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A Systematic Review on the Effect of Pain on Short-Term Memory in Preclinical Studies

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Abstract

Background: This study is about one of the most important non-physical consequences of pain; Pain can affect a patient's memory and quality of life. Understanding such a relationship can enable clinicians, friends, family, employers and coworkers to implement appropriate interventions to mitigate the consequences of such problems.

Material and methods: The purpose of this study was to evaluate and compare the results of articles that investigated different memory tests for various kinds of pain in animals. Therefore, databases including MEDLINE, EMBASE, SCOPUS, and Web of Science were searched. The primary eligibility criteria for inclusion was whether STM and/or WM were measured as an outcome variable in an animal study involving neuropathic pain. The risk of bias criteria for animal studies were applied.

Results: Finally, by removing unrelated articles, 13 studies met the inclusion criteria. There is sufficient evidence to support the hypothesis that NP disrupts STM and WM in the animal model. Such effects are probably due to structural changes in different areas of the brain, such as the hippocampus. Lesion side, age and gender hormones can also play a role in mediating hypersensitivity to pain and its effect on learning and memory.

Conclusion: The results of studies have shown that pain can cause STM and WM impairment. The small number of articles on the relationship between acute pain and memory, as well as studies that have examined the structural relationship between the brain and memory and pain, are the main limitations of this study.

Keywords: Pain; Memory; Short term Memory; Working Memory

Background

Although 'pain' is difficult to define, the IASP latest definition is: an unpleasant sensory and emotional experience associated with actual or potential tissue damage," and that the accompanying notes to a bulleted list containing the etymology [1]. In animals, pain can be measured through behavior [2]. If pain is a purely physical experience, the only behavioral changes we expect to observe in humans and animals are avoidance, such as avoiding contact or movement in the affected area. Cognitive functions would be expected to remain unaffected but according to published results, cognition and behavior also change after pain [3-8].

Neuropathic pain (NP) is a type of pain that is associated with damage to the central or peripheral nervous system and may detect in areas with no tissue damage [9]. Its symptoms include hyperalgesia (increased sensitivity to pain) and allodynia (Sensitive to pain with stimuli that are not painful) and are usually accompained by cognitive and emotional complaints such as confusion, anxiety and depression [1,9-10]. Recent clinical studies have reported that patients with pain also suffer from memory deficits resulting in impairments in their daily life activities to such an extent that it negatively affects their quality of life [6,8,11].

In studies of the hippocampus of animal models of chronic pain, some histological changes have been reported in areas which are primarily related to stress depression and learning but also play a causal role in memory [12-14]. On the other hand, studies in humans and animal models have shown metabolic and morphological changes occurs in the brain with pain which

may lead to memory loss [15]. Pain induced memory loss has recently attracted the attention of researchers.

Classically, memory is generally divided into two categories; shortterm memory (STM) and longterm memory (LTM) ([16,17]. Currently, this classification is considered a basic principle in modern cognitive psychology [18]. Some researchers consider STM and working memory (WM) to be different theoretical concepts reflecting different cognitive functions [19]. It is argued that STM relates to unprocessed information whilst WM is where some level of interpretation ("manipulation") is involved. However, correlation studies have not been able to separate both constructs consistently and there is evidence of large or even complete overlap [19,20].

Studies have shown that impairment of both STM and WM reduce person general aptitudes and interfere with their daily life [21,22]. For example, certain situations, such as intension, depend on WM [10]. WM is also sometimes applied to a much broader concept. For example, long-term information storage is attributed to working memory. In addition, many of our day to day tasks rely on WM [23-25]. Other WMrelated functions include reasoning, mindfulness, quick and fluid reasoning, coordinated processing, intelligent and attention.

STM is thought to hold symbols that are not yet present in LTMand its impairment will have lasting effects. The ability to learn new relations between familiar stimuli, new words and new digit arrangements is impaired in patients suffering from STM disorders [6].

Despite the above general differences, in current literature, the terms STM and WM tend to be used interchangeably and inconsistently. In this study, we treated the two constructs as being equivalent unless the researchers made specific distinctions between STM and WM.

There are review articles on the relationship between memory and pain, especially the works of Sandkühler [26], Cunha [27], Almeida [28], Liu [29] and Moriarty [30] however; these have not been systematic reviews.

Of course, there have been review studies that have looked at the relationship between pain and memory in human particularly by Berryman [31] and Mazza [32], but a systematic review of animal studies offers several advantages.

