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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

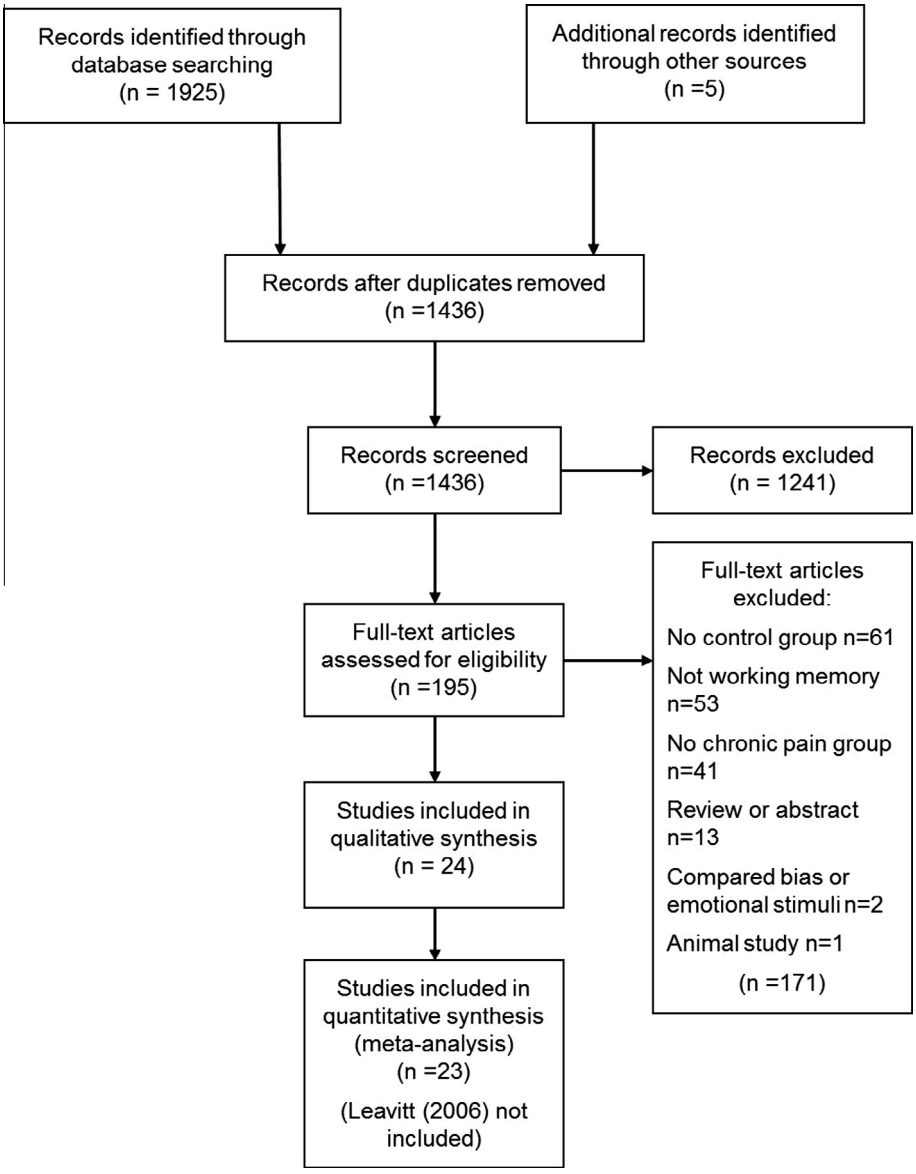

Fig. 1. Flow chart of the search process. n = number.

standard deviations, the standardised mean difference (Hedge's g) was calculated for each working memory outcome. In 2 studies [73,74] where error and/or omission rates were presented, the data were transformed into percentage correct, for ease of further analysis. Data for each working memory construct were pooled when results were available from at least 2 studies. When the same study provided numerous results for one working memory construct under one outcome (eg, verbal working memory construct under the outcome of number of correct answers), the sample size was reduced based on the number of times it was present in that subgroup. Quantitative analysis was undertaken in Review Manager (Revman v.5.1)[60]. Studies were excluded from the quantitative analysis if they did not report sufficient data, if the necessary data could not be obtained from the study authors, or if the mean and standard deviation values could not be estimated from group-level statistical results. The presence of statistically significant heterogeneity was decided on the basis of χ^2 $P < 0.10$, and substantial heterogeneity on the basis of $I^2 > 60\%$ [27]. Effect estimates were interpreted as small (0.2), moderate (0.50), or large ($\geqslant$0.80) [11]. Because group sample sizes were small for many studies (ie, owing to studies using numerous tests for working memory requiring their sample sizes to be reduced in the forest plots), a sensitivity analysis was performed, including only studies with group sample sizes of at least 10 participants [47]. When a study used more than one test for working memory, we were conservative in the tests we kept: either the first test applied by the trial (Attention and working memory subgroup: digit symbol substitution [69]; Immediate visual memory: first figure drawn [63]) or the test that most accurately represented working memory [Verbal working memory: digit span backwards, Running memory: 2-back task [65]; Latency and amplitude results: contingent negative variation (CNV), N2 and P3 [14,29,32,63,70,71]). We have included the sensitivity analysis forest plots as Appendix A.

3. Results

From the 1935 records identified by the search methods, the full text of 215 studies was retrieved (see Fig. 1). Of these 215 studies, 24 met the inclusion criteria. The reviewers disagreed over the inclusion of 5 studies [41,55–57,61] and a third reviewer was consulted. Four of these studies were excluded as it was considered that they compared the effects of the emotional value of stimuli

Table 1
Study characteristics and included populations.

Article (author [ref.])	Condition	Matched for IQ or education	Participants					
			Chronic pain			Healthy control		
			Age	Gender	N	Age	gender	N
Studies evaluating behavioural outcomes of working memory								
Antepohl et al. [1]	CWAD	Y	35.1 (–)	7 M 23 F	30	34.6 (–)	7 M 23 F	30
Apkarian et al. [4]	CLP	Y	43.7 (21–71)[a]	8 M 18 F	26	43.6 (25–64)[a]	14 M 12 F	26
Dick et al. [16]	FM	Y	49.6 (12.54)	30 F	30	46.56 (10)	30 F	30
Grace et al. [24]	FM	Y	45.87 (9.79)	1 M 29 F	30	44.73 (9.35)	1 M 29 F	30
Jongsma et al. [29]	Chronic pancreatitis	Y	49.5 (11.9)	10 M 6 F	16	48.0 (11.3)	10 M 6 F	16
Jorge et al. [31]	NSLBP	Y	52.66 (8.75)	5 M 16 F	21	Recruited over normative database 16–89	Unable to confirm numbers M and F	1032
	RA		57.4 (10.7)	3 M 20 F	23			
Landro et al. [32]	FM	Y (sign. diff.)	46.4 (10.4)	25 F	25	40.1 (9.6)	4 M 14 F	18
Leavitt and Katz [33]	FM	Y	42.4 (10.1)	35 no stated	35	Standardized normative data	Currently under request	
Lee et al. [34]	CWP	Y	59.8 (11)	266 M	266	59.7 (10.8)	1273 M	1273
Luerding et al. [38]	FM	Y	53.6 (7.7)	1 M 19 F	20	20 matched healthy controls		
Melkumova et al. [43]	CLBP	Y	46.57 (9.36)	22 M 42 F	64	53.55 (6.22)	40 total "comparable to chronic pain group"	40
Oosterman et al. [52]	CP	IQ matched	51.5 (20.4)	7 M 27 F	34	55.4 (22)	12 M 20 F	32
Park et al. [54]	FM	Y	47.83	23 F	23	47.83	23 F	23
Pearce et al. [55]	CP	Y	50.36 (15.73)	13 M 12 F	25	50.36 (15.73)	13 M 12 F	25
Roldan-Tapia et al. [63]	FM	N	48.5 (7.49)	15 F	15	44.33 (5.99)	15 F	15
	RA	N	44.33 (5.99)	15F	15			
Sjogren et al. [67]	CP	N	40.4 (15.5)	39 M 52 F	91	47.6 (17.4)	29 M 35 F	64
Suhr [69]	FM	Y	48.1 (10.9)	2 M 21 F	23	45.9 (12.7)	4 M 17 F	21
	CP		49.5 (13.8)	4 M 16 F	22			
Veldhuijzen [73]	CP	Y	46.9 (8.5)	10 M 4 F	14	50 (7.5)	7 M 7 F	14
Walteros et al. [76]	FM	N	50.4 (4.6)	15	15	49 (6.7)	15	15
Studies evaluating physiological outcomes of working memory								
Demirci and Savas [14]	CLBP	N	47.6 (12)	1 M 22 F	23	45 (8.6)	1 M 21 F	22
Tandon and Kumar [71]	CP	N	32.85 (8.9)	Not described	14	28.2 (7.1)	"Age- and sex-matched healthy subjects"	14
Tandon and Kumar [70]	CP	N	43.3 (8.8)	20	20	39.6 (7.7)	20	20
Veldhuijzen et al. [74]	CP	Y	47 (2.3)	10 M 4 F	14	48 (1.6)	15 M 15 F	30
Seo et al. [65]	FM	Y	38.73 (7.65)	19 F	19	38.27 (8.48)	22 F	22

