What are the predictors of altered central pain modulation in chronic musculoskeletal pain populations? A Systematic review.

Jacqui Clark, Gillian Yeowell, Jo Nijs, Peter Goodwin

Introduction

Chronic pain is experienced when, subsequent to the subacute phase of healing, pain persists beyond the expected healing time frame, leading to poor outcomes. Existing studies have investigated predictors of poor outcomes associated with musculoskeletal pain including disability (Sterling et al, 2006; Walton et al., 2011), and failure to return to work (see Iles et al., 2008, 2009 for reviews). However, there remains little consensus, probably due to the heterogeneity of outcomes studied and, moreover, the heterogeneity of pain mechanisms. Hence, the transition from acute musculoskeletal pain to chronic pain is currently difficult to predict.

Common to a significant proportion of chronic musculoskeletal pain populations is the phenomenon of sensitisation of the central nervous system pain pathways, i.e. altered central pain modulation. Altered central pain modulation manifests as a predominantly non-nociceptive, non-neuropathic pain mechanism (Smart et al., 2012; Nijs et al., 2014) and is defined as a dysregulation of the central nervous system causing neuronal hyper-excitability, characterised by generalised hypersensitivity of the somatosensory system to both noxious and non-noxious stimuli (Nijs et al., 2010; Smart et al., 2012). Altered central pain modulation involves impaired modulatory mechanisms within the central nervous system whereby nociceptive pathways are less inhibited and nociceptive facilitatory pathways enhanced, resulting in augmentation of nociceptive transmission (Baert et al., 2015).

Poor outcomes such as disability are not necessarily an indication of altered central pain modulation *per se*, despite being commonly associated with each other (Sterling et al, 2003; Ferrari, 2010). Disability may be the result of psychological factors that may not be predominantly a result of altered central pain modulation, such as fear avoidance (Vlaeyen and Linton, 2000). Similarly, poor outcomes such as chronic pain may or may not be an indication of altered central pain modulation, depending on the predominant pain mechanism. It is proposed that the phenomenon of altered central pain modulation should be investigated specifically in the aetiology of poor outcomes.

A strong clinical predictor of altered central pain modulation is "disproportionate, non-mechanical, unpredictable pattern of pain provocation in response to multiple/non-specific aggravating/easing factors" (Smart et al., 2012; p.342). Altered central pain modulation is associated with many non-specific chronic musculoskeletal pain conditions and the aetiology is poorly understood. It is considered by some that altered central pain modulation is a disease in itself rather than a disease of the particular presenting musculoskeletal condition (Mogil, 2012). From a clinical perspective, identifying predictors of altered central pain modulation may help to sub-classify "at-risk" patients at baseline after acute musculoskeletal pain onset. Appropriate management could then be prioritised accordingly to minimise the risk of altered central pain modulation and poor outcomes.

Therefore, the aim of the current study is to firstly, identify predictors of altered central pain modulation in adults with general musculoskeletal pain conditions and secondly, if data allow, determine predictors for altered central pain modulation in patients with non-specific low back pain. The scope of the current review follows the type of model intended to inform clinicians' therapeutic decision making, in accordance with Moons et al., (2014). It intends to focus on prognostic studies designed to predict a future health outcome (altered central pain modulation) as opposed to diagnostic predictor models or models designed to identify suspected existing disease (Moons et al., 2014).

Methods

The review protocol was registered prior to commencement of the search with PROSPERO, protocol no.: PROSPERO 2015:CRD42015032394. The methods used in the current study follow the guidelines published in the PRISMA Statement for systematic reviews (Moher et al., 2009). This is supplemented by methodological guidelines specific to systematic reviews of prognostic studies by Dretzke et al., (2014) and Moons et al., (2014).

Search strategy

The following electronic databases were searched from their inception up to March 2016: EMBASE (via Ovid), Medline (via Ovid), CINAHL (EBSCO), Scopus, Web of Science (via Web of Knowledge) and Google Scholar. Reference lists of the eligible studies were hand searched and 31 other researchers in the field were contacted by email by JC in order to identify any missed, potentially important studies.