Animal studies have fewer practical limitations that allow for more extensive studies. Second, the comparison of animal and human studies allows us to evaluate the extent to which animal models are applicable to humans.

In addition, comparisons of human and animal studies can highlight technical and conceptual factors that may be critical in interpreting observations such as the importance of the correlations between pain and memory and their causes, drug treatment history, behavior and attention. Animal studies allow these factors to be considered more closely. Lack of such complementary information can lead to erroneous conclusions [32,33].

Materials and methods

Search strategy, inclusion and exclusion criteria and data extraction

The following electronic databases were used to identify relevant studies; PubMed, SCOPUS, Web of science, Embase and Google Scholar. An example of the search strategy (for Web of Science) is shown in table 1. Searches included all studies up to April 2, 2020 and language restrictions were not applied. Given that, the same search strategy does not work in different databases, so a separate search was written for each database.

Table1: Designed search strategy of applied keywords in Web of Science.

Pain AND memory AND TS= ("Memory, Short-Term*" OR "Memories, Short-Term" OR "Memory, Short Term" OR "Short-Term Memories" OR "Short-Term Memory" OR "Memory, Shortterm" OR "Memories, Shortterm" OR "Shortterm Memories" OR "Shortterm Memory" OR "Working Memory" OR "Working Memories" OR "Memory, Immediate" OR "Immediate Memories" OR "Immediate Memory" OR "Memories, Immediate" OR "Immediate Recall" OR "Immediate Recalls" OR "Recall, Immediate" OR "Recalls, Immediate") AND TS= ("Neuralgia*" or "Neuropathic Pain" OR "Pain" or "Neurodynia" or "atypical Neuralgia" or "Iliohypogastric Nerve Neuralgia" or "Iliohypogastric Nerve Neuralgias" or "Paroxysmal Nerve Pain*" or "Perineal Neuralgia" or "Stump Neuralgia" or "Supraorbital Neuralgia*" or "Vidian Neuralgia*" or "Nerve Pain*" or "Ilioinguinal Neuralgia*" or "Hyperalgesia*" or "Hyperalgesic Sensations" or "Mechanical Allodynia" or "Mechanical Hyperalgesia" or "Tactile Allodynia" or "Allodynia" or "Thermal Hyperalgesia" or "Thermal Allodynia" or "chronic pain*" or "Widespread Chronic Pain*" or "Nociceptor*" or "Pain Receptor*" or "Nociceptive Neuron*" or "causalgia" or "Type II Complex Regional Pain Syndrome" or "CRPS Type II*" or "Deafferentation Pain" or "Causalgia Syndrome*" or "Somatosensory Disorder*" or "Somatic Sensation Disorder*" or "Pain Sensation Diminished*" or "Thermal Sensation Disorder*" or "Position Sense Disorder*" or "Proprioceptive Disorder*" or "Proprioceptive Disorder*" or "Light Touch Sensation Impairment" or "Pinprick Sensation Diminished*")

Studies focusing on LTM were excluded. The following is a list of eligibility criteria that were applied to the remaining articles returned by the database searches.

Inclusion criteria:

- Peer-reviewed studies based on an animal model involving pain.
- Study has a no pain control group (intact animals).
- STM or WM using standardized memory tests as an outcome variable was mesured.

The standardized memory tests found in the studies were Tmaze, Moris water maze, Figure-8-shaped maze, Novel-object recognition, Elevated plus-maze, Air-puff passive avoidance, Object recognition test, Open field (OF), social memory, Novel location recognition (NLR), and Zero maze.

Initially, two co-authors independently screened the studies that were returned by the searches based on title and abstract. Where there was doubt, the full text of article was inspected. Conflicting eligibility determinations were decided by consensus. A third reviewer was invited to resolve disagreements between the 2 reviewers, including for the ROB assessment (see below).

Exclusion criteria were as follows: review articles, in-vitro studies, articles not sufficiently elevant to experimental Pain and studies that did not use appropriate memory test, those that did not report the control group.

Due to the diversity of pain models and memory tests in individual studies, pooling of data in a meta-analysis was not possible.

Risk of bias assessment

The SYRCLE Risk of Bias (ROB) instrument [20], based on the Cochrane Risk of Bias tool but adapted for animal studies was also used to objectively assess the quality of the studies that met the inclusion criteria [21]. This scale consists of 10 items assessing 5 broad categories (Table 2). The following scale was used to convert the quantitative measure obtained into a qualitative assessment: <50% (weak), 50%–69% (fair), 70%–79% (good), and 80%–100% (very good).