Values provided are mean (standard deviation) unless otherwise specified.
M = male; F = female; CWAD = chronic whiplash associated disorder; CLP = chronic lumbar pain; FM = fibromyalgia; NSLBP = nonspecific low back pain; RA = rheumatoid arthritis; CWP = chronic widespread pain; CLBP = chronic low back pain; CP = chronic pain.
[a] Range.

Table 2
Risk of bias assessment.

Study [ref.]	Are cases representative?	Were initial numbers accounted for?	Were cases diagnosed according to accepted criteria?	Were controls screened using the same diagnostic criteria?	Were psychiatric disorders screened for?	Were outcome assessors blinded to group status?	Were sample sizes calculated a priori?	Were confounding variables controlled for?	Was subgroup evaluation appropriate?	Were there any missing data?	Appropriate methods to deal with missing data?	Were all outcomes and groups reported?	Are the cognitive tests used valid?	Are the cognitive tests used reliable?
Antepohl et al. [1]	Y	Y	N	N	Y	Y	N	Y	NA	N	NA	Y	Y	?
Apkarian et al. [4]	?	Y	Y	N	Y	?	N	Y	Y	Y	?	Y	Y	Y
Demirci and Savas [14]	?	Y	Y	N	Y	N	N	Y	NA	Y	N	N	Y	Y
Dick et al. [16]	N	Y	Y	N	Y	Y	Y	Y	Y	N	NA	Y	Y	Y
Grace et al. [24]	?	Y	Y	N	N	N	N	Y	NA	N	NA	Y	Y	Y
Jorge [31]	Y	Y	Y	N	Y	Y	N	Y	NA	N	NA	Y	Y	Y
Jongsma et al. [29]	Y	N	Y	N	N	?	N	Y	NA	Y	N	Y	Y	Y
Landro et al. [32]	N	Y	Y	Y	Y	?	N	Y	Y	N	NA	Y	Y	Y
Leavitt and Katz [33]	Y	Y	Y	?	Y	?	N	Y	Y	Y	N	Y	Y	Y
Lee et al. [34]	Y	Y	Y	?	N	?	N	Y	NA	N	NA	Y	Y	Y
Leurding et al. [38]	?	Y	Y	?	N	N	N	Y	NA	N	NA	Y	Y	Y
Melkumova et al. [43]	?	Y	N	N	?	N	N	Y	NA	?	?	Y	Y	Y
Oosterman et al. [52]	N	Y	N	Y	Y	N	N	Y	NA	N	NA	Y	Y	Y
Park et al. [54]	?	Y	Y	N	Y	N	N	Y	NA	N	NA	Y	Y	Y
Pearce et al. [55]	?	Y	N	Y	N	N	N	Y	NA	N	NA	Y	Y	Y
Roldan-Tapia et al. [63]	N	Y	Y	Y	Y	?	N	Y	NA	N	NA	Y	Y	Y
Sjogren et al. [67]	Y	Y	N	Y	N	N	N	Y	Y	Y	N	Y	Y	Y
Seo et al. [65]	Y	Y	Y	Y	N	N	N	Y	NA	N	NA	Y	Y	Y
Suhr [69]	?	Y	Y	N	N	N	N	Y	NA	N	NA	Y	Y	Y
Tandon and Kumar [70]	?	Y	N	Y	Y	Y	N	Y	NA	N	NA	N	Y	Y
Tandon and Kumar [71]	?	Y	?	Y	Y	Y	N	Y	NA	N	NA	N	Y	?
Veldhuizen et al. [73]	?	Y	N	Y	Y	Y	N	Y	NA	N	NA	Y	Y	Y
Veldhuizen et al. [74]	?	Y	N	Y	Y	Y	Y	Y	NA	N	NA	Y	Y	Y
Walteros et al. [76]	?	Y	N	Y	Y	N	N	Y	NA	N	NA	Y	Y	Y

Y = yes; N = no; ? = indeterminate; NA = not applicable.

Table 3
Behavioural outcomes of number correct (count data) and percentage errors and omissions by working memory construct.

	Test	Outcome	Studies that use this [ref.]
1. Verbal working memory	a. Digit span	1. # Correct answers counting forward	Roldan-Tapia et al. [63], Leurding et al. [38], Jongsma et al. [29]
		2. ∑ Correct answers counting forwards and backwards	Leavitt and Katz [33], Walteros et al. [76], Roldan-Tapia et al. [63], Leurding et al. [38], Jongsma et al. [29]
		3. # Correct answers counting backwards	Roldan-Tapia et al. [63], Leurding [38], Jongsma et al. [29], Oosterman et al. [52]
		4. Unsure	Suhr [69]
	b. Reading span	1. # Words correctly recalled	Antepohl et al. [1], Dick et al. [16]
		2. # Words correctly recalled and questions correctly answered	Park et al. [54]
	c. WMS immediate verbal WM	∑ Correct responses	Grace et al. [24], Jorge et al. [31]
2. Non-verbal working memory	a. Corsi block span	# Correct blocks + sequences	Leurding et al. [38]
	b. PASAT 2.0	# Correct answers adding the last digit to previous (2 s between digits)	Sjorgren et al. [67], Leavitt and Katz [33]
	c. PASAT 2.4	# Correct answers adding the last digit to previous (2.4 s between digits)	Suhr [69], Sjorgren et al. [67], Grace et al. [24]
	d. PASAT 3.0	# Correct answers adding the last digit to previous (3.0 s between digits)	Leavitt and Katz [33]
3. Spatial working memory	Matrix test	# Correct moves recalled	Antepohl et al. [1]
4. Attention and working memory	a. TEA test	∑ Correct responses for each task Overall ∑ is ∑ of means for each task	Dick et al. [16]
	b. Arithmetic	∑ Correct responses	Suhr [69]
	c. Letter number sequencing	∑ Correct responses	Suhr [69], Leavitt and Katz [33]
	d. Digit symbol substitution	∑ Correct substitutions of symbols for digits	Suhr [69], Lee et al. [34], Melkumova et al. [43]
	e. WMS working and general memory	∑ Correct responses	Grace et al. [24], Jorge et al. [31] Leavitt and Katz [33], Dick et al. [16]
	f. Auditory consonant Trigram	# Consonant letters correct	
5. Immediate recall (auditory/ verbal)	a. Recall test of neutral, negative, and pain words	∑ Words recalled correctly	Pearce et al. [55]
	b. Story recall test	∑ Correct parts recalled	Oosterman et al. [52]
	c. WMS immediate memory	∑ Correct responses	Jorge et al. [31]
6. Immediate visual memory	a. Visual reprod. test	Five different line drawings are presented one at a time, removed, and then the participant immediately draws the figure from memory ∑ Patterns correctly reproduced	Roldan-Tapia et al. [63]
	b. WMS immediate visual memory	∑ Correct responses	Grace et al. [24], Jorge et al. [31]
7. Running memory	a. Sternberg test	% Errors	Veldhuijzen et al. [73]
	b. Difficult probe test	1. % Errors	Veldhuijzen et al. [74]
		2. % Omissions	
	c. N-back test	% Correct	Seo et al. [65]