A pilot search was carried out to test preliminary search terms identified from related literature. With a view to finding studies detailing prognostic indicators which predict altered central pain modulation, the search term "Prognos*" was piloted. This was with the intention of capturing terms such as prognosis / prognostic indicators / prognostic factors / poor prognosis and was initially focussed on low back pain (LBP) populations. However, it became clear that the studies with chronic LBP and prognos* were generally looking at the natural course of LBP or the response to management regarding whether or not they would return to work. Therefore the pilot search was altered to acute low back pain AND prognos* because this would potentially yield prognostic indicators for a poor outcome in acute LBP. However, poor outcome in acute LBP can lead to various outcomes such as disability or

persistent pain, which are not specific to altered central pain modulation. Therefore, specific terms for the outcome measures of altered central pain modulation had to be developed, with the assistance of examples drawn from other review studies in altered central pain modulation (Roussel et al., 2013; Malfliet et al., 2015).

The term predict* was chosen because statistically logistic regression models are used to find predictors (Field, 2009). Dretzke et al., (2014) advises the use of both prognosis- and predictor-related terms, without filters, so as to minimise loss of relevant studies.

The term "central sensitisation" was also piloted. It became clear that there are two spellings, English and American, the latter using "z", as in "sensitization." Both spellings had to be included. No word filters were applied to the search strategy.

Subsequently, the systematic search was conducted to locate studies relevant to three key subject areas of the research question: 1) central sensitisation pain due to altered central pain modulation, 2) predictors and 3) musculoskeletal pain known to be associated with altered central pain modulation (Yunus, 2008), using the tested search terms. Keywords or database specific search terms (e.g. MeSH, subject terms, subject headings, and CINAHL headings) or a combination of both were used. The Boolean operators "OR" and "AND" were used to combine search terms within and between each of the subject areas. No time limits were applied to any of the databases. No filters were used in the search strategies, as recommended by Dretzke et al., (2014). Only full text studies reported in English were to be included. The systematic search was carried out independently by JC and PG. The search terms are detailed in table 1.

Table 1. Search terms

Target Population: Musculoskeletal pain	("low back pain" OR backache OR lumbago OR "ache, low back" OR "Low* back pain" OR "neck pain" OR "cervical pain*" OR cervicalgia OR cervicodynia OR "temporomandibular pain*" OR "widespread pain*" OR "musculoskeletal pain" OR "shoulder pain" OR whiplash)
	And:
Target condition: Central sensitisation pain; altered central pain modulation	("Central pain" OR "central sensitisation" OR "central sensitization" OR "central sensitivity" OR "central hypersensitivity" OR "endogenous analgesia" OR "descending nociceptive inhibition" OR "descending facilitation" OR "nociceptive facilitation" OR "central pain modulation")
	And:
Methodology: prospective predictive cohort studies using regression analysis	(inception OR prognos* OR predict* OR prospective OR cohort OR longitudinal OR "follow-up" OR "follow up study" OR Risk)

Eligibility Criteria

The review included only predictive or prognostic studies where baseline predictive factor measurements were taken pre-morbidly or at the acute stage of musculoskeletal pain onset. The primary outcome measurements were those that indicate a likelihood of the pain mechanism being specific to altered central pain modulation, measured at least 3 months after the initial acute pain onset. Longitudinal data were used in logistic regression models of analysis to identify predictors of altered central pain modulation.

Although prognostic longitudinal cohort studies using logistic regression models of analysis were expected in the search, it was agreed at the outset not to restrict the search to those only using logistic regression models of analysis. This decision was made in anticipation of a small number of studies eligible for inclusion to avoid unnecessary exclusion. It was proposed, *a priori,* that authors of potentially relevant studies could be contacted for

permission to re-run their data through a logistic regression analysis if necessary and if possible.

