Review Article

ASSOCIATION BETWEEN MATERNAL-NEONATAL SEPARATION STRESS AND THE DEVELOPMENT OF ALGIAS IN PRECLINICAL TRIALS: AN INTEGRATIVE LITERATURE REVIEW

ABSTRACT

Introduction: Maternal separation (MS) is a frequent neonatal stress experience, given the diverse social inequalities and needs in modern society. It is known that social losses or separations are experiences that considerably affect people's psychological patterns, but there is still no review of the associations between the stress caused by the separation of mothers from their children and its impact on the onset or increase in pain. From this perspective, the study in question aimed to review the literature in an integrative manner to seek to elucidate the association between neonatal MS and the onset or increase in pain in later stages of life, in animal models.

Methodology: For this purpose, the PubMed, Web of Science, Embase, Scopus, Lilacs and Google Scholar databases were used, without date or language restrictions, to search for related literature, using the "PICO" strategy.

Results: A total of 843 articles were found and, after applying the inclusion and exclusion criteria, a total of 35 articles were selected for this review, all of which were in animal models. Evidence indicates that the experience of neonatal MS is associated with the development of not only psychological but also neurophysiological disorders, which tend to reduce the threshold of sensitization of nociceptors, amplifying their receptivity to stimuli, generating painful sensations of varied natures and through different mechanisms, inherent to each type of pain generated.

Conclusion: However, despite advances in research, new studies still need to be conducted focused on Orofacial Pain, since there is only one study on this topic.

Keywords: Pain. Maternal Separation. Acute Pain. Chronic Pain. Orofacial Pain.

1. INTRODUCTION

In organized civil society, it is a fact that situations of social loss or social separation are among the most painful psychosocial experiences that humans go through, especially in the psychological field. Over the last few decades, several researchers have asked themselves whether such experiences, in addition to promoting considerable psychological changes in people, also have the capacity to promote physiological disorders that could stimulate painful sensations not only in the realm of ideas, but also in a nociceptive way. And

yet, evidence has shown that the neurobiological substrates and neural pathways of physical and emotional pain do, in fact, overlap [12, 37, 33, 32].

Studies have shown that the level of psychological and neurophysiological impairment associated with pain varies across life stages, with much greater impacts in early life than in later life. It is therefore believed that traumatic social experiences during early life, more specifically in the period from 0 to 6 years of age, not only induce mood impairment but also cause lasting changes in pain processing systems, which may contribute to increased sensitivity to pain in later life stages. Thus, a better understanding of the overlap between emotional and physical pain may reveal factors that contribute to physical pain and facilitate the development of therapies for pathological conditions, including mood disorders, based on a concept of 'total pain', which encompasses all subdivisions and nuances of the pain experience [12, 25, 33, 32].

The analysis of studies on the subject showed that many researchers have focused on the role of stress in pain, considering the psychological aspect of pain. In general, stress maintains and amplifies the severity of pain. The acute stress response is beneficial because it protects the individual from damage and injury and is essential for adapting to and surviving adverse situations. However, if an individual is exposed to stress for a long period, adaptation to stress is impaired, and pathological changes such as hypercorticism and mood disorders may appear. Several studies have shown that the pain response and associated damage are increased under physically stressful conditions. However, little is known about whether psychosocial stress in childhood, presumably leading to subsequent emotional impairment, is related to the expression or development of acute or chronic pain in adulthood [12, 9, 33, 32].

Various situations can result in the separation of newborns from their mothers, especially when all the inequalities and social needs that exist in the world are considered. Given this scenario, a hypothesis that has long been raised by researchers was whether an experience of maternal separation (MS) would have the capacity to generate both psychological and physiological changes that would exacerbate painful sensations or increase sensitivity to the development of pain during later stages of life, such as adolescence and adulthood. Based on this hypothesis, studies were carried out with animal models of MS to observe its relationship with painful characteristics [24, 34, 23, 29].

