

Memory impairment in chronic pain patients and the related neuropsychological mechanisms: a review

Liu X, Li L, Tang F, Wu S, Hu Y. Memory impairment in chronic pain patients and the related neuropsychological mechanisms: a review.

Objective: This study provides a comprehensive review of the literature on memory impairment and the potential effective factors in patients with chronic pain.

Methods: A literature search of databases PubMed, EMBASE, SpringerLink, and PsycINFO until September 2012 was conducted using the keywords 'memory' and 'chronic pain'. The study emphasises on publications over the past 20 years.

Results: Memory impairment in chronic pain patients is substantial, but the aspects of memory (e.g. working memory, long-term memory, and autobiographical memory) in chronic pain patients and the potentially related factors (e.g. age, level of education, pain conditions, emotion, neural network, and use of analgesics) are modest. Memory impairment is interpreted with the attention-narrowing hypothesis and the capacity-reduction hypothesis.

Conclusions: The currently available data and theory have explained memory impairment in chronic pain patients, but many controversies remain. Future research should focus on the subclinical characteristics of chronic pain, enlarging the sample size, and emphasise on the experimental intervention method and the cognitive neuroscience method.

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Summations

- The findings in the literature show impaired memory functions in chronic pain patients.
- The findings suggest that memory dysfunction in chronic pain patients is partially attributable to depressive mood and pain intensity, whereas other potential effective factors remain controversial.
- Most of the existing studies on chronic pain have consistently shown that pain and memory share a common central nervous pathway, including the insula, anterior cingulate cortex, prefrontal cortex, hypothalamus, amygdala, and hippocampus.

Considerations

- The subtypes of chronic pain and the variations of pain conditions are complex and inadequately characterised.
- Large-scale trials in a wide variety of chronic pain patients are needed.

Introduction

Chronic pain is a common health-care problem. Breivik et al. (1) had a survey conducted in 15 European countries and Israel involving 46 000 people, and found

that 19% of the people had pain lasting more than 6 months. In an Australian epidemiological survey, 21% of the 17 543 adults were suffering from chronic pain (2). An epidemiological survey in 17 countries showed that the prevalence of chronic pain lasting more than

12 months in developing countries was 37.3%, whereas in the developed countries the prevalence was 41.1% (3).

As defined by the International Society for the Study of Pain, chronic pain means the feeling and experience of actual or potential tissue damage, or the patient's subjective description. Chronic pain is a non-malignant pain that persists in the healing tissue (4). A time of 3 months is a common demarcation point distinguishing acute and chronic pain. However, a time of 6 months is often selected for research purposes (4).

Chronic pain negatively affects a patient's physical activity, daily communication, cognitive function, and mood. Memory loss is one of the main complaints in chronic pain patients. In 1957, Jones (5) found that chronic pain patients can hardly recall the episodic memory that is associated with the pain. Then research concerning the memory of pain started. There were few studies on this issue during the following 20 years. From the 1980s, many findings about memory impairment in chronic pain patients have been reported (6–12). Studies on the memory of chronic pain patients are important because of the following reasons. First, it is helpful for diagnosis and treatments, because diagnosis and treatment rely on the patient's memory. If the memory is distorted, precise diagnosis and treatment evaluation would be difficult. Second, it is helpful for the study of the theory of memory in chronic pain patients.

This review analyses memory function and the potentially related factors in chronic pain patients. The databases PubMed, EMBASE, SpringerLink, and PsycINFO were searched using the keywords 'memory' and 'chronic pain'. Publications until September 2012 were included and analysed, with an emphasis on the empirical research published over the past 20 years.