Two independent assessors completed the form for each study and their answers were compared. Any disagreements were resolved through discussion or by involving a third reviewer.

Table2: Characteristics evaluated articles based on SYRCLE's ROB tool.

Selection bias: 1 ✓ = Describe the methods used, if any, to generate the allocation sequence in sufficient detail to allow an assessment whether it should produce comparable groups. Not describe: x 2 ✓ = Describe all the possible prognostic factors or animal characteristics, if any, that are compared in order to judge whether or not intervention and control groups were similar at the start of the experiment. Were the groups similar at baseline or were they adjusted? x = Not describe. 3 ✓ = Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen before or during enrolment; x = no describe.
Performance bias: 4 ✓ = Evidence of random housing of animals; = unknown housing arrangement. 5 ✓ = Confirmation of caregivers blinded to intervention; x = no confirmation of caregivers blinded to intervention.
Detection bias: 6 ✓ = Evidence of random selection for assessment; x = no evidence of random selection for assessment. 7 ✓ = Evidence of assessor blinded; x = no evidence of assessor blinded.
Attrition bias: 8 ✓ = Explanation of missing animal data; x = no explanation of missing animal data.
Reporting bias: 9 ✓ = State how selective outcome reporting was examined and what was found (statistic section)? = insufficient reporting; x = selective reporting. 10 ✓ = Free of other high bias risk (Model of injury, number of animal per group, animal welfare regulations); = insufficient data to determine risk of other bias.

Results

This search returned 953 results from SCOPUS, 594 from PubMed, 610 from EMBASE, 505.from Web of science were selected for more investigations. After removing the duplicates 1634 article remained (Fig 1).

After a final review and remove articles based on predefined category, 13 related articles were found [14,34-45] (Table3). The periods of studies were between 1 and 126 days. Ten of them were performed on rat [14,36-43] and 4 studies investigated on mice [14,34,44,45]. One study performed on the both rat and mice [46]. 9 of the 13 reports clearly identified that they measured WM, while others only mentioned short-term memory. The following table 4 shows the pain models employed.

Table3: Abstract of all 13 articles eligible for systematic review.

Author Year	animal/ gender /Age	pain model/ Direction of lesion	Time of study (Day)	STM/ WM	Learning & Memory test	Pain assessment test	Molecular and Histological study	Other behavior tests	Results
Cardoso-Cruz 2018(47)	Rat/ Male/ Young	Spared nerve injury/ side of injury	27	WM (sWM)	T-maze behavioural task	Von Frey	Single-cell, local field potential recordings :neural activity	-	Chronic pain via deficient dopaminergic receptors effect on the memory and causes development of cognitive deficits
Cardoso-Cruz 2013(48)	Rat/ Male/ Young	Spared nerve injury/ NR	21	WM (sWM)	T-maze forced-choice task, figure-eight spatial alternation task	Von Frey	Nissl staining: visualize the electrode tracks Neural recordings: neural	-	Working memory deficits after functional instabilities in the fronto-hip

							activity		pocampal connectivity might because for pain-related working memory deficits.
Cardoso-Cruz 2014(**49**)	Rat/ Male/ Young	Spared nerve injury/ NR	28	WM (sWM)	Figure-8-shaped maze, Experimental timeline test	Von Frey	Real time of dopamine receptors, single-cell and local field potential recordings: neuronal activity	-	disruption of the dopaminergic balance in the hippocampus may be a reason for cognitive deficits
Leite-Almeida 2009(**50**)	Rat/ Male/ Child, young old	Spared nerve injury/ Left	30	WM	Morris water maze	Von Frey	NO	Forced swimming test :depressive-like behaviour, Elevated plus-maze: anxiety like beh	Influence of neuropathic pain on cognitive behaviors probably is age dependent. Mid-

								aviour. Open field: anxiety-like exploratory and locomotor behaviours	aged animals are more susceptible to depression and cognitive deficient associated to chronic pain than young and old animals.
Leite-Almeida 2012(**51**)	Rat/ Male/ Young	spared nerve injury left and in the right/ Left and right	41	WM (sWM)	Morris water maze	Von Frey	NO.	elevated plus-maze: anxiety like behavior	Left- and right-sided neuropathic pain differentially affects emotional behavior. Left injury increased anxiety-like behaviors and but righ

