuals with anxiety and depressive disorders. Neuroimaging studies highlight the ability of cognitive reappraisal to activate the prefrontal cortex, thereby reducing amygdala hyperactivity and adjusting emotional responses. In clinical practice,

graduated exposure, systematic desensitization, and the modification of dysfunctional beliefs are widely implemented to reduce emotional avoidance and enhance coping strategies in anxiety-provoking situations (Goldin et al., 2008; Buhle et al., 2013; Ochsner et al., 2004; Silvers et al., 2015). Furthermore, integrated with CBT, Mindfulness-Based Stress Reduction (MBSR) and Mindfulness-Based Cognitive Therapy (MBCT) have been increasingly incorporated into the treatment of anxiety and depressive disorders, demonstrating significant structural and functional benefits (Guendelman et al., 2017). These interventions contribute to emotional regulation, attentional control, and self-referential processing, facilitating prosocial behaviors (Guendelman et al., 2017). Mindfulness practices can be applied individually or in group settings, effectively reducing rumination and enhancing treatment outcomes across different therapeutic modalities.

Emotion-Focused Therapy (EFT), which centers on transforming distressing emotions, facilitates experiential processing and the restructuring of maladaptive emotional schemas (Warwar, 2024; Greenberg, 2010). This approach emphasizes empathy and experiential interventions, such as emotional evocation techniques, to foster emotional regulation and interpersonal skill development (Warwar, 2024; Greenberg, 2010). As indicated by several studies, Emotion-Focused Therapy (EFT) has proven to be effective in addressing symptoms commonly observed in anxiety and depression disorders, such as self-criticism and feelings of disconnection, thereby promoting emotional regulation (Shahar, 2020; Greenman et al., 2022)

Given that managing worry and emotions represents a primary challenge for individuals with anxiety disorders, Dialectical Behavior Therapy (DBT)—which incorporates emotional regulation techniques, distress tolerance, mindfulness, and interpersonal effectiveness training—has emerged as an effective intervention for enhancing cognitive flexibility and emotional regulation (Lee et al., 2023). Originally developed for borderline personality disorder, DBT has demonstrated significant benefits in improving cognitive flexibility and emotional control in individuals with anxiety disorders, particularly generalized anxiety disorder (GAD) (Lee et al., 2023).

Considering the structural and functional alterations common to anxiety and depressive disorders, as well as the challenges associated with their treatment, integrating emotional regulation techniques, cognitive flexibility training, mindfulness, and interpersonal skills development becomes essential for optimizing treatment efficacy. The literature suggests that in cases of comorbidity between anxiety and depressive disorders, greater symptom severity may necessitate a combination of psychological and pharmacological interventions to achieve optimal therapeutic outcomes (Goodwin et al., 2021).

Limitations

Like any narrative review, this study has some limitations that should be considered. While it provides a comprehensive synthesis of the literature on the interplay between social isolation, anxiety, and depressive disorders, it lacks the systematic rigor of meta-analyses, making it susceptible to selection and publication biases. The heterogeneity of study designs, including differences in sample sizes, methodologies, and assessment tools, may limit the generalizability of findings. Additionally, most studies reviewed are cross-sectional, restricting conclusions about causality and the long-term impact of social isolation on mental health. Although this review focuses primarily on neurobiological mechanisms, it is important to acknowledge the role of sociocultural and environmental influences, which require further exploration. Moreover, the potential influence of confounders, including personality traits and pre-existing psychiatric conditions, was not systematically addressed, which may impact the interpretation of results. These limitations do not diminish the value of the findings but highlight opportunities for future research to incorporate longitudinal studies and a more integrative approach to better understand the complex relationship between social isolation, anxiety, and depression.

Conclusion

Social relationships are essential for physical and mental health, playing a key role in fostering a sense of belonging - an intrinsic human predisposition. Within this framework, social isolation is widely recognized as a major risk factor for numerous illnesses, such depression and anxiety. While patients with anxiety and depressive disorders may find temporary relief from social stressors through isolation, their fundamental need for social connection remains critical. An understanding of the neurobiological mechanisms that drive social interactions, as well as the integration of social and personal information is essential for promoting healthy interpersonal relationships in clinical settings. In this regard, assessing the impact of relational difficulties is critical, especially since these challenges frequently emerge from anxiety and depressive disorders. Identifying the neurobiological foundations linking the social and cognitive aspects of these disorders is imperative. Such insights may pave the way to understand the interplay between these factors and support the development of more effective therapeutic interventions. This understanding is particularly important in strengthening the therapeutic alliance between patient and therapist, thereby enhancing treatment outcomes.

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4. General discussion

The primary objective of this dissertation was to explore the relationship between social isolation and anxiety and depression disorders. To achieve this, Carioca rats selected for high and low conditioned freezing were subjected to social isolation for 14 days, after which their behavior was analyzed using the Forced Swim Test. In addition to this specific aim, the research also provided an exploratory perspective on the neurobiology of anxiety and depression disorders, considering the high prevalence of comorbidity between these conditions and their impact on social interactions. By analyzing the latency time to cessation of swimming in the CHF, CLF, and CTL groups under both isolated and grouped conditions, we observed the significance of social interactions as a potential source of stress and relief from depressive-like behaviors. Through our analysis of the interference of these disorders, we found that dysfunctional interactions can exacerbate psychological distress; consequently, our findings may assist psychologists in effectively addressing these individuals with appropriate interventions

The study involving animals indicated a potential phenomenon of contagion stress among those exhibiting high levels of conditioned freezing behavior while remaining in groups. This finding suggests that the exacerbated expression of fear can interfere with the emotional states of conspecifics cohabiting the same enclosure, even in the absence of any aversive stimuli (Chun et al., 2022; Debiec & Olsson, 2017; Dimitroff et al., 2017; Peen et al., 2021). We formulated this hypothesis when we observed that the animals exhibiting high conditioned freezing behavior, when isolated, demonstrated a longer latency period before ceasing swimming, which implies a relief from depressive-like behavior.

The extensive literature review has revealed the inherent human tendency to interact and develop through social interactions, as well as the neurobiological alterations present in anxiety and depression disorders that clearly impair pro-social behaviors. This underscores the necessity of empathy, active listening, collaboration, and respect for the socialization boundaries that individuals affected by these disorders may temporarily endure. The common feeling of well-being that arises from social engagement is not always experienced by these individuals, who often grapple with

compromised perceptual and interpretative abilities (Cacioppo et al., 2009; McRae et al., 2020). Consequently, their resilience to withstand the demands of socialization is diminished, leading to a prevalence of avoidant behaviors as a means to reduce emotional activation (Heinrich et al., 2006; Porcelli et al., 2019; Saris et al., 2020).

5. Final considerations

The consequences of anxiety and depression disorders have considerable effects on social interactions. Exacerbated perception of danger, emotional contagion due to stress, and impaired evaluative capacity are significant factors that can lead to a diminished pursuit of social engagement. When we take into account the challenges posed by the persistent mental disturbances experienced by individuals with anxiety and depression, we recognize the necessity for support that respects their unique experiences. Therefore, it is essential for professionals such as psychologists and discomforts that often transcend the logic of human nature, such as the duality of social interactions.

Both studies present limitations that underscore the need for further investigations. Nonetheless, they provide a clear understanding of how the changes associated with anxiety and depression disorders affect the perceived quality of social relationships. This connection highlights the importance of deepening our knowledge of these disorders and their implications for social interactions, which may contribute to the development of more effected comprehensive interventions.

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