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Evidence for working memory deficits in chronic pain: A systematic review and meta-analysis

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ABSTRACT

People with chronic pain commonly report impaired cognitive function. However, to date, there has been no systematic evaluation of the body of literature concerning cognitive impairment and pain. Nor have modern meta-analytical methods been used to verify and clarify the extent to which cognition may be impaired. The objective of this study was to systematically evaluate and critically appraise the literature concerning working memory function in people with chronic pain. The study was conducted along Cochrane collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines. A sensitive search strategy was designed and conducted with the help of an expert librarian using 6 databases. Twenty-four observational studies evaluating behavioural and/or physiological outcomes in a chronic pain group and a control group met the inclusion criteria. All studies had a high risk of bias, owing primarily to lack of assessor blinding to outcome. High heterogeneity within the field was found with the inclusion of 24 papers using 21 different working memory tests encompassing 9 different working memory constructs and 9 different chronic pain populations. Notwithstanding high heterogeneity, pooled results from behavioural outcomes reflected a consistent, significant moderate effect in favour of better performance by healthy controls and, with the exception of one study, pooled results from physiological outcomes reflected no evidence for an effect. Future research would benefit from the use of clearly defined constructs of working memory, as well as standardised methods of testing.

1. Introduction

Working memory refers to a limited-capacity, short-term, information retention system, essential to the skill of maintaining and manipulating behaviourally relevant information [8]. Although working memory as a construct appeals intuitively, it has proven difficult for the field to converge upon a definition. The term "working memory" was first used in 1960 [44] to describe the memory store necessary to execute a plan. Further developments came from physiological psychology; a neural correlate of immediate memory and the transient retention of information was reflected in activity in single neurons of the prefrontal cortex (a unitary model)[20] and cognitive psychology; and the instantiation of the multicomponent model of working memory [9]. Conceptual integration of these models occurred in 1990 [23] and the "standard model" of working memory became a popular framework for research, spawning many valuable advances [7,58]. However, evidence from the advances suggests this model has outgrown its usefulness, and current studies integrate the drivers of working memory, such as motivation, emotion, and attention [5–7,12,35,58]. For this review we considered working memory as a non-unitary construct consisting of a network of neurons that, on activation, make the bridge between perception and memory, and attention and action [8]. Effective working memory function is necessary for guiding behaviour, making decisions, learning a language, reasoning, and planning [58].

Clinical observation reveals that many people with chronic pain report poor memory and concentration. That pain could impede working memory function has also long been suggested in the literature [1,3,17,25,26,28,46] and it seems so well accepted that there are currently several behavioural and imaging observations of how this impedance occurs. First, the same neural networks

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are used for many cognitive functions, and if one function (nociceptive processing) engages a majority of neural resources, there are fewer left for other functions [4]. Second, bodily sensations may take on increased attentional weight in people with chronic pain (hypervigilance) and divert attention away from other cognitive tasks [36]. Third, a stimulus previously defined by a given feature will be more efficiently processed on subsequent presentation (attentional set), even when it is irrelevant [37,42]. This impedes an effective response to new information. Fourth, pain disrupts cortical inhibitory mechanisms and impedes deactivation of certain brain areas during and after stimulus evaluation [10]. These observations underpin the dynamic "neurocognitive model of attention to pain" [37] in which pain modulates the priority access working memory has to behaviour- relevant signals from top down or bottom up.

There is an established view that people with chronic pain have a deficit in working memory [15,48,54]. However, there has been no attempt to systematically evaluate the literature and use meta-analytical methods to verify, and clarify, this entrenched belief. At the present juncture, when cognitive-, behavioural-, and education-based treatment approaches for chronic pain are gaining popularity, such a step is critical. We applied a systematic review and meta-analytical approach to determine the evidence that chronic pain is associated with working memory deficit.