Neonatal exposure to stressful environments has been widely believed to be associated with deficiencies in brain development and adult behavior. Stress, physical abuse, and mental neglect in newborns and children are major environmental risk factors associated with the development of visceral pain and multiple psychiatric disorders, such as major depressive disorder and anxiety disorders [44, 48, 38, 18].

Studies in animal models have observed that neonatal stress is established by the interruption of mother-infant interaction through repetition of the MS paradigm, altering the normal response of the hypothalamic-pituitary-adrenal (HPA) axis and the neuroimmune response to stress. This modeling leads to the enhancement of neuroendocrine and neuroinflammatory responses in rodents and has adverse effects on rodent brain anatomy and function, synaptic plasticity and emotional responses in adulthood [24, 34, 23, 2].

Other studies also consider MS as a model of early stress that can affect postnatal development, in addition to inducing neurodevelopmental disorders and altering the morphology of the prefrontal cortex, hippocampus and glial cells in rodents. Furthermore, studies indicate that maternal separation can induce abnormal responses to stress and

painful stimuli and is known to modulate serotonergic transmission in adulthood [20, 19, 26, 16].

Existing evidence also indicates that, among the molecular mediators involved in nociceptive transmission and the onset of neuropathic pain, several key players such as the glucocorticoid receptor, glutamate receptors and transporters, cytokines and neurotrophins are modulated by MS experiences. Thus, it seems plausible that MS may have an impact on neuropathic pain vulnerability, at least in a subset of individuals. Furthermore, alterations in the neuroimmune and/or neuroendocrine systems induced by chronic stress may facilitate or hinder the development of chronic pain independently of classical stress processing pathways [20, 14, 19, 26].

Therefore, given the hypotheses and premises raised regarding the topic in question and, based on the observation that the scientific field has shown interest in elucidating the relationship between MS and pain in recent decades, the objective of the present study was to review the existing literature on MS and pain in an integrative manner. This review aimed to elucidate the association between neonatal MS and the onset or increase in pain in later stages of life, in animal models [48, 38, 18].

2. MATERIAL AND METHODS

The study in question is an integrative literature review, which included experimental studies in animals. The search strategy was developed using the acronym PICO, which stands for:

1. Population (P): Rats and mice.

2. Intervention (I): MS.

3. Comparison (C): Without MS.

4. Outcome (O): Pain.

2.1 Literature search strategy

An integrative literature search was conducted between January and February 2022 in the PubMed, Web of Science, Embase, Scopus, and Lilacs databases. The search was updated on two subsequent occasions, in January 2023 and August 2024, and no other studies that met the inclusion and exclusion criteria were found. The Google Scholar database was used to collect information from the gray literature. Six search strategies (A, B, C, D, E, F) were established, one for each database (Table 1). No language or date restrictions were applied to the search. All results were imported into the Mendeley reference manager (https://www.mendeley.com/), and duplicates were also removed using the Rayyan platform (https://www.rayyan.ai//).

Table 1 – Layout of strategies, platforms and search keys used in the review.

Search platform	Search key
A (PubMed)	((("maternal deprivation" OR "maternal separation")) AND (("Pain" OR "Physical Suffering" OR "Ache" OR "Chronic Pain"))) AND (("rat" OR "mouse" OR "mice"))