∑ = sum; # = number;% = percentage; WMS = Wechsler Memory Scale; WM = Working Memory; TEA = Test of Everyday Attention; PASAT = Paced Serial Addition Test (2, 2.4 and 3 s between digits).

Table 4
Behavioural outcome of reaction time by working memory construct.

Construct	Test	Outcome	Studies that use this [ref.]
1. Running memory	a. Difficult probe test	Reaction time to correct button press	Veldhuijzen et al. [73]
	b. Sternberg test	Reaction time to correct button press	Veldhuijzen et al. [74]
	c. N-back test	Reaction time to correct button press	Seo et al. [65]
2. Attention and working memory	a. Sequential digit letter combination	Reaction time for substitution	Melkumova et al. [43]
	b. Sequential letter task	Reaction time for substitution	Jongsma et al. [29]
3. Expectancy/orientation/selective attention	a. CNV paradigm	Reaction time to correct button press	Tandon and Kumar [71]

CNV = contingent negative variation.

[57] or were not evaluating working memory [41,56,61]; Pearce et al. [55] was included. Five authors were contacted to gain additional information (3 to get mean and standard deviation data, and 2 to clarify the working memory construct they were testing). The key characteristics of the included studies are summarised in Table 1. Briefly, 40% of the included studies evaluated working memory in patients with fibromyalgia and the remaining 60% evaluated working memory in other chronic pain conditions (ie, rheumatoid arthritis, chronic low back pain, chronic widespread pain, chronic neck pain, and chronic pancreatitis).

Table 5
Physiological outcomes of latency, amplitude, and BOLD signal changes by working memory construct.

Physiological measure	Construct	Test	Outcome	Interpretation	Studies that use this [ref.]
1. EEG latencies	Working memory	Auditory oddball	EEG latencies at 1. N1 2. N2 3. P2 4. P3	↓Latency = earlier cognitive engagement	Demirci and Savas [14] Tandon and Kumar [70]
	Expectancy/orientation/ selective attention	CNV Warning sound (click) primes the response to an imperative stimulus (flashes). Orientation wave is thought to show a general response to a salient stimulus – working memory	1. N1 2. P3 3. Orientation wave (O) 4. Expectancy wave 5. CNV		Tandon and Kumar [71]
2. EEG amplitude	Working memory	Auditory oddball	1. P3 amplitude	↑ Amplitude = ↑ synaptic activation	Demirci and Savas [14] Tandon and Kumar [70]
	CNV	CNV	1. Orientation amplitude 2. Expectancy amplitude 3. CNV amplitude amplitude		Tandon and Kumar [71]
	Running memory	Probe task	1. P3 amplitude		Veldhuijzen et al. [74]
3. fMRI BOLD signal changes	Working memory	N-back task	BOLD signal changes	↑ Signal = ↑ synaptic activation	Seo et al. [65]

EEG = electroencephalography; fMRI = function magnetic resonance imaging; CNV = contingent negative variation.

3.1. Risk of bias of included studies

All studies were deemed to have a high risk of bias, owing primarily to the lack of blinding of the outcome assessors and/or patients (see Table 2). The study with the least risk of bias was that of Dick et al. [16] – scoring a low risk in the majority of categories. Four findings are noteworthy. First, selection of a representative sample was an area of uncertain or high risk in 70% of included studies. Although most chronic pain participants were recruited from representative sources, such as pain management clinics, it was often unclear as to whether recruitment was selective or sequential. Second, only 13 studies reported using accepted diagnostic criteria (eg, the International Association for the Study of Pain definition of chronic pain) to determine the presence of chronic pain. Third, only 2 studies [16,74] reported an a priori sample size calculation (although the former did not achieve the sample size). Last, included studies had a low risk of reporting and performance bias; complete data were present for the majority of outcomes of interest, and all studies bar one [71] used valid and reliable cognitive tests.

3.2. How working memory was evaluated – tests and test outcomes

Of the 24 included studies, 22 used neuropsychological tests that required a behavioural response to a working memory test (see Tables 1, 3 and 4). In total, 28 different test outcomes resulted from tests of 9 different working memory constructs. The most commonly used test was the digit span.

Of the 24 included studies, 4 [14,70,71,73] used electroencephalography (EEG) and 1 [65] used functional magnetic resonance imaging (fMRI) to record the physiological response to a working memory task. Each EEG study reported latency (ms) and/or amplitude (μV) outcomes calculated from the grand mean waveform of the (working memory) event related output. The fMRI study reported BOLD signal changes to a working memory test. Four different test outcomes resulted from tests of 3 different working memory constructs (Table 5). Two of the 4 EEG studies used the auditory oddball test [14,70].

3.3. Behavioural outcomes

Behavioural outcomes were divided into two major outcome types.

3.3.1. Outcome 1: number or sum of correct responses

Twenty-one studies used the number or sum of correct participant responses as an outcome for working memory performance and evaluated 7 different working memory constructs (Table 3; Fig. 2). Two studies evaluated errors and omissions (% incorrect) although, as mentioned, these were transformed into a measure of accuracy. One study [65] evaluated accuracy (% correct).

3.3.1.1. Verbal working memory. Pooled results of 22 comparisons across 14 studies show that chronic pain is associated with decreased verbal working memory – a moderate, significant effect estimate of −0.47 [95% confidence interval (CI) −0.64 to −0.30)] in favour of a better performance by healthy controls. Nine studies used the digit span test to evaluate verbal working memory, but in 3 different ways – the number of digits recalled forwards, the number of digits recalled backwards, and the sum of the number of digits recalled forwards and backwards. Three studies evaluated working memory function using the reading span task [1,16,55]. Two studies evaluated working memory using the Wechsler Memory Scale (WMS) immediate verbal memory test [24,31]. Significant heterogeneity was detected for verbal working memory (χ^2 35.14, $P = .03$, $I^2 = 40\%$). An additional study [33], with insufficient data to include in the forest plot, evaluated digit span and found no difference between a standardised normative mean score and the mean score generated by a group with fibromyalgia.