Research on memory complaints of chronic pain patients

Memory complaint is one of the chief complaints in chronic pain patients with cognitive deficits. Memory complaint is an important source of anxiety in chronic pain patients. For example, (i) they often complain about their 'bad memory' of forgetting the once familiar phone number and a friend's name; (ii) they have thinking interruptions and often forget the topic of conversation a moment ago; (iii) they forget the appointment time and where to go (13). This brought a lot of trouble to their daily lives, and therefore their family and friends often complained. There is not enough related research on the memory complaints, although it is a very common issue. For example, Jorge et al. (13) reported that 73–81% of chronic pain patients complained of memory decline. The earliest

research was conducted in 1988 by Jamison et al. (6). They divided 363 chronic pain patients into high- and low-memory complaint groups by the score of two questions on the SCL-90: (i) the extent to which you find it difficult to concentrate and (ii) the extent to which you find it difficult to remember things. There were no significant differences in age, gender, education level, marital status, drug use, long pain, and pain intensity between these two groups. It is found that patients in the high-memory complaint group suffered from emotional problems (such as depression, anger, irritability, and tension), lack of family support, dissatisfaction of social activities, and sexual life significantly more than those of the low-memory complaint group (6). Schnurr and MacDonald (7) found that memory complaint in chronic pain patients is significantly more than that in mental patients or patients receiving psychotherapy. The degrees of depression and chronic pain are related to the number of memory complaints (7). Although patients often attribute memory complaint to codeine or psychoactive drug use, they are not related (7). McCracken and Iverson (14) found that 23.4% of the 275 patients with chronic persistent pain complained of forgetfulness. Memory complaint is moderately correlated with anxiety, depression, pain intensity, and antidepressants, but it is not related to opioid (14). Muñoz and Esteve (15) found that of the 149 patients with chronic benign pain, 61% cannot remember movie and book contents. Of them, 44% have forgetfulness, 38% are forgetful in dealing with the day-to-day affairs, and 38% forget conversation topics. Memory complaint is mainly associated with depression and anxiety, and not related to benzodiazepine, age, and pain duration (15). Of the three components (rumination, helplessness, and magnification), only rumination is positively correlated with memory complaint (15).

Studies on memory complaint have shown that the complaints of memory decline are prevalent in chronic pain patients. The memory complaints are closely related to negative emotions (depression and anxiety). However, the relationship between memory complaints and other factors, such as pain and drug, needs to be further studied. Analyses in the currently available studies of memory complaints are based on the subjective experiences of patients, which are not objective measurements. In addition, although most studies exclude traumatic brain injury and stroke history, potential brain damages cannot be completely ruled out, which may affect the results.

Research on the working memory of chronic pain patients

Working memory plays an essential role in the cognitive function and has an important impact on other cognitive functions. Working memory is also

closely associated with other memory. For example, the autobiographical memory theory greatly emphasises on the role of working memory in the specific autobiographical memory recall (16). It indicates that the impaired working memory makes the resources required to retrieve specific autobiographical event tasks to be not enough, which leads to generalisation of autobiographical memory retrieval and response delay. This point has been supported by a lot of studies on autobiographical memory of patients with depression, schizophrenia, and post-traumatic stress disorder (17–19).

However, there were few studies on working memory of chronic pain patients. Etherton et al. (20) found in two studies that chronic pain patients usually have attention and working memory impairments, which is further supported by Jorge and Dick (13,21). However, Sjøgren et al. (22) found that there was no significant difference in working memory between the chronic pain patient group and the healthy control group. Although brain injury, neurological diseases, mental illness, and cancers were excluded from these studies, drug types, doses, and duration used in these studies are inconsistent. Various measurement tools used for working memory in these studies, such as Working Memory Index (13,20), Paced Auditory Serial Addition the Task (22), Reading Span Test (21), and Spatial Span Test (21), may result in inconsistency.

The factors related to the working memory impairment in chronic pain patients are as follows. (1) *Pain conditions*: Dick and Rashiq (21) found that the impaired memory and pain are closely related to the interference of the memory trace. They believe that pain may interfere with the retention of memory traces, and memory trace is important for information processing and long-term memory storage (21). Etherton et al. (20) found that working memory impairment and pain intensity were not related in chronic pain patients. Jorge et al. (13) also found that there was no significant relationship between the degree of memory impairment and duration of pain. However, Sjøgren et al. (22) found that pain intensity and working memory scores are significantly negatively correlated. (2) *Emotions*: Jorge et al. (13) found a positive correlation between the intensity of anxiety and the degree of memory impairment. (3) *Analgesic drugs*: Sjøgren et al. (22) explored the impact of drug therapy on the working memory of chronic pain patients, and found that working memory of patients without drug treatment was significantly better than that of the patients who had oral opioid therapy. (4) *Age*: Dick and Rashiq (21) found there was no significant relationship between age and working memory of chronic pain patients, which is further supported by Oosterman et al. (23).