B (Web Of Science)	(“maternal deprivation” OR “maternal separation”) AND (“Pain” OR “Physical Suffering” OR “Ache” OR “Chronic Pain”) AND (“rat” OR “mouse” OR “mice”)
C (Scopus)	(("maternal deprivation" OR "maternal separation") AND ("Pain" OR "Physical Suffering" OR "Ache" OR "Chronic Pain") AND ("rat" OR "mouse" OR "mice"))
D (Embase)	('maternal deprivation'/exp OR 'maternal deprivation' OR 'maternal separation'/exp OR 'maternal separation') AND ('pain'/exp OR 'pain' OR 'physical suffering' OR 'ache' OR 'chronic pain'/exp OR 'chronic pain') AND ('rat'/exp OR 'rat' OR 'mouse'/exp OR 'mouse' OR 'mice'/exp OR 'mice')
E (Lilacs)	(“maternal deprivation” OR “maternal separation”) AND (“Pain” OR “Physical Suffering” OR “Ache” OR “Chronic Pain”) AND (“rat” OR “mouse” OR “mice”)
F (Google Scholar)	(“maternal deprivation” OR “maternal separation”) AND (“Pain” OR “Physical Suffering” OR “Ache” OR “Chronic Pain”) AND (“rat” OR “mouse” OR “mice”)

2.2 Inclusion and exclusion criteria

The selection of articles for this integrative review adopted the following inclusion criteria: Studies in Animals (Rats and Mice); Studies with outcomes on changes in nociceptive behavior and nociceptive response; Studies in which the neonatal stress assessed is related to MS. In turn, the exclusion criteria established were Literature Reviews; Studies with Outcomes on Anxiety; Studies on treatments; Studies with outcomes on Visceral Hypersensitivity, but without a direct association with pain; Studies in which the neonatal stress assessed is not through MS; Studies not related to pain; Research not directly related to the theme.

2.3 Data synthesis and analysis

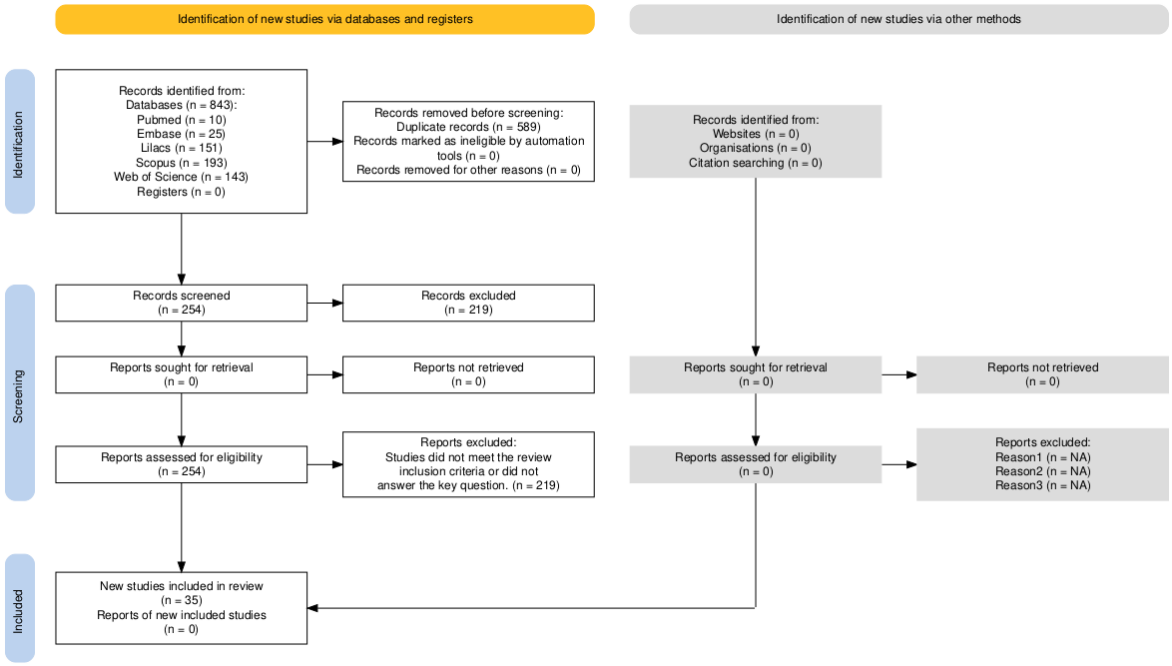
Data were collected including author, year of publication, type of study, type of animal analyzed, age of animals, types of pain, pain locations, controls and experimental groups, pain assessment parameters, pain assessment time, MS time, and study conclusions.