3.3.1.2. Non-verbal working memory. Pooled results from 6 comparisons across 4 studies show that chronic pain is associated

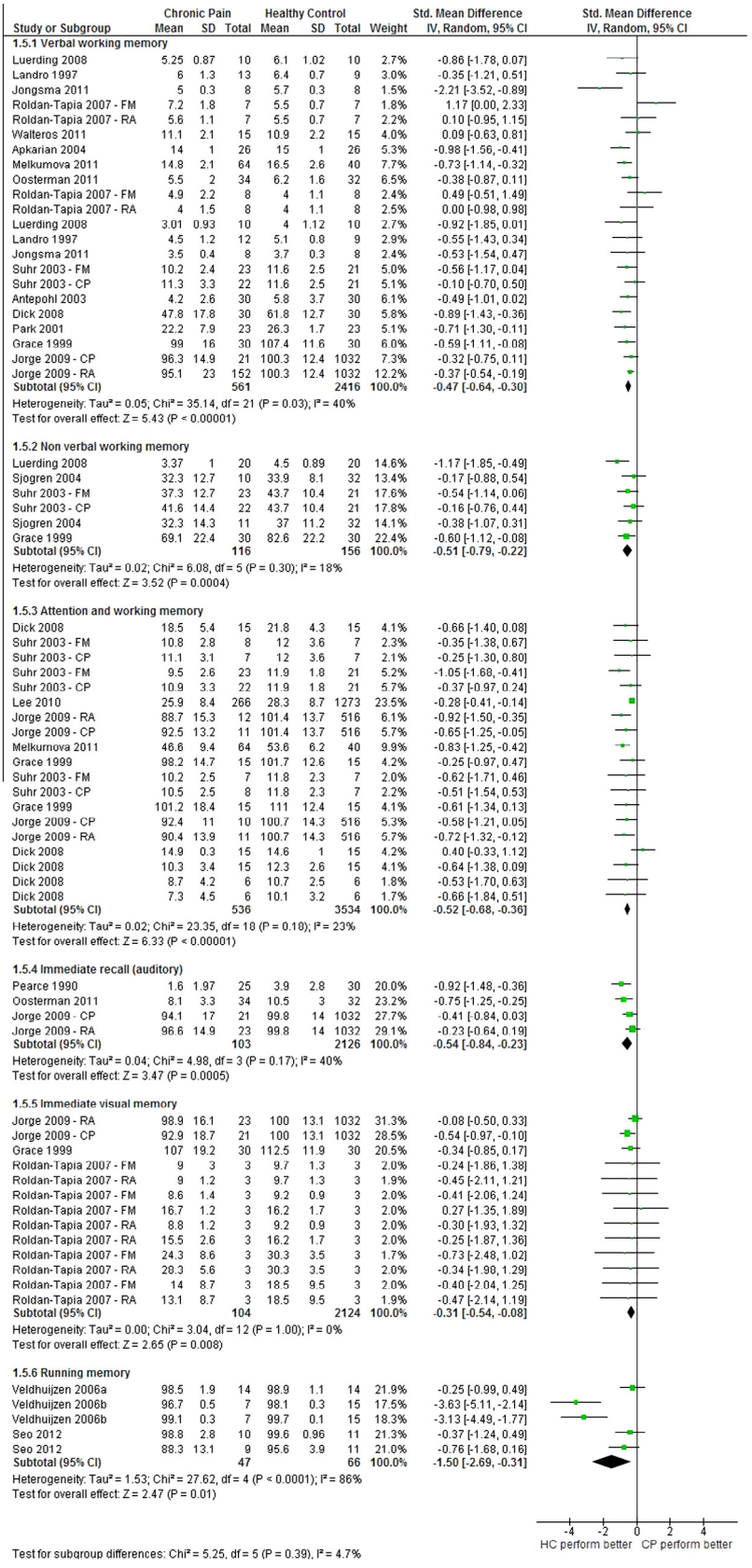

Fig. 2. Forest plot of outcome 1: the number of correct responses. IV = inverse variance; CI = Confidence Interval; CP = Chronic Pain; FM = Fibromyalgia; RA = rheumatoid arthritis; HC = healthy controls; df = degrees of freedom.

with decreased nonverbal memory – a moderate, significant effect estimate of −0.51 (95% CI −0.79 to −0.22) in favour of a better performance by healthy controls. Nonverbal memory was evaluated [24,38,67,69] using either the Corsi Block span test or a version of the Paced Serial Addition Test (PASAT). Of the 4 studies, 1 study provided results for 2 versions of the PASAT

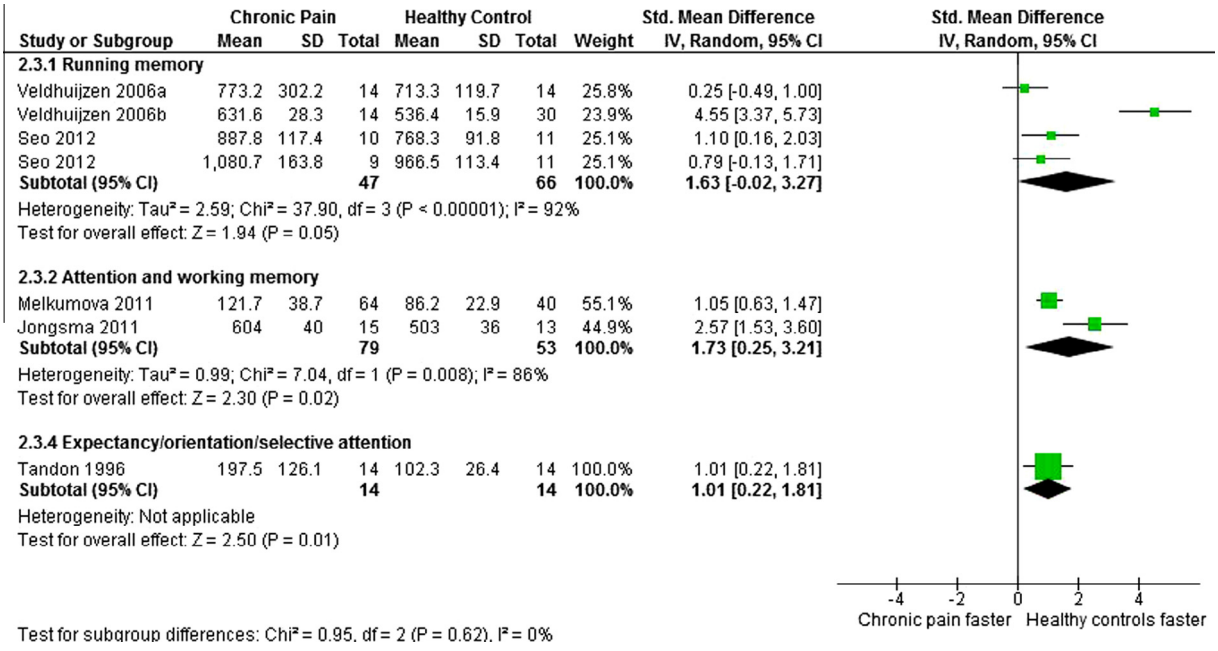

Fig. 3. Forest plot of outcome 2: reaction time. IV = inverse variance; CI = confidence interval; df = degrees of freedom.

[67] and 1 study evaluated 2 different chronic pain groups [69], resulting in a total of 6 comparisons. An additional study [33] (with insufficient data to allow inclusion in the forest plot) provided 2 more results for the PASAT test, using 2 and 3 s between digits. The fibromyalgia group performed significantly ($P < 0.05$) below normative mean on the 2-s test [fibromyalgia mean 5.2 (2.5); normative mean 10 (3.0)], but there was no significant difference in the 3-s test [fibromyalgia mean 7.2 (2.9); normative mean 10 (3.0)].