(5) *Other psychosocial factors*: Jorge et al. (13) found that working memory impairments in chronic pain patients were affected by the environment and individual effort, whereas Dick and Rashiq (21) did not find any obvious relationship between this impairment and sleep problems or psychological pressure. Altogether, because of the relatively few studies on the working memory of chronic pain patients, influencing factors and mechanisms of the working memory impairment are still worth further exploring because of the important role of working memory in cognitive functions.

Research on the long-term memory in chronic pain patients

Long-term memory impairment is also found in chronic pain patients by various studies. Landro et al. (24) found that it was more difficult for fibromyalgia patients to complete the long-term memory recall task requiring sustained efforts (e.g. the Randt Memory Test, the Code Memory Test, the Word Fluency task, the Kimura Recurring Recognition Figures Test). Grisart (25) found that the recognition operations were significantly more difficult for chronic pain patients than the control group and that the chronic pain patients had more ‘understanding’ reactions, whereas the control group had more ‘remember’ reactions. Oosterman (23) investigated the visual and verbal episodic memory in chronic pain patients, and found that their episodic memory scores were significantly lower than the control group. Busch (26) adopted the computerised memory experiment to test chronic pain patients: he found that the long-term memory in chronic pain patients was not all reduced but was closely related to the stimulus materials.

Thus far, there have been some studies on the long-term memory impairments in chronic pain patients, showing several kinds of influencing factors. (1) *Pain conditions*: Thomas et al. (27) found that the more serious the pain is, the worse is the memory of chronic pain patients. Iezzi et al. (28) also found that the severity of the pain really predicted the memory performance. Hart et al. (29) believed that pain interfered with memory process rather than memory-encoding process. However, Grisart et al. (25) believed that there was no relationship between recognition results and the pain intensity in the ‘remember’ reaction of the chronic pain patients. Jorge (13) thought that the long-term memory was not influenced by pain intensity and pain duration. This inconsistency may result from sampling differences, because samples in the studies of Thomas and Iezzi included patients with different subtypes of chronic pain (27,28), whereas Jorge (13) only studied patients with chronic low back pain. (2) *Emotions*: Iezzi (8)

found that the more emotional stress patients have, the more difficulties they have to recall the word materials or the non-word materials. Landro (24) found that when depression was controlled in fibromyalgia patients, only the patients with a history of depression showed worse long-term memory grades than the healthy control group. Hart (29) believed that similar to the impacts of pain on memory, emotion influenced the recall process, rather than the memory-encoding process. Grisart (25) found that the recognition grade was not related to anxiety and depression. (3) *Analgesic drugs*: Iezzi et al. (8) investigated the relationship between the analgesic drugs and long-term memory in chronic pain patients, and found no obvious relationship between the drugs and the memory impairment, which was further supported by Grisart et al. (25). (4) *Attention*: Jorge et al. (13) found that the decrease in the long-term memory was closely related to attention. Oosterman (23) also believed that the decrease in the episodic memory scores may be due to the impaired attention of chronic pain patients. (5) *Other psychosocial factors*: It is found that long-term memory in chronic pain patients is associated with education time, post-traumatic stress, psychological pressure, and study skills (13,27,28). In conclusion, the long-term memory impairment in chronic pain patients has been widely recognised and analysed. However, specific aspects of the long-term memory, such as word logical memory, scene memory, and the memory of feeling-channel effects, needed to be further studied.

Research on the autobiographical memory of chronic pain patients

Since the late 1980s, study on the autobiographical memory became a hot spot of memory research, especially favoured by clinical scientists, including our lab (16,30). The autobiographical memory status of chronic pain patients also attracted the interests of researchers.

It is believed that the pain experience will be influenced by negative or pain-related autobiographical memory (31). Morley (32) used questionnaires and interviews to assess autobiographical memory in chronic pain patients, and found the close relationship between the pain experience (e.g. distress, pain intensity) and vivid original pain events.