Of critical importance to this review was the primary outcomes specific to altered central pain modulation. An anticipated potential difficulty was the lack of a single gold standard measurement tool for the determination of altered central pain modulation. Quantitative sensory testing (QST) is an acceptable measurement procedure for sensory hypersensitivity (Shy et al.; 2003), a manifestation of altered central pain modulation. Another acceptable measure of altered central pain modulation is the Central Sensitisation Inventory (CSI) questionnaire (Mayer et al., 2012) validated in 2013 by Neblett et al., (2013). The CSI gives a score that indicates the likelihood of symptoms being attributed to altered central pain modulation. More recent clinical guidelines have been available detailing how to clinically identify altered central pain modulation (Smart et al., 2012; Nijs et al, 2014). Outcome measurements paralleling any of these guidelines were anticipated as being acceptable in the search process, especially for studies published before 2012 which did not use QST as the primary outcome measure.

Table 2. Eligibility criteria for study screening

Inclusion Criteria	Exclusion criteria
Prognostic longitudinal studies	Non musculoskeletal pain populations
Participants - Adult (age 18-65)	people aged under 18 or over 65;
Recruited pre-morbidly or at the acute pain onset with follow-up at least 3 months after pain onset.	Specific pathologies; post-surgical pain studies;
musculoskeletal pain (known to be associated with altered central pain modulation)	rheumatoid arthritis or any other rheumatic, neurological, oncological or internal disease.
measuring an outcome of altered central pain modulation according to clinical guidelines [5] (if described) or using QST	Functional outcomes not specific to altered central pain modulation such as return to work or disability-only outcomes.

Study selection:

Studies were screened according to titles and then by abstracts, based on the inclusion and exclusion criteria listed in table 2. All studies were independently screened by two reviewers (JC/PG) before collaboration on the screening. In the case of disagreement a third reviewer was available for consultation (GY). Discussion between reviewers enabled a consensus to be reached regarding the eligibility of the final studies for inclusion.

Risk of bias (quality) assessment:

At the study level, the QUIPS (Quality in Prognostic Studies; Hayden et al., 2013) risk of bias tool for prognostic studies was used to assess the quality of each study. This was tailored to the requirements of the review and supplemented by recommendations from the CHARMS (Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies) checklist by Moons et al., (2014). The final seven-part risk of bias check list was used to grade each study with an overall score of low, moderate, or high risk of bias, according to the QUIPS grading guidelines. The risk of bias grades were taken into consideration when evaluating the strength of findings in each predictive study.

Overall quality of evidence and strength of recommendation was determined using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) criteria (Guyatt et al., 2008). The final GRADE score incorporated the 4 categories, quality, consistency, directness and effect size. Evidence quality was based on the overall GRADE scores for each comparison and graded: high (at least 4 points overall), moderate (3 points), low (2 points), or very low (1 or less).

Data extraction (selection and coding)

JC and PG independently extracted results from the included studies.

Given the small number of studies and the variation in predictors and outcome measures across the selection, statistical pooling of data was not feasible. Instead, findings were synthesised qualitatively.

Results

The initial search yield was n=2,368 hits from the databases and n=13 from additional sources (Fig 1). After removal of duplicates, n=171 articles were selected from the initial hits. Screening of the titles, using the inclusion and exclusion criteria reduced the yield to n=107. Further screening by abstract reduced the yield to n=36. N=1 article was excluded as it could not be retrieved (Murphy and Cornish, 1984). Further exclusions were made based on non-English language reporting (n=2), primary outcomes not specific to altered central pain modulation (n=22), too short a follow-up time (n=1), subjects being above age 65 (n=1) and only associations being calculated (n=1). The total number of full articles selected was n=9. Full text articles were screened by JC and PG and there was no disagreement requiring consultation with the third reviewer (GY). Based on the research question, the inclusion and exclusion criteria and clinical knowledge of altered central pain modulation, it was agreed by consensus that the n=9 studies meeting study eligibility were: McBeth et al., (2001), Sterling et al., (2003), Harkness et al., (2004), Diatchenko et al., (2005), Gupta et al., (2007), Wynne-Jones et al., (2006), Ferrari, (2010), Slade et al., (2014) and Markkula et al., (2016).