3.3.1.3. Spatial working memory. One study evaluated spatial working memory by asking participants to recall symbol movements within a matrix [1]. The results show a nonsignificant effect estimate of −0.37 (95% CI −0.88 to 0.14), which suggests no difference in performance between the healthy control group and people with chronic pain.

3.3.1.4. Attention and working memory. Pooled results from 19 comparisons across 6 studies show that chronic pain is associated with decreased attention and working memory – a moderate, significant effect estimate of −0.52 (95% CI −0.68 to −0.36) in favour of a better performance by healthy controls was found. One study used the test of everyday attention [16], 3 studies used the digit symbol substitution test [34,43,69], 2 studies used WMS working and general memory tests [24,31], and 1 study used the Auditory Consonant Trigram (ACT) test [16]. Because 1 study, Suhr [69], used arithmetic and Letter–Number Sequencing tests in addition to the digit symbol substitution test, and also had 2 chronic pain group comparisons, and a second study used the ACT (4 tests) [33], this resulted in a total of 19 comparisons. One further result [33], again with insufficient data to allow inclusion to the forest plot, found a group with fibromyalgia performed 2.5 standard deviations below the normative mean for the ACT, but found no difference between performance on a Letter–Number Sequencing test.

3.3.1.5. Immediate recall (auditory). Pooled results from 4 comparisons across 3 studies show that chronic pain is associated with decreased immediate auditory recall – a moderate, significant effect estimate of −0.54 (95% CI −0.84 to −0.23) in favour of a better performance by healthy controls. Two studies evaluated immediate auditory recall using a story recall task [52] and a neutral word recall task [55], and 1 study reported 2 comparisons on WMS immediate memory test [31].

3.3.1.6. Immediate visual memory. Pooled results from 13 comparisons (10 from a single study [63] and 3 from 2 other studies [24,31]) suggest that chronic pain is associated with decreased immediate visual memory – a small, significant effect estimate of −0.31 (95% CI −0.84 to −0.08) was found in favour of better performance by healthy controls. One study evaluated immediate visual memory using 5 different versions of the Visual Reproduction Test in 2 different chronic pain groups [63]; the other 2 studies used the WMS immediate visual memory test and 1 [31] compared 2 different chronic pain groups, resulting in 13 comparisons.

3.3.1.7. Running memory. Pooled results from 5 comparisons across 3 studies [65,73,74] show that chronic pain is associated with decreased running memory – a large, significant effect estimate of −1.50 (95% CI −2.69 to −0.31) was found, suggesting better performance in favour of healthy controls. Significant heterogeneity was detected for running memory ($\chi^2 = 27.62$, $P = .0001$, $I^2 = 86\%$).

3.3.1.8. Sensitivity analysis. The findings were unchanged in the sensitivity analysis, with the exception of 1 subgroup: running memory (see Appendix A, Fig. A.1). In the sensitivity analysis, running memory was no longer significantly impaired in those with chronic pain (effect estimate of −1.52 95% CI −3.29 to 0.24).

3.3.2. Outcome 2: reaction time

Six studies used reaction time as a measure of working memory impairment. These studies evaluated 3 working memory constructs (see Table 4, Fig. 3).

3.3.2.1. Running memory. Pooled results from 3 studies that used 3 different tests show that chronic pain is not associated with decreased running memory – a nonsignificant effect estimate for reaction time of 1.63 (95% CI −0.02 to 3.27) was found. Significant heterogeneity was detected for running memory ($\chi^2 = 37.90$, $P < 0.00001$, $I^2 = 92\%$).

3.3.2.2. Attention and working memory. Pooled results from 2 studies show that chronic pain is associated with decreased attention and working memory – a large, significant effect estimate of 1.73 (95% CI 0.25 to 3.21) in favour of a faster performance by healthy controls. Significant heterogeneity was detected in attention and working memory (χ^2 = 7.04, *P* = .008, I^2 = 86%).

3.3.2.3. Expectancy/orientation/selective attention. One study, that by Tandon and Kumar [71], used a CNV paradigm to evaluate working memory. The CNV paradigm is used in EEG research to record the time taken to orientate and respond to a novel or salient stimulus, and, as such, has been considered a measure of working memory [62]. Despite a large amount of research using this paradigm, agreement about the interpretation of the components of the output is elusive – for a comprehensive discussion of the arguments please see Rohrbaugh and Gaillard [62]. Bearing that in mind, a large, significant effect estimate of 1.01 (95% CI 0.22 to 1.81) was found in favour of faster performance by healthy controls.

3.3.2.4. Sensitivity analysis. There was no change in any of the outcomes in the sensitivity analysis (see Appendix A, Fig. A.2).

3.3.3. Physiological outcomes

Physiological outcomes were divided into three major outcomes: latency and amplitude from EEG recordings (ie, in response to a task), and BOLD activity captured by fMRI. Interpretation of EEG results was considered in light of both latency and amplitude outcomes where they were provided; in many cases, latency was the only outcome reported.

3.3.4. Outcome 3: latency and amplitude of EEG responses

Four studies evaluated the latency and amplitude of response, and, based on the test used, evaluated 3 different constructs: auditory working memory, expectation/orientation and selective attention via a CNV paradigm, and running memory (Table 5). A forest plot of the latency results is presented as Fig. 4 and amplitude results in Fig. 5.

3.3.4.1. Auditory working memory. Pooled results from 7 latency comparisons across 2 studies show that chronic pain is not associated with decreased latency of auditory working memory – a nonsignificant effect estimate of 0.05 (95% CI −0.67 to 0.76) was found for latency and 0.41 (95% CI −0.09 to 0.91) for amplitude. Two studies used the auditory oddball test, and, in total, reported latencies for 4 components (N1, N2, P2, P3) [14,70] and amplitude for 1 component (P3). Demirci and Savas [14] also included 2 trials of the task reporting the P3 component (in order to correct for habituation). Significant heterogeneity was detected (χ^2 = 14.55, *P* = .02, I^2 = 59%).

3.3.4.2. Expectancy/orientation and selective attention. One study investigated expectancy, orientation, and selective attention (to a salient stimulus) using a CNV paradigm [71]. Five different latency components were reported [N1, P3, orientation (O), expectancy (E), and CNV] and 3 corresponding amplitude values were reported (O, E, and CNV). Pooled latency results found a nonsignificant effect estimate of 0.28 (95% CI −0.52 to 1.08), indicating no difference between the groups. Pooled amplitude results also found a nonsignificant effect estimate of 0.32 (95% CI −0.43 to 1.07), indicating no difference between the groups.

3.3.4.3. Running memory. One study evaluated P3 amplitude in the 400–600 ms latency range using the difficult probe test and found a large significant effect estimate of 2.72 (95% CI 1.85–3.59), suggesting a larger neural activation to a salient stimulus in the chronic pain group [74]. Although the raw data were not available, Veldhuijzen et al. [74] reported no significant difference between latencies of the 2 groups.

3.3.5. Outcome 4: BOLD signal changes

One study [65] evaluated the percentage change in BOLD signals between a chronic pain group and a control group during an n-back working memory task. A significant difference in favour of a stronger BOLD activity in the control group at all involved brain regions was reported. Specifically, in people with chronic pain there was decreased activation in the dorsolateral prefrontal cortex bilaterally (*P* < 0.01), right parietal cortex (*P* < 0.01), supplementary motor area bilaterally (*P* < 0.05, *P* < 0.01; right, left respectively), and the ventrolateral prefrontal cortex bilaterally (*P* < 0.01).