3. RESULTS

3.1 Identification of eligible studies

The search found a total of 843 articles in the evaluated databases and read the gray literature articles found in the first 15 pages of the Google Scholar platform. Duplicates were first removed, and titles and abstracts were then analyzed, resulting in 37 articles. Of the 37 articles, it was found that 2 of the articles did not meet the inclusion and exclusion criteria (Figure 1). Thus, 35 articles were selected for full reading and described as shown in Table 2.

Figure 1 – Flowchart for identifying eligible studies.



Source: Authors

3.2 Description of studies

3.2.1 Animal models

The studies included in the review for full reading are studies conducted with animals. Most of the studies (80.56% - 29/36) were conducted with rats, with the Sprague-Dawley species being the most used in the studies (38.89% - 14/29). Mice were used in (19.44% - 07/36) of the studies, with the NMRI species being the most used (5.56% - 02/07).

3.2.2 Year of publication

Among the 35 studies analyzed, the years 2018 and 2020 concentrated most studies published on the topic in question, with 4 publications (11.43% (04/35)) in each of these years. The first study published on this topic dates to 1995, demonstrating that research on MS and pain is relatively recent. It is also observed that, from 2016 onwards, there was a greater tendency to publish studies on this topic, some of them being developments of previous publications on MS and pain.

3.2.3 Type of pain

Acute and inflammatory pain was the most studied type of pain in association with maternal separation with 11 studies and 30.6% (11/35), followed by Chronic Visceral Hyperalgesia 13.9% (05/35); Peripheral Inflammatory Nociception 11.1% (04/35); Visceral Nociception and Iatrogenic Acute Pain 8.3% (03/35). Peripheral Inflammatory Hyperalgesia, Nociception, Repetitive Acute Nociception, Inflammatory Nociception 5.6% (02/35) each and Neuropathic Pain, Supraspinal Pain 2.8% (01/35) each.

3.2.4 Induction

Regarding the type of nociception induction in animals, induction by Thermal Effect 34.21% (13/35) was the most performed. Inductions by Formalin 23.68% (09/35) and Colorectal Distention-CRD 21.05% (08/35) were also widely used by researchers. Some studies also performed nociception inductions by Needling, Nerve Injury, MS/Spontaneous 5.26% (02/35) each and Subcutaneous Saline Injection, Clamping 2.63% (01/35) each.

3.2.5 Maternal Separation Time

Regarding maternal separation time, most studies, 17.14% (06/35) used maternal separation for 180 min/day, from the 2nd to the 14th postnatal day. 3 studies 8.57% (03/35) studied MS for 180 min/day, from the 2nd to the 15th postnatal day. MS times of 180 min/day, from the 1st to the 21st postnatal day and 180 min/day, from the 2nd to the 12th postnatal day, were used by 2 studies, 5.71% (02/35), each. 3 studies, 8.57% (03/35) did not detail the days of maternal separation, only the minutes/hours (180 min, 240 min/day, 30 min, 4x a day, 4 to 6 hours, 60 min/day). 1 study 2.86% (01/35) used the times of 420 min/day, from the 10th to the 28th postnatal day and 45 min/day, during 3 to 6 days post-birth. 2 studies 5.71% (02/35) performed variable times of MS, and 2 studies 5.71% (02/35) did not mention the time of MS analyzed.

Table 2 – Evaluation parameters and outcomes of the reviewed articles.

Quote	Evaluation parameters	Outcomes
Blass, et al. 1995	Nociceptive behavior; Evaluation of the effect of opioid treatment (Naltrexone); Statistical analysis.	MS was not mediated by MU or kappa opioid receptors.
D'Amato, et al., 1999	Nociceptive behavior; Morphine treatment; Statistical analysis.	MS did not show any action on opioid receptors.
Kalinichev, et al., 2001	Nociceptive behavior; Antinociceptive treatment with Morphine and evaluation; Statistical analysis.	Repeated neonatal MS may alter endogenous opioid systems.
Stephan, et al., 2002	Nociceptive behavior; Lipopolysaccharide (LPS) exposure; Additional tactile stimulation; Effects of chronic imipramine treatment; Statistical analysis.	Neonatal MS may favor pain in adulthood.
Walker, et al., 2003	Nociceptive behavior; Stress tests; Assessment of maternal behavior after the pups are returned to their mothers.	MS can alter the pain physiology of rat pups.
Schwetz, et al., 2005	Nociceptive behavior; WA stress; Experiments with CRF-R antagonists; Treatment with the drug CP-154,526 (Pfizer); Statistical analysis.	Neonatal MS leads to pain in adulthood due to acute stress on the central CRF/CRF 1 R system.
Chung, et al., 2007	Nociceptive behavior; Western-Blot; Immunohistochemistry; Statistical analysis.	Modulations of NGF signaling and MS-induced visceral hyperalgesia are associated.
Zhang, et al., 2008	Nociceptive behavior; Western-Blot; Immunohistochemistry; Statistical analysis.	Positive association between elevated ERK activity and upregulated neuronal sensitivity in MS rats.
De Medeiros, et al., 2009	Nociceptive behavior; Determination of thermal sensitivity with Hargreaves test; Statistical analysis.	Neonatal MS amplifies nociception in adulthood.
Dickinson, et al., 2009	Hargreaves and Elevated Plus Maze tests; Analgesia;	MS leads to changes in thermal

	Statistical analysis.	nociception and sensitivity to buprenorphine and morphine.
Chung, et al., 2009	Nociceptive behavior; Immunohistochemistry; Densitometry measurement; Statistical analysis.	MS modifies BDNF and TrkB in the amygdala-RVM circuit and neuronal response to CRD.
Uhelski, Fuchs; 2010	Nociceptive behavior; Statistical analysis.	MS may be related to peripheral nociception in adolescents or adults.
Hu, et al., 2012	Nociceptive behavior; Cell labeling; Dissociation of dorsal root ganglion (DRG) neurons and patch-clamp recording; Isolation of sodium (Na V) currents; Immunohistochemistry; Real-time PCR for Na V 1.8 mRNA; Statistical analysis.	MS significantly increased the visceromotor response to nociception.
Burke, et al., 2013	Nociceptive behavior; PT-PCR; Statistical analysis.	MS induces sexually dimorphic effects on nociceptive behavior.
Mikhailenko, et al., 2015	Nociceptive behavior; Elevated Plus Maze Test (Anxiety); Forced Swimming Test (Depression); Spatial Learning Ability in Aquatic Maze; Statistical analysis.	MS causes a long-term increase in formalin-induced tonic pain in adolescent rats.
Butkevich, et al., 2016	Nociceptive behavior; Maternal behaviors; Statistical analysis.	Neonatal MS increases sensitivity to peripheral inflammatory pain during adolescence.
Juif, et al., 2016	Nociceptive behavior; Electrophysiological recordings and analysis; Patch-clamp analysis; Immunofluorescence; Histological analysis; PCR; Statistical analysis.	MS can lead to changes in the function of nociceptive pathways.
Barr, Butkevich, Mikhailenko; 2016	Nociceptive behavior; Immunohistochemistry; Histological analysis; Serotonergic cell count; Statistical analysis.	MS reduces 5-HT immunoreactive cells in the dorsal root ganglion.
Yasuda, et al., 2016	Nociceptive behavior (Von Frey test); Serum CORT levels; P2X3R expression in TG neurons; Effect of P2X3R antagonist on mechanical allodynia; CORT receptors in TG neurons; Statistical analysis.	MS resulted in orofacial mechanical hypersensitivity in adulthood.
Nakamoto, et al., 2017	Nociceptive behavior; Elevated plus maze test; Partial sciatic nerve ligation; Immunofluorescence; Evaluation of cultured astrocytes; Evaluation of lipopolysaccharide stimulation of astrocytes; Evaluation of astrocytes after microinjection of supernatant; Statistical analysis.	MS-related astrocytes are sex-dependently activated in the Lateral Cortex (LC).
Amini-Khoei H, et al., 2017	Nociceptive behavior; Investigation of the role of the Otergic and Opioidergic systems in the modulation of nociception in MS state; Assessment of Restraint Stress; Statistical analysis.	MS induced abnormal nociceptive responses, mediated by opioidergic and OT-ergic systems.
Vilela, et al., 2017	Nociceptive behavior; Animal weight; Assessment of maternal behavior; Statistical analysis.	MS increased pain sensitivity in adult offspring.
Mooney-Leber, et al., 2018	Observation of maternal care (in pups wrapped in tea balls); Tissue collection with magnetic resonance	MS increased cortisol levels and altered glutamate levels in the

	spectroscopy (MRS) imaging; Statistical analysis.	frontal cortex and hippocampus.
Melchior, et al., 2018	Nociceptive behavior; Forced swimming stress; Inflammatory pain and influence of Carrageenan; In vivo spinal cord neuron analysis; Spinal cord PCR analysis; Neonatal rescue pharmacological treatment; Statistical analysis.	MS induced basal pain hypersensitivity and oxytocin receptor dysfunction.
Zhang, et al., 2018	Drug administration (P2X3 receptor agonist and P2X3 receptor antagonist); Western blotting; Histological evaluation of brain tissue; Histology and immunofluorescence studies; Real-time quantitative PCR; Statistical analysis.	Purinergic signaling in the Right Insular Cortex may lead to visceral pain under MS.
Mizoguchi, et al., 2018	Nociceptive behavior (Von Frey); Sucrose Preference Test; Social Interaction Test; Forced Swimming Test; Crossed-Plus Maze Test; Immunohistochemistry; Statistical analysis.	MS is associated with pain.
Ströher, et al., 2019	Nociceptive Behavior; Anxiety-Like Behavior; Exploratory Behavior and General Measures of Activity; Neuromotor Reflexes; Statistical Analysis.	MS anticipates the maturation of inhibitory nociceptive pathways.
Burenkova, et al., 2019	Nociceptive Behavior; Administration of Sodium Valproate and evaluation of early stress through the involvement of epigenetic mechanisms.	Neonatal MS reduces maternal care and causes pain in adulthood, which can be treated.
Du, et al., 2019	Nociceptive behavior to CRD; Drug administration (Butoxamine, Propranolol, Phentolamine); Norepinephrine (NE) measurement in blood plasma; Western blotting; Real-time qPCR; Dissociation of DRG neurons and whole-cell patch-clamp recordings; Statistical analysis.	MS is associated with visceral pain.
Hu, et al., 2020	Nociceptive behavior (After colorectal distension and AMS protocol); Evaluation of treatment with Butoxamine (BUTO); Western Blotting; Real-time PCR; Immunofluorescence; Statistical analysis.	MS potentiates visceral hyperalgesia.
O'Sullivan, et al., 2020	Nociceptive behavior; Quantification of endocannabinoid levels in the PFC using LC-MS/MS; Expression of endocannabinoid-related catabolic enzymes and receptors in the PFC; Statistical analysis.	MS alters brain physiology and amplifies nociceptive sensitivity in adulthood.
Borzadaran, et al., 2020	Nociceptive behavior; Statistical analysis.	MS leads to thermal hyperalgesia, in addition to inducing pain.
Paniagua, et al., 2020	Nociceptive behavior and body weight; Electrophysiological recordings using the in vitro skin-saphenous nerve preparation in males; Statistical analysis.	Only a longer time interval of MS induces nociceptive changes in adulthood.
Chang Li, et al., 2021	Nociceptive Behavior, Electrophysiological Analysis, Western Blotting, Immunofluorescence, Real-time Quantitative PCR, Drug Administration, Data Analysis.	MS increases visceral sensitization and nociception in animals with Irritable Bowel Syndrome (IBS).
Vilela, et al., 2021	Nociceptive behavior; Treatment with fluoxetine or	MS increases pain sensitivity in

	desipramine, under saline vehicle, applied by intrathecal injection; Immunohistochemistry; Statistical analysis.	the locus coeruleus.

3.3 Discussion

The study in question analyzed the correlation between stresses generated by MS and its repercussions related to the appearance or increase of pain in later stages of life, in adolescence or adulthood, in animal offspring. With this integrative review, it was observed that studies show that there are associations between neonatal stresses of MS and the appearance or increase of pain during adolescence and adulthood.

Regarding changes in the pattern of nociceptive behavior, studies [3, 13, 15, 47, 6, 33, 7, 52, 44, 37, 4, 38, 48] have shown that the levels of nociceptive responses to thermal or mechanical stimuli that induce acute or chronic pain were always higher in groups of animals under MS than in groups without MS stress, even in animals pretreated with analgesic drugs. Studies also indicate that the longer the period of MS, the higher the levels of nociception when assessing nociceptive behavior.

Regarding changes in physiological patterns, evidence [27, 10, 11, 54, 21, 6, 53, 36, 1, 34, 53, 44, 16] reveals the existence of modifications in cellular signaling, electrophysiological and receptor patterns, in addition to a reduction in the threshold of nociceptor sensitization in animals under MS, compared to animals that did not undergo this neonatal stress. Changes in signaling and receptors of the opioid system were also observed in animals under MS, which indicate the participation of opioid receptors in nociception mediated by MS and a potential antinociceptive treatment pathway, to be explored pharmacologically.

More specifically regarding the oral and maxillofacial complex, a single study [52] demonstrated an association between neonatal stress caused by MS and the development of orofacial pain, in which it was observed that MS induced mechanical allodynia in mice. The study in question showed an increase in the number of TG P2X3R-IR neurons in the whisker skin of mice, which was induced by increased CORT signaling, which was directly associated with MS, which resulted in orofacial mechanical hypersensitivity in the animals when they reached adulthood.

Acute and chronic pain are also caused by MS. The association between acute pain, of diverse and idiopathic causes, and the experience of MS in animals has been reported [3, 13, 27, 43, 51, 15, 52, 1, 50, 35, 5, 37, 8, 38]. These authors observed that the stress caused by MS generates greater sensitization in nerve fibers that conduct acute nociceptive stimuli to the central nervous system, and that, therefore, the thresholds for immediate pain sensation, in thermal or mechanical tests, were reduced in animals separated from their mothers, when compared to animals that did not undergo such stress.

Regarding chronic visceral pain resulting from Irritable Bowel Syndrome (IBS) and MS, the authors [42, 53, 54, 10, 11, 17, 22] investigated whether there were relationships between IBS and the stresses caused by MS, finding that MS increases the levels of visceral sensitization and, consequently, visceral nociception in animals with IBS, as well as increases the levels of nociceptive markers and the activation of signaling pathways, from the dorsal horn of the spinal cord, reducing the sensitivity levels of these neurons and favoring the pain caused by IBS. MS, therefore, amplifies the effects generated by IBS.

Other types of pain investigated to assess the existence of associations with MS were inflammatory, peripheral, neuropathic, and supraspinal pain, as well as nociception generated by direct exposure of nervous tissue to the external environment. In all the reviewed literature, the pain characterized as inflammatory was induced by Formalin (10% Buffered Formalin), a classic pro-inflammatory chemical agent that is well established in the literature as a model of inflammatory pain in animals. Thus, the literature [31, 33, 48, 49, 4, 36] reported the presence of a relationship between MS and the exacerbation of inflammatory nociception caused by the injection of formalin into the tissues of animals. Physiologically, the studies observed that MS increases the animal's sensitivity to painful chemical stimulation and reduces the activity of serotonergic neurons in the dorsal raphe nucleus and noradrenergic neurons in the locus coeruleus, in animals treated with Formalin and subjected to maternal deprivation stress, which may explain the mechanism of action that favors the interrelationship between both factors.