									t injury causes cognitive deficits in all tasks except in the reference memory
Seideh Saffarpour 2017(**52**)	Rat/ Male/ Young	Chronic Constriction Injury(CCI)/ Left	21	STM&LTM	Moris Water Maze	Von Frey	Western blotting :glutamate concentraion & BDNF expression	-	Chronic pain result in imp airs spatial learning and memory. This effect exerts through the increase in GABA concentration and decrease in the glutamate and BDNF levels in the CA1 region of

									the hippocampus.
Orla Moriarty, 2014(**4**)	Rat/ Male/ Mid-aged	L5–L6 Spared nerve ligation/ Left	67	STM	Novel object test Moris water maze	Von Frey, acetone, Hargreaves	Immunohistochemistry: synaptophysin ,vGAT and vGlut	rotarod test ,social transmission of food preference :Motor coordination	Chronic pain cause deficiency in recognition memory and cognitive flexibility, but these deficits are not associated with alter in synaptophysin expression or distribution in the mPFC and CA1.
Wen Jie Ren 2011(**53**)	Rat and Mice/ Male/ Young	spared nerve injury/ Left	43	WM	Eight-arm radial maze	Von Frey	mmunofluorescence staining:Electrophysiological Recording	-	Over-Expression of TNF-α following peripheral nerve injury

							Presynaptic Terminal Puncta and TNF-alpha,		might lead to neuropathic pain and memory deficits.
Chun-Lin Mai 2019(**54**)	Rat/ Female/ Young	Spared nerve injury/ Left	45	STM	Novel object recognition test	Von Frey	Western blotting :GSK 3t,-GSK-3b (Tyr216) and p-GSK-3b (Ser9) expression	-	Increase of interleukin-1beta induces pain hypersensitivity and memory deficits in the chronic pain situation. GSK-3β inhibitors might treat cognitive disorders
Ilaria Ceccarelli 2001(**55**)	Rat Male and female/ Young	Formalin injection/ Right	2	WM	Object recognition test	Formalin	Corticosterone assay, Vaginal cytology	-	Circulating gonadal hormones significantly affecte

									d the performance of male but not female rats when exposed to the object recognition test in the pain situation.
Jasper Andreasen 2016(**56**)	NMRI mice Female / Young	Spared nerve injury/ Left	1	STM/ WM	V-maze test	Von Frey	NO	-	Using postsynaptic density protein-95 inhibitor after pain induction by SNI and CFA model reversed pain hypersensitivity. NMDAR/ PSD-95/ nNOS interaction

									as an alternative analgesic is effective on the short term memory deficiency following chronic pain.
Stefanie Hardt 2017(**57**)	Knock out mice (Grn-/-)/ Young	Spared nerve injury/ NR	64	STM	Novel Object Recognition Test, Novel Odor Recognition Test, Touchscreen IntelliCage	Von Frey		Elevated plus maze: anxiety test Tail suspension test :depression-like behavior	Neuropathic pain may precipitate cognitive and psychopathological symptoms of an inherent. Dietary zinc supplementation partly normalized the attention deficit following pain induction
Maral Tajerian 2014(**58**)	Mice/ Male/ Young	Complex regional pain syndrome (CRPS) by tibia fracture/ cast immobilization/ Right	126	WM	Novel location recognition, Novel object recognition, zero maze: social memory	Von Frey	immunohistochemistry: Synaptosome and BDNF expersion	Open field: general anxiety zero maze: anxiety	Model of tibia fracture/ cast immobilization showed impairment in working memory and social memory. Anxiety related behavior also increased.

* Not reported (NR)

With regards to the short term memory tests, Novel object recognition test was most popular popular [34,41,42,45,59, 60]. But the method of pain induction was different which prevented from meta-analysis.

Table 4: Pain models employed by the 13 studies that met the eligibility criteria.

Pain model	Animal	Reference	Total
Spared Nerve Injury (SNI)	Rat/Mice	(**38**, **48-51**, **53**, **54**, **56**, **61**)	8
Chronic constriction injury (CCI)	Rat	(**52**)	1
Sciatic nerve injury	Rat	(**57**)	1

Complex regional pain syndrome (CRPS)	Mice	(**62**)	1
Formalin Injection	Rat	(**55**)	1

Table 5: Memory tests employed by the 13 studies that met the eligibility criteria.