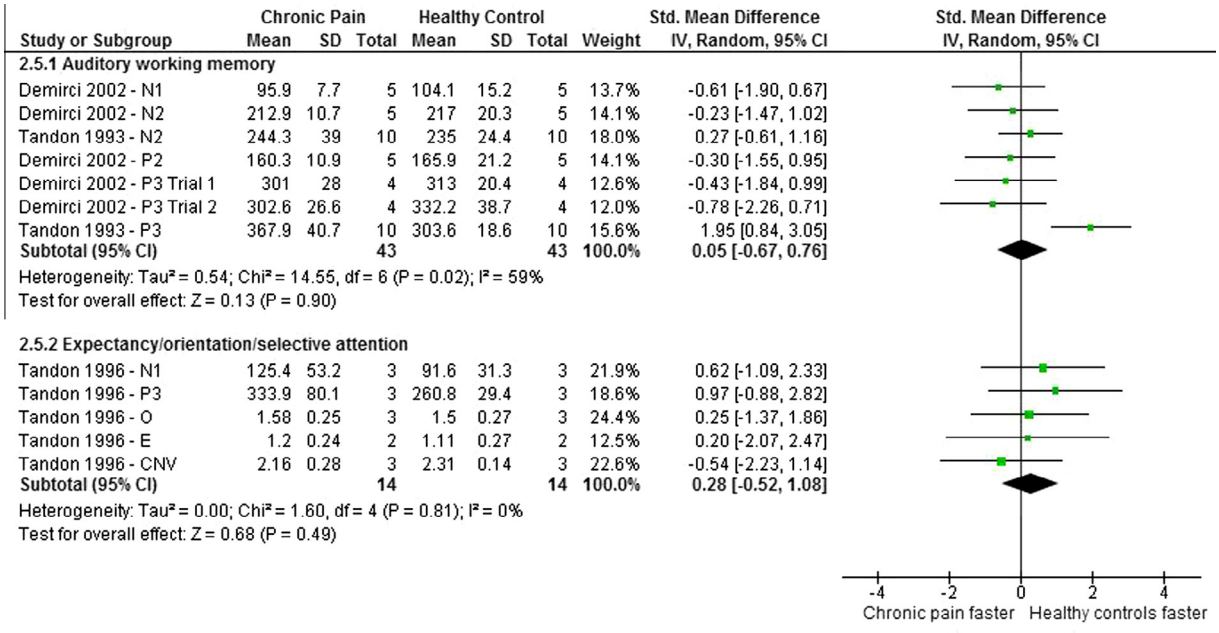

Fig. 4. Forest plot of outcome 3: latency results. IV = inverse variance; CI = confidence interval; O = orientation wave; E = expectancy wave; CNV = contingent negative variation; df = degrees of freedom.

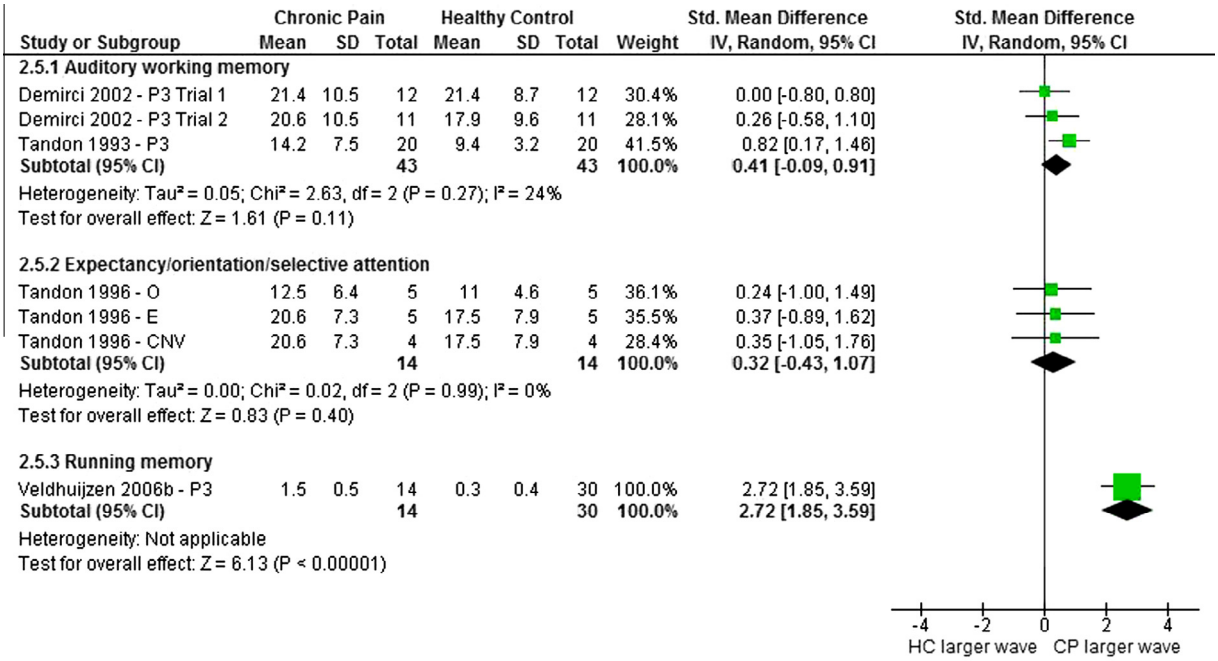

Fig. 5. Forest plot of outcome 3: amplitude results. IV = inverse variance; CI = confidence interval; O = orientation wave; E = expectancy wave; CNV = contingent negative variation wave; HC = healthy controls; CP = chronic pain; df = degrees of freedom.

3.3.5.1. Sensitivity analysis. We chose to leave in comparable results between subgroups (N2 and P3 for latency, and P3 and CNV for amplitude). There was a shift in the expectancy/orientation/selective attention subgroup P3 latency results; a significant, large effect estimate of 1.18 (95% CI 0.36 to 1.99; see Appendix A, Fig. A.3) was found. There was no overall change to the amplitude results (Appendix A, Fig. A.4).

4. Discussion

We aimed to determine the evidence that chronic pain is associated with working memory deficits. Notwithstanding the high heterogeneity within the field, pooled results from behavioural outcomes reflect a consistent, significant, moderate effect, which was not altered by sensitivity analyses. With the exception of 1 study [73], pooled results from physiological outcomes provide no evidence for an effect.

If working memory tests reflect brain processing and a behavioural difference exists, so too must a physiological difference. That we found no evidence of physiological effects suggests that studies may have been underpowered and/or have measured the wrong thing. Reports of grey matter changes in several relevant brain areas in chronic pain [3,40] would support this suggestion. That sensitivity analysis altered a latency result in 1 subgroup also diminishes the confidence we would place in these results. Alternatively, perhaps behavioural studies are confounded by inadequate removal of bias (see later).

Measuring the "right thing" is a challenge in this field. The exact mechanisms that underpin the complex relationship between pain and attention are not understood [37]. People with chronic pain do display working memory deficits, at least behaviourally, but what does this mean? Impairment in working memory will limit planning, mental flexibility, and decision making; it will disrupt attention and thus impede the effectiveness of cognitive behavioural and "Explain Pain"-type interventions; it might hamper return to activities of daily living and disrupt problem solving responses to get out of pain [8]. But how do we investigate the specific nature of the deficits?

One model – the neurocognitive model of attention posited by Legrain et al. [37] – encourages hypothesis generation in a clinical research setting to consider specific cognitive functions, such as decision making and inhibitory control. In this model, working memory acts to process competing stimuli and prioritise the allocation of attention according to implicit and explicit cognitive goals, and the salience of sensory signals. Factors such as high somatosensory expectations (the expectation of pain from a task) or previous reward for behaviour may implicitly alter the attentional set [5], while attention to a task may promote ongoing action and maintain desired behaviour [22]. Clearly, cognitive impairment in people with chronic pain needs to be investigated in a standardised and targeted manner, and it seems we need to develop different paradigms in order to untangle the physiological mechanisms associated with behavioural deficits.