The association between peripheral pain and MS has been reported by studies [47, 7, 32]. This evidence indicates that MS promotes neurochemical changes in type C sensory neurons and increased synaptic inhibition in spinal cord neurons. It was also observed that MS promotes a spinal inhibitory barrier that prevents the excitation of WDR neurons by nociceptive synapses of type C fibers. MS also significantly increased nociceptive responses to formalin and decreased the number of 5-HT-immunoreactive neurons in the dorsal root ganglion in animals under MS, compared with animals in the control group, revealing an association between MS occurring during childhood and repercussions in terms of peripheral nociception in adolescents and adults.

The association between neuropathic pain and MS was evaluated [35]. It was observed that MS stress induced an increase in GFAP protein expression in the lateral cortex area of female mice, but not in males, concluding that sex-dependently activated astrocytes in the lateral cortex, as indicated by increased GFAP expression, are related to increased anxiety-like behavior. These MS stress-induced activated astrocytes in the lateral cortex may contribute to the exacerbation of neuropathic pain. It was also noted that male mice may acquire resistance to MS-induced stress during growth.

Supraspinal pain has been linked to MS [43], as it has been observed that MS can alter supraspinal and spinal pain pathways, especially in short periods of exposure to the stressor. MS can also lead to dysfunction of the hypothalamic-pituitary-adrenal axis throughout life, resulting in increased serum corticosterone; in addition, MS increased exploratory activity in males and reduced it in females, showing a sex-dependent effect.

A study [34] evaluated the association between MS and nociception induced by surgical procedure of sciatic nerve exposure and observed that MS induces abnormal behavior in adult mice. Treatment of animals with fluoxetine improved anxiety- and depression-like behavior induced by MS. Neuropathic pain was aggravated in mice with MS, and treatment with fluoxetine after MS inhibited the increase in neuropathic pain. Microglia were activated to a greater degree in the spinal cord of mice that underwent MS stress.

4. CONCLUSION

It has been observed that there are associations between the most different types of pain (acute, chronic, orofacial, inflammatory, peripheral, neuropathic, supraspinal and others) and the stresses caused by MS in rat and mouse pups. MS occurring during the neonatal period also promotes changes in the nociceptive, social and emotional behavior of adolescent and adult animals, making them more susceptible to pain. Regarding the association between MS and orofacial pain, only one study has been carried out, and there

are still no studies regarding the analysis of the association between Temporomandibular Disorders (TMDs) and the stress of MS. Furthermore, it is concluded that MS stress can promote physiological and behavioral changes in animal pups, leading them to develop or increase pain in adolescence and adulthood.

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DEFINITIONS, ACRONYMS, ABBREVIATIONS

MS/NMD/NSM/MSSI/MD/MR/EMS: Maternal Separation/Maternal Deprivation

CRD/CKD: Colorectal Distention

IBS: Irritable Bowel Syndrome

DS: Sprague-Dawley

MAS/MAS/WA: Multiple Adult Stressors

NE: Norepinephrine

PCR: Polymerase Chain Reaction

DRG: Dorsal Root Ganglion

HPA: Hypothalamic-Pituitary-Adrenal Axis

MRS: Magnetic Resonance Imaging

CL: Lateral Cortex

FOR: Formalin

SAL: Saline

COM/SHAM/NAÏVE: Control

5-HT: Serotonin/Serotonergic(s)

PFC/CPF: Prefrontal Cortex

PN: Postnatal

IMI: Imipramine

LPS: Postnatal Endotoxin

SNL: Spinal Nerve

EE: Enviromental Enrichment