Memory Test	Animal	Reference	Total
Novel object recognition test	Rat/Mice	(**54**, **57**, **61**, **62**)	4
T-maze	Rat	(**47**, **49**)	2
Figure-8-shaped maze,	Rat	(**48**)	1
Morris water maze	Rat	(**50-52**, **61**)	4
Eight-arm radial maze	Rat and Mice	(**53**)	1
Object recognition test	Rat	(**55**)	1
V-maze test	Rat	(**56**)	1
Novel Odor Recognition Test	Mice	(**57**)	1
Touchscreen	Mice	(**57**)	1
Social memory	Mice	(**62**)	1
Novel location recognition	Mice	(**62**)	1
Experimental timeline test	Rat	(**49**)	1

With regards to the short term memory tests, novel object recognition test was most popular [34,41,42,45,59,60]. But the method of pain induction was different which prevented from meta-analysis.

Quality assessment of articles

After scoring the articles based on ROB scale form, it was found articles were in good and 10 articles in very good quality (Table4).

Table 6: All articles score based on ROB scale.

Study	1.	2.	3.	4.	5.	6.	7.	8.	9.	10	%
Hugo Leite-Almeida (2009)											
Hugo Leite-Almeida (2012)	✓	✓	✓	✓	✓	?	✓	✓	✓	×	80
Chun-Lin Mai (2019)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100
Orla Moriarty (2014)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100
Wen-Jie Ren (2011)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100
Mar al Tajerian (2014)	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	90
Jasper Andreasen (2016)	✓	✓	×	✓	✓	✓	×	✓	✓	×	70
Helder Cardoso-Cr	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	90

uz (2018)											
Helder Cardoso-Cruz (2014)	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	90
Ilaria Ceccarelli (2001)	?	✓	✓	✓	✓	✓	✓	✓	✓	×	90
Sepideh Saffarpour (2017)	✓	✓	✓	✓	✓	×	×	✓	✓	×	70
Stefanie Hardt (2017)	?	✓	✓	✓	✓	✓	✓	✓	×	×	70
Helder Cardoso-Cruz (2013)	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	90

Discussion and Conclusions

The primary purpose of this study was to investigate the relationship between pain and memory. The results obtained from the various methods of pain induction showed that, pain specially chronic pain caused deficits in STM/WM; spatial reference memory, learning, spatial reversal, recognition memory and cognitive flexibility [14,34-45]. Although neuropathy status impairs short-term memory, other intervening variables such as ag, side of body in which pain is induced and gender are also involved that may worsen the condition. Age is known to be an important factor that, along with NP, affects STM as well as motor function. Research has shown SNI induced behavioral impairments are more noticeable in middle-aged animals [35].

An intriguing finding was that the effect of pain on emotional and cognitive functions varied depending on the direction of the body in which the pain was induced [51]. Side of injury is also important in the perception of the severity of pain and its effects on the brain. It was found that left-sided nerve damage leads to more anxiety and emotional disturbance than similar right-sided injury. The reason for this finding can be attributed to the domains available in prefrontal cortex that are more affected in NP conditions, particularly when the lesions are right-sided. Left-sided injuries are more likely to affect emotional behavior, while right-sided injuries affect cognitive presentation [63,64].

In addition, it has been shown that the left and right hemispheres of the brain process information differently, with processing in the left hemisphere is more confined while information processing in the right hemisphere is more distributed [65]. There is also evidence that activity in the left and right cerebral hemispheres is associated with different emotional responses [40], with the right hemisphere discriminating more for negative emotions and vice versa. Giving that somatosensory impulses from the left side of the body are processed by the right hemisphere and vice versa, here, we speculate that this is a combination of somatosensory lateralization and valence-specific lateralization leading to the behavioral differences observed when pain is induced in both sides of the body. Furthermore, there is evidence that this lateralization is mediated by gender, whereby women observed to show more lateral discrimination of negative emotions than men [66, 67].

Also, a clinical study has shown that pain in the left side of the body is more likely to be associated with anxiety [68] and the effect of anxiety on memory has been identified [69,70]. Although only one study focused on each of the mentioned variable) age and body side), they appear to be more important subjects and further studies are needed.

According to information on the effect of gender differences on memory [71-73], it is notable that only a study of how gender differences can focus on the relationship between pain and memory [45].