It was also found that when chronic pain patients extract autobiographical events, emotions and pain response appeared. Patients intended to extract negative emotions and pain-related autobiographical events, rather than positive emotions or related autobiographical events. Wright and Morley (33) found that there was no difference in the number of recalled autobiographical events to neutral and pain-

related cue words between the patients and the control group; however, chronic pain patients recalled more memories associated with body pain and recalled pain events significantly faster than the non-pain event memories. Oosterman (34) found a positive correlation between memory and the self-reported pain experience, regardless of the pain intensity and memory. Kelly (35) found that chronic pain patients recalled more pain-related autobiographical events, which activated more in the anterior cingulate cortex and left inferior frontal gyrus.

One of the main concerns in this field is whether chronic pain patients accurately retrieve their pain-event memories. Feine (36) found that the chronic pain patients had an inaccurate memory of the pre-treatment pain. Moreover, the longer time there is, the more errors there are in memories (36). Memory accuracy of the pre-treatment pain depends on the degree of pain. Patients with slight pain may exaggerate pain before treatment, whereas patients with severe pain may underestimate the pain before treatment. Regardless of the actual decreased degree of pain, most patients tend to overestimate the levels of pain relief (36). However, Salovey et al. (37) found that patients had an accurate memory of the pain event. Matera et al. (38) found that the chronic pain patients tend to overestimate the intensity of their pre-treatment pain. Bryant (39) had the 6-week treatments of 40 chronic pain patients, where the patients recorded their sensory and affective pain intensity, anxiety, and depression intensity before treatments, and they were re-evaluated at the end of the treatments. They found that the patients who report increased pains and depressions tend to overestimate their pain and depression before treatment (39). McNamara (40) found that the self-report of pain intensity of 'scene mode' (from the first-person perspective to re-experience the event memory) was higher than the 'observer mode' (from the perspective of the observer), using the Edinburg Handedness Inventory.

In conclusion, the research on autobiographical memory in chronic pain patients is mainly related to the accuracy of pain event, extraction number, and extraction response tendencies, as well as the factors affecting autobiographical memory retrieval. Studies in this area are still in a preliminary stage. There is no consensus conclusion about the accuracy of pain as the subtypes of chronic pain patients in each study are different. In addition, they used different pain assessment tools. Thus, further research in this field is necessary.

Neuropsychological mechanisms of memory deficits in chronic pain patients

It is shown that pain and memory share a common central nervous pathway (41). The nervous pathway

of memory includes the insula, anterior cingulate cortex, prefrontal cortex, hypothalamus, amygdala, and hippocampus (41). The prefrontal cortex is considered to be the main structure of the nerve pain and neural network of memory. The insula is the pain perception hub, which is involved in maintaining memory trace. The hippocampus is generally considered to be a central nervous tissue of memory. Recently, some neuroimaging studies have shown that the structure of the hippocampus has changed in chronic pain patients, suggesting that pain and memory may have intrinsic neural connections. In addition, there exists a partial overlapping between the neural network systems of pain and memory. Most neuroimaging studies on pain and memory have shown that these regions are activated during the pain and the memory processes (12). Some regions of the limbic system, such as the amygdala, are closely related to persistent pain (42).

The psychological mechanism of memory deficits of the chronic pain patients can be explained by 'attentional resources'. There are mainly two theories. One is the narrow attentional resources hypothesis, and the other is the diminished capacity hypothesis. The narrow attentional resources hypothesis assumes that attention is focused on the feeling or emotion of pain (9). The attentional resources required by the task of processing is limited, resulting in decreased memory operation performance. Grisart et al. found that, compared with the healthy control group, the awareness in the patient group significantly reduced and the unconscious memory did not change significantly. It shows that the weakened memory attention control is a predisposing factor of memory efficiency. At the same time, the fear of pain and catastrophising beliefs can better explain the influences on the intention memories than the socio-demographic characteristics and feeling of pain (9). The diminished capacity hypothesis assumes that the memory deficits in chronic pain patients are the results of the overall decrease in attention resources (42). It is suggested that the chronic pain interferes with the cognitive operations and increases the workload of task attention, resulting in the lack of general attention resources, thus affecting the memory task (42). However, the assumption has been challenged by Christianson et al. and Kelly et al., as they found that the self-related memory content is better than the neutral content in chronic pain patients (31,35). In addition, on the basis of the antagonism of the self-related processing promotion (cognitive biases) and the cognitive interference on neutral information processing (cognitive impairment), a general pattern of cognitive function can be drawn. However, it still remains unknown whether the basic ability of the attention task is limited by the chronic pain, or chronic pain decreases spontaneous initiative of the controlling processing.