2. Methods

2.1. Data sources

This systematic review was conducted according to Cochrane Collaboration [27] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement guidelines [45]. A review protocol was written a priori and can be accessed in Supplementary File 1. A sensitive search strategy was designed with input from an expert librarian and used the following databases from inception to June 18, 2012: Medline (via OvidSP), Embase (via OvidSP), PsychINFO (via EBSCOhost), Cinahl (via EBSCOhost), Amed (via OvidSP), and Scopus (via EBSCOhost). There was no restriction on the language of articles. We limited the search to studies that used human subjects. Each database was searched separately (see Supplementary File 2 for Medline search). Citations related to working memory, executive function, and chronic pain were retrieved and exported to RefWorks (Proquest LLC Ann Arbor, MI) where duplicates were removed. Review articles published in the area of chronic pain and cognitive function, identified through background reading and systematic searching, were hand searched for citations containing original data. The final list of included studies was sent to key authors in the field for identification of any missing studies. As a result, 5 more full-text studies were screened and included, and 1 set of additional test results from an included paper were added to the data set [16]. A flow chart of the search process is included as Fig. 1.

2.2. Study selection

To be included in this review, studies had to evaluate working memory performance in a chronic pain population and compare this performance with that of healthy controls or with population normative values. Studies that stated explicitly that they were measuring working memory, or used testing paradigms that are generally accepted to test for working memory constructs as defined by the multicomponent mode of working memory described by Baddeley [8] were included. For a list of tests that were included see Tables 3–5. Because working memory and any variation of "short-term memory" have been used interchangeably in the literature we included tests for both constructs in this review. Studies were excluded on the following basis:

- more than 15% of participants were younger than 18 years of age
- they recruited participants with traumatic brain injury, Alzheimer's disease, or any event-related or disease-related change that would be expected to impair cognition
- they were commentaries, editorials, letters to the editor, or review articles
- they compared the effect of context and/or emotional value between stimuli.

2.3. Study inclusion

Two independent reviewers screened the titles and abstracts of all citations, excluding obviously irrelevant studies. Full text was retrieved for any articles with inclusion potential, to which the same two reviewers independently applied the eligibility criteria using a custom form that was piloted on 2 studies prior to use. Any disagreements between reviewers were resolved through discussion. If a consensus could not be reached, an independent third reviewer was consulted.

2.4. Risk of bias assessment

We constructed a customised risk of bias form that was based on relevant items from the Cochrane Collaboration risk of bias tool and relevant forms of bias relating to case-control study designs (ie, selection, attrition, detection, reporting, and performance biases). Two independent reviewers (CB and JB) completed this form for each study and responses were compared. Any disagreements were resolved through discussion or by inclusion of a third reviewer if necessary.

2.5. Data extraction

Two independent reviewers (CB and JB) used a piloted, custom-designed form to extract data, and the results were compared to ensure accuracy. The following data were extracted: (1) group-specific data (type of chronic pain, definition of chronic pain and/or healthy control, sample size in each group, gender, and mean and standard deviation for age and pain scores); (2) statistical method data (variables used to match groups, covariates used in the analysis); (3) cognitive test data [name of cognitive test (eg, reading span), working memory construct evaluated, outcome measure of test (eg, number of answers correct), interpretation of test]; (4) group-specific outcomes on cognitive tests [mean and standard deviation for each group, z-scores, statistical test results (eg, mean differences)]. If additional information was required we contacted the authors a maximum of 3 times; after which, we considered the information to be un-retrievable.

2.6. Data synthesis and analysis

Cognitive outcome data were first divided into behavioural and physiological tests of working memory function. These groups were then subdivided into outcomes: for behavioural tests – the number or sum of answers that were correct and reaction time; for physiological tests – amplitude of response, latency of cortical responses, and changes in Blood Oxygen Level-Dependent (BOLD) signal. To account for the non-unitary nature of working memory, the groups were then subdivided into the working memory constructs that were reported to be assessed for each outcome (eg, verbal working memory, immediate recall, and so on). Using the mean cognitive outcome data from each group and the pooled