Interestingly, after gonadectomy, females having lower levels of corticosterone (a stress related hormone), which affects memory. After removing sex hormones, they were able to find the target more easily [43]. In males, however, corticosterone levels did not change significantly before and after gonadectomy, nor did their ability to find a target [10,74].

This emphasizes the importance of stress on memory [75]. After gonadectomy (males and females), the delay in reaching to the target did not different between the sexes. Pain induction after gonadectomy, increased the delay in reaching to the goal but does not affect the time spent in contact with the goal [48]. Significantly, pain reduces the time spent exploring the

environment and other exploratory parameters. The animals, also, recognized the targets despite persistent noxious stimulation. However, in painful situations, males can maintain their focus, while no strategy seems to be effective in female's sensory pain [46]. Despite neuro-protective nature of female hormones, they appear to increase female's response to environmental stimuli and make pain difficult to control and even, increase the risk of chronic pain [76,77].

In rats, a significant increase in the latency in making each choice was observed during the post-delay test session, while in humans the highest level of spatial ability was occurred in the low estrogen- phase of the menstrual cycle [43]. It has also been suggested that the underlying mechanisms of pain processing differ as a function of gender and gonadal hormone status.

Noxious input as a result of brain injury or inflammation of the nervous system, may causes structural and functional changes which lead to the persistent pain [78]. The prefrontal cortex, amygdale and CA1 of the hippocampus are areas that have been found to be highly affected by pain [37,41,79]. However these conclusion is controversial [80]. In another study, grey matter (GM) atrophy was reported in patients after chronic pain [15,81]. GM damage causes severe memory impairment [82,83]. Interestingly the duration and intensity of pain , and even the interaction between both factors is effective in destruction [84].

Comparison of groups of patients with chronic pain revealed a decrease in the association of the medial prefrontal cortex with the posterior constituents of the default mode network and an increase in association with the insulating cortex in proportion to pain intensity [85].

Impaired dopaminergic balance in the hippocampus through the D2 receptor and prefrontal after pinning are suggested reasons for loss of STM and WM [38,39]. Also a decrease in the hippocampal BDNF, expression, and glutamatergic activity along with an increase in GABA concentration reported on days 14 and 21 after CCI surgery [37]. Also, synaptophysin, that is a presynaptic protein, and commonly used as a marker of presynaptic terminals due to its high quantity and localisation to synaptic vesicles decrease after induction of pain [61,79].

In BDNF knockout mice, synaptophysin level in the hippocampal synapses decrease. There is also an association between BDNF and synaptophysin expressions. The greatest expression of these neuroplastic markers (BDNF/TrkB/Synaptophysin) pathway associated with STM improvement [86]. Loss of synaptophysin leads to dysfunction of the glia gap junction communication and memory impairment [87].

Decreasedprogranulin, a protein with neuroprotective and immune-regulatory functions and a zinc transporter that has been reported to work together after pain [45]. Another suggested mechanism of NMDAR-dependent NO neuronal plasticity occurs after induction of pain in the lateral, peripheral, spinal and supra spinal nociceptive pathways [44].

Post-pain metabolic abnormalities have also been reported in patients with NP and chronic pain [88] this may be due to alters in human brain chemistry such as a decrase in N-acetyl aspartate and glucose [88]. Despite structural changes in the brain following chronic pain, it is hoped that these changes will improve with pain relief [89,90].

Summary of conclusions

Although pain induction methods and the memory tests were different in the literature, all of them (13 articles) concluded that NP distrupts STM / WM. This change is likely due to structural changes in different areas of the brain. Criteria, such as lesion side, age and gender hormones, may affect pain sensitivity and memory changes. While, they are important, but little attention has been paid to them.

The body of evidence suggests that the causal relationship between chronic pain in STM/WM impairment highlights the need to consider this effect when dealing with patients suffering from Pain. Appreciation this effect can improve personal relationships by increasing empathy and economic efficiency though with greater understanding by co-workers, colleagues and employers. Just as importantly, it can help healthcare professionals to anticipate and mitigate the cognitive consequences for people with NP.

One of the limitations of the current study is that it is not possible to discuss further the structure of the brain and its relationship to pain and memory, and this interesting topic requires further study. Another limitation is, the articles included in this study, only one article worked on acute pain, and the gap between articles that worked on the relationship between acute pain and memory and the comparison of results with NP and chronic pain is felt.

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