4.1. Behavioural evidence of working memory deficit in chronic pain

We defined working memory as a non-unitary construct. Our search strategy reflected the possibility that one may perform poorly in one construct, but well in others by including and then grouping tests for different working memory constructs. Overall, pooled performance on number count data constructs was remarkably similar. Reaction time data also showed very similar pooled effect estimates across constructs. This suggests that neuropsychological tests may not be specific to the constructs or that people with chronic pain have similar deficits in most constructs or even that working memory is a unitary construct (early and current research would not support this view [13,58,68]).

4.2. Physiological evidence of working memory deficit in chronic pain

EEG results demonstrated no difference between chronic pain patients and controls. The 2 auditory oddball studies [14,70] found contrasting results for P3 component latency, and neither study found an amplitude effect. Different chronic pain conditions and age groups might explain the discrepancy, but that healthy controls could be worse than one chronic pain condition and better than another seems unlikely. Differences were not explained by medication effects; patients were either not on medication [70] or the use of analgesics by patients was prohibited for the week before testing [14].

Whether people with chronic pain use more or less cortical resources to complete a working memory task is not answered by this review. Tests of "running memory" show a larger EEG amplitude for people with chronic pain in 1 study [74] yet a weaker BOLD signal in another [65]. The difference between EEG and fMRI measures may reflect differences in the way these tools measure background "resting state" activity of cortical neurons, or perhaps the results reflect medication effects – the EEG study [74] controlled for medication, but the fMRI study [65] did not. Further investigations are needed to clarify such diverse findings.

4.3. Risk of bias

The risk of bias was high. Only 7 studies [1,29,31,33,34,65,67] reported serial recruitment of cases. The belief that working memory is impaired in people with chronic pain raises the risk that patients who appear to demonstrate working memory deficits are recruited preferentially – a clear selection bias and a fundamental threat to validity. Ten studies did not reference their diagnostic criteria for chronic pain and 10 did not screen controls using the same criteria that were used to include cases. These problems raise the risk of false inclusions in either group. Eight studies failed to screen for a psychiatric disorder. This is important – post-traumatic stress disorder, for example, is associated with working memory deficits [21] and has known comorbidity with chronic pain [53]. Only 7 studies reported that their outcome assessors were blind to group, which raises the risk of reporting and outcome bias. Although most studies matched for the confounding variables of age, gender (the exceptions were studies [31,33] that presented standardised normative data), and education, most did not control for medication use or sleep, which are known to affect working memory [30,59,64]. It may be that impaired working memory found in chronic pain reflects medication use or lack of sleep, not chronic pain.

The potential importance of this aspect of our study should be emphasised – that our only empirical evidence of working memory deficits in chronic pain are at high risk of bias should leave us open to the possibility that no such deficits really exist. Ideally, the positive findings reported in the literature need to be replicated under more stringent methodological conditions.

4.4. Strengths and weaknesses

Although several comprehensive narrative reviews of working memory and chronic pain exist [25,48], this is the first systematic and exhaustive review, or meta-analysis, of the extant literature. Because working memory tasks are often embedded within a larger study, the search strategy in this field is particularly important. We included all tasks that explicitly stated they were evaluating working memory, regardless of the terminology used for the task (eg "short term memory", "running memory", "executive function"). Although it is technically possible that we missed relevant studies, we made every attempt to minimise this possibility.

Several issues made the current meta-analysis very complex. We pooled data regardless of diagnosis on the basis that the central nervous system changes associated with chronic pain are common across body areas [19,39,49,50,75,77] and there are not particular brain areas in which dysfunction is idiosyncratic to particular chronic pain diagnoses [2,72]. This approach allowed us to calculate pooled results and thus offers greater confidence in the results, but it also dilutes any condition-specific working memory deficits that may exist.

The literature offers no clear systematic method by which to investigate moderators of working memory. Further data extraction and analysis using meta-regression might quantify the contribution of such moderators as anxiety, depression, and medication use, which could explain some of the heterogeneity we found. Our a priori decision to subgroup the data via working memory constructs, which is in line with gold-standard recommendations [27], aimed to minimise the heterogeneity and improve confidence in the results. However, heterogeneity among experimental approaches also presented challenges for pooling. We used what appears to be the dominant understanding of working memory – the non-unitary model [8] – but it is by no means the only understanding (see Postle [58]). It is likely that some of the papers included in this review had a different understanding of what working memory actually is, a problem compounded by authors not clearly defining working memory.

4.5. Future research

The clear threats to validity that were identified in our risk of bias assessments provide obvious recommendations for future studies. Studies should use sequential recruitment, apply recognised diagnostic criteria for chronic pain, screen the control group for chronic pain and both groups for psychiatric disorder, and blind both assessors and patients. It is also pertinent that larger studies are performed, as many current studies have small sample sizes. We strongly recommend the development of standardised definition, terminology, testing, and interpretation of working memory and its moderators. We propose an international database similar to the successful BrainNet database currently banking cognitive performance data from healthy controls and those diagnosed with a psychiatric disorder [18,66,78]. Such a collaborative approach would increase statistical power and decrease the chance of redundant experiments by separate groups, and would greatly enhance our collective pursuit of a better understanding of what is a huge and costly problem (US$100 billion dollars per year [51]). Finally, we would recommend simultaneous fMRI and EEG so as to optimise both spatial and temporal aspects of assessment.

5. Conclusions

People with chronic pain perform worse on tests of working memory than healthy control participants do. Moderate effects were observed consistently across studies and paradigms, but threats to validity suggest cautious interpretation of the main result. In contrast to the behavioural data, there seems to be no physiological evidence of differences between patients and controls during working memory tests.

Conflict of interest statement

The authors had no conflicts of interest.

Acknowledgments

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Appendix A.

See Figs. A.1–A.4.