One corresponding author was contacted in order to clarify a reporting error – the study reported that high tender point counts significantly predict WP but quoted a non-significant p value of 0.157 (Gupta et al., 2007). It was confirmed by the author as a typographical error in the article and corrected as p=0.042.

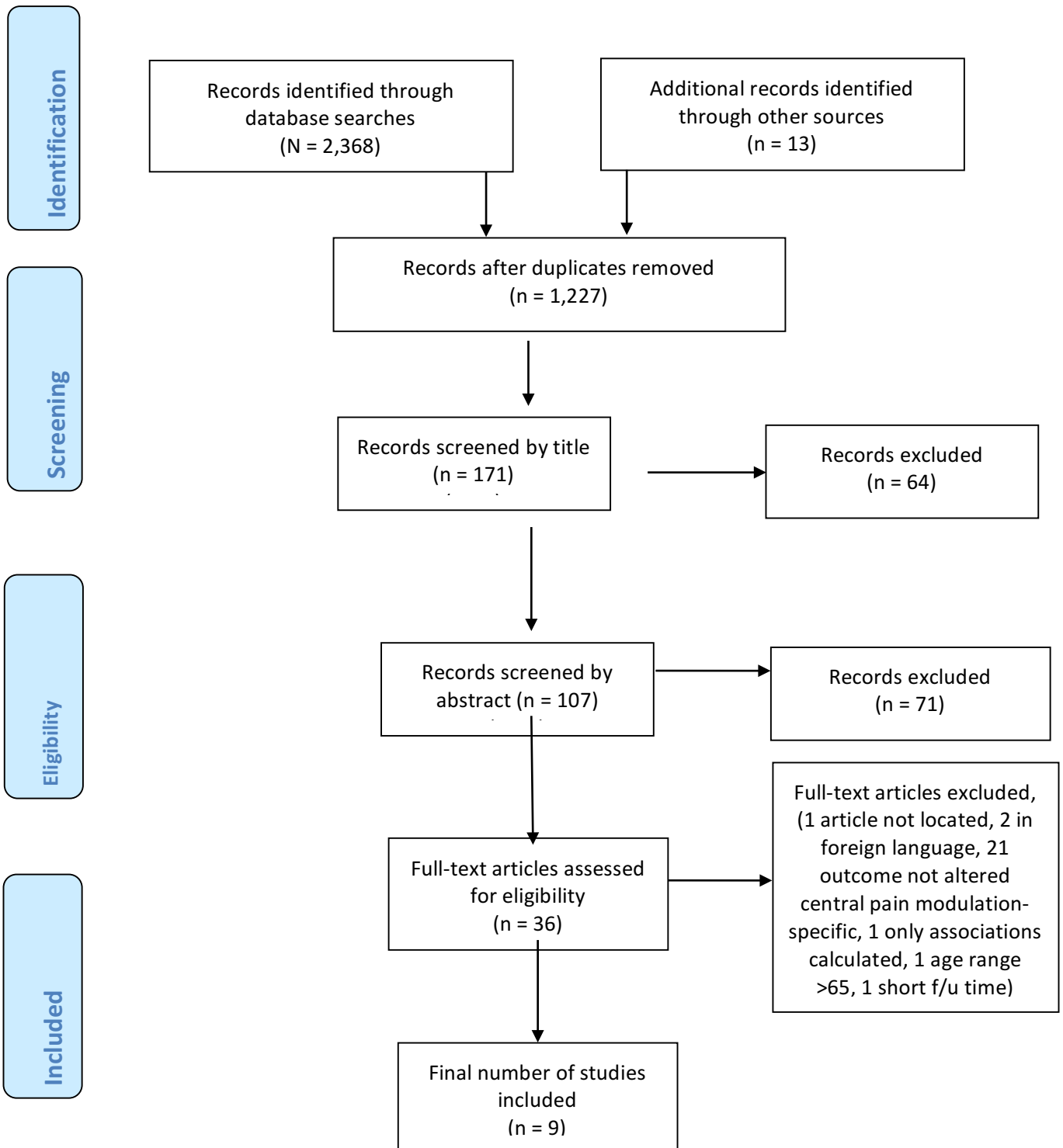Figure 1. PRISMA flowchart describing the selection of articles.