Limitations and prospective of studies on the memory of chronic pain patients

Chronic pain patients are from a special group, with common symptoms of cognitive deficits. Therefore, the studies of memory in chronic pain patients help in understanding the etiology of chronic pain, promote the clinical diagnosis and treatment, and improve memory theory. The currently available data and theory have explained memory impairment in chronic pain patients, but many controversies remain.

First, because the reason of chronic pain is very complex, the homogeneity of samples is relatively poor. Chronic nociceptive pain (caused by tissue damage or inflammation), chronic neuropathic pain (caused by nerve damage or disease), composite pain (nociceptive pain and neuropathic pain combined), and chronic psychological pain have different pathological mechanisms and different impacts on memories. Large-scale studies usually collected different subtypes of chronic pain patients with a great difference in the sample size of subtypes, resulting in inconsistent results. For small-scale studies, single subtype is preferred, such as chronic low back pain patients. For the large-scale sample study, the number of each subtype should be roughly equal, which would enhance the validity of research and facilitate the investigation of differences between the various subtypes of chronic pains.

Second, because of the individual measurement, sampling is more difficult. Most cross-sectional studies are with small samples, which greatly limit the validity of results. For example, some studies found no relationships between memory and pain duration that may result from the type II statistical error. Therefore, a large-scale sample is necessary for effective parameter analysis, which can study the psychological factors and the potential impacts on memory function of chronic pain patients.

Third, the influence of pain intensity on memory function in chronic pain patients is a controversial issue. Some experiments determined the relationship between pain intensity and memory function by experimentally inducing pains. Despite its convenience (such as the pain intensity spectrum from light to serious), there are many differences in experimentally induced pains and the natural pains, especially for chronic pains. Natural pain involves the context, persistent or chronic, related muscles, internal tissues, and organs, rather than just skins. In clinical studies, patients with light chronic pains may not come to look for medical care, and patients with serious pain are unwilling or unable to complete a memory task. Therefore, in the study, there are mainly patients with medium or partial chronic pains. Thus, the linear relationship between the pain intensity and the memory

performance may be masked. In the intervention study, the speed of memory function recovery and the speed of pain reduction may be different. Therefore, in the repeated measurements, the latter timing is an important influencing factor. Therefore, future research, in addition to outpatient sampling, should also include community sampling. Improved evaluation method is also necessary in order for patients with serious pains to complete the memory test, so that the chronic pain intensity changes linearly from light to severe. In the intervention study, the repeated measurement tracking design is recommended to overcome the deficiencies of the experimental design.

Fourth, there are limited studies on the influence of analgesic drugs on memory function of chronic pain patients. Analgesic drugs relieve pain, thereby improving patient's memory function. However, analgesic drugs often have side effects for the potential impact on patient's memory function. Meanwhile, there are considerable differences between the peripheral anti-pyretic analgesic drug and the central analgesic drug. In addition, conditions such as dosages, time (taking/stopping taking), administration (oral/injection), and concomitant medications should all be considered. These factors make it more complex and difficult, often resulting in inconsistent results in previous studies. Therefore, future research should include these factors during studies on the memory function of chronic pain patients.

In addition, despite the shared central nervous pathway between pain and memory, it is not sufficient to show the neuropsychological mechanisms of memory defects in chronic pain patients. For example, there is no specific neuropsychological study on the mechanisms and interaction of pain and working memory, long-term memory, and autobiographical memory, respectively. Thus, cognitive neuroscience is important for understanding the neuropsychological mechanisms of chronic pain patients with memory deficits. Future research should focus on the subclinical characteristics of chronic pain, enlarge the sample size, and emphasise the experimental intervention method and cognitive neuroscience method.

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Authors' contributions

Xianhua Liu and Li Li contributes equally to this work. All authors read the final manuscript, and all

have given final approval of the version submitted for publication.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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