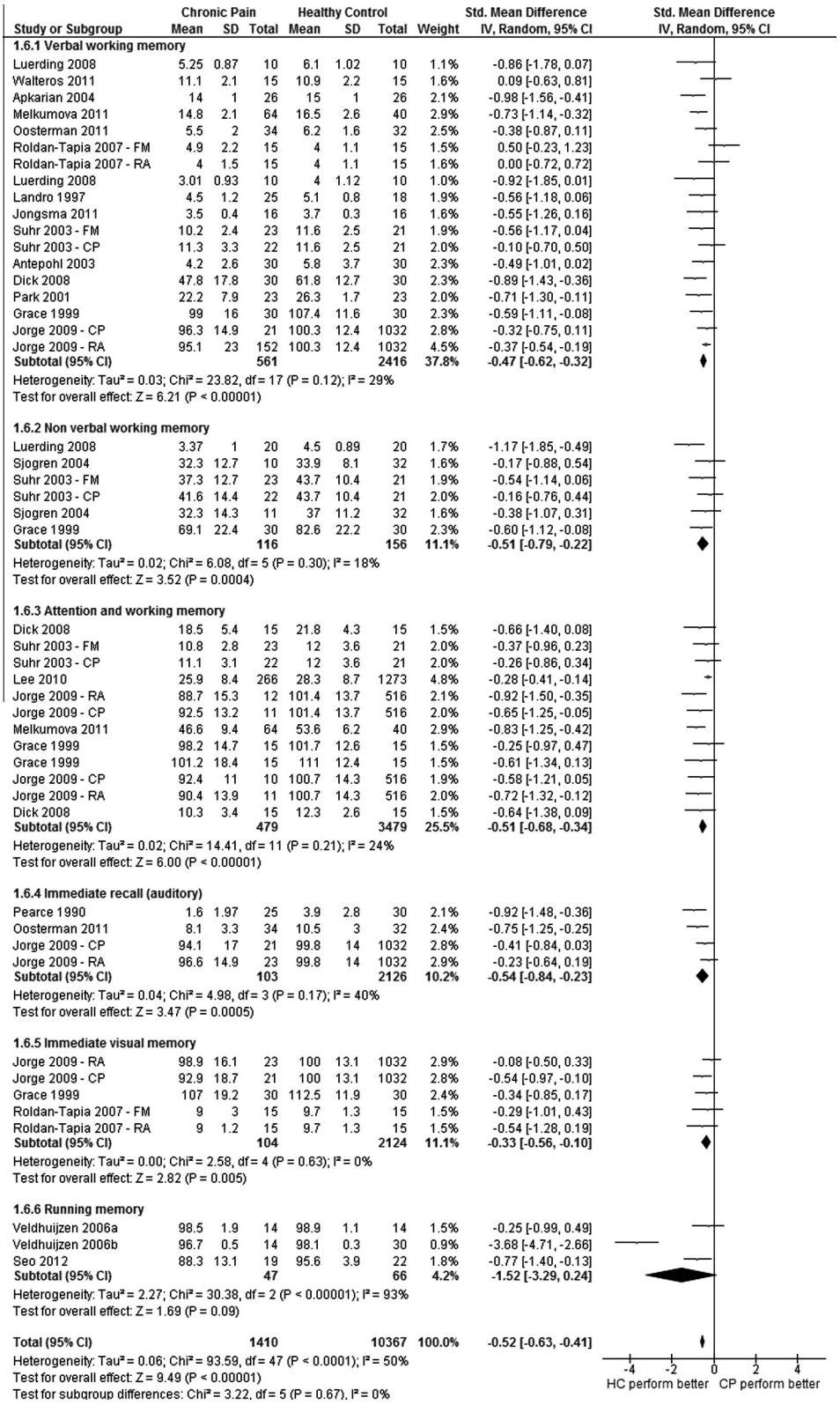

Fig. A.1. Forest plot of outcome 1: the number of correct responses. Sensitivity analysis for groups of ⩾10. IV = inverse variance; CI = confidence interval; CP = chronic pain; FM = fibromyalgia; RA = rheumatoid arthritis; df = degrees of freedom.

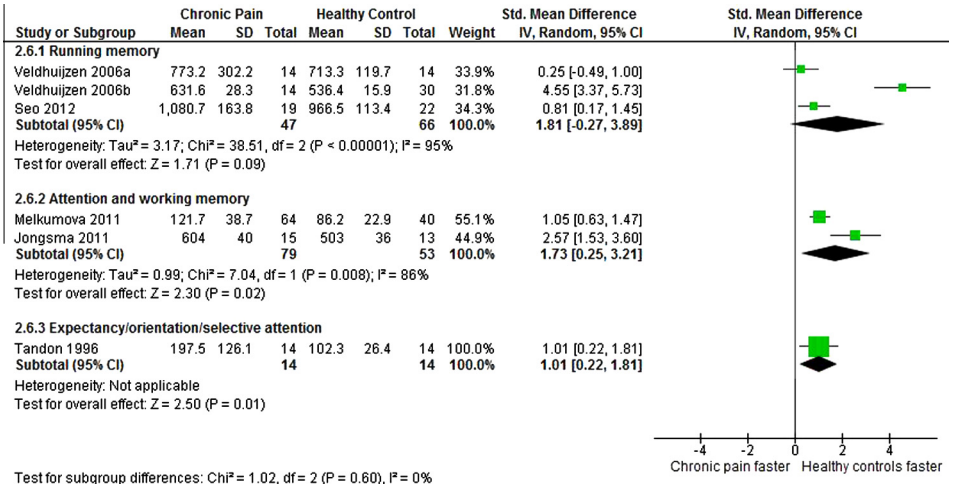

Fig. A.2. Forest plot of outcome 2: reaction time. Sensitivity analysis for groups of ⩾10. IV = inverse variance.

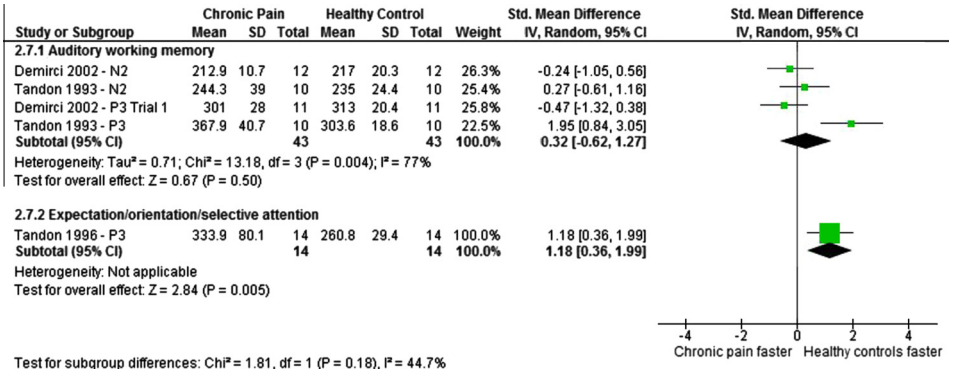

Fig. A.3. Forest plot of outcome 3: latency results. Sensitivity analysis for groups of ⩾10. IV = inverse variance; CI = confidence interval; df = degrees of freedom.

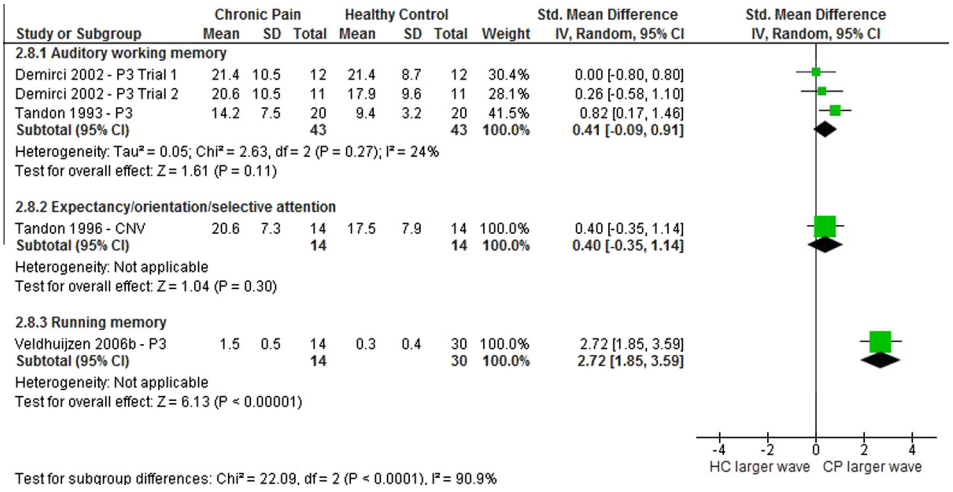

Fig. A.4. Forest plot of outcome 4: amplitude results. Sensitivity analysis for groups of ⩾10. IV = inverse variance; CI = confidence interval; CNV = contingent negative variation wave; HC = healthy controls; CP = chronic pain; df = degrees of freedom.

Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.pain.2013.03.002.

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