Identification

Records identified through database searches (N = 2,368)

Additional records identified through other sources (n = 13)

Records after duplicates removed (n = 1,227)

Screening

Records screened by title (n = 171)

Records excluded (n = 64)

Eligibility

Records screened by abstract (n = 107)

Records excluded (n = 71)

Full-text articles assessed for eligibility (n = 36)

Full-text articles excluded, (1 article not located, 2 in foreign language, 21 outcome not altered central pain modulation-specific, 1 only associations calculated, 1 age range >65, 1 short f/u time)

Included

Final number of studies included (n = 9)

Table 4: Study Demographics

Study	Age (years)	Male / female	Setting
McBeth et al. 2001	Range = 18-64	Male n=608, Female n=796.	Random population sample, UK
Sterling et al. 2003	Mean = 36.27(SD+/-12.69) Controls: mean = 40.1 (SD+/- 13.6 years)	Male n=24, Female n=56, 20 controls 8 males, 12 females,	Hospital accident and emergency departments, primary care practices (medical and physiotherapy) and media advertisements
Harkness et al. 2004	Median = 23	Male Approx. 1/3	12 diverse occupational settings
Diatchenko et al. 2005	Range = 18-34	Females n=202	Setting not mentioned ? population study implied
Wynne-Jones et al. 2006	Median = 41 yrs. [IQR= 33–50]	Female = 51%	UK based vehicle insurance co.
Gupta et al. 2007	25–39 n=66 (28.6%) 40–49 n=54 (23.4%) 50–65 n=111 (48%)	Male n=71 (30.7%) Female n=160 (69.3%)	Three population-based primary care registers covering two socio-demographically mixed suburban areas
Ferrari 2010	Mean = 37.5 (SD+/-13)	Male n=32, Female n=37	Single primary care walk-in clinic in Canada
Slade et al. 2014	Range = 18-44	Not stated	OPPERA (Orofacial Pain: Prospective Evaluation and Risk Assessment) research clinic USA
Markkula et al. 2016	Mean = 27.7 (SD± 7.3)	Male = 46.2% Female = 53.8% .	Finnish Twin Cohort, Finland

Table 5: Summary of study characteristialtered central pain modulation

Study	Study Design	Condition	Inclusion / exclusion criteria	Base-line time point	Predictors	Primary outcome measure	Follow-up	Results as presented in study
McBeth et al. 2001	Population based prospective study	WP	Included if free of WP pre-morbidly and showed evidence of somatisation	Pre-morbid	ACR criteria for WP Somatising Q'aires: somatic symptoms checklist Illness Attitudes Scale General health Questionnaire Fatigue questionnaire All described and valid	ACR criteria for WP	12 months	Illness Behaviour Scale and Somatic Symptom scores most strongly predicted new onset chronic WP at 12 months. Strong relationships between baseline test scores and subsequent risk of chronic WP (odds ratio for the Somatic Symptom Checklist 3.3; odds ratio for the Illness Behavior subscale of the Illness Attitude Scales 9.0). All 95% confidence intervals excluded unity. These associations were independent of baseline pain status.
Sterling et al. 2003	Prospective cohort	Whiplash	Quebec Task Force Classification of WAD II or III Exclusion: WAD IV, experienced concussion, LOC or head injury, previous history of whiplash, neck pain/ headaches that required treatment.	Within 1 month	Thermal (hot, cold) pain thresholds Brachial plexus provocation test (BPPT) Sympathetic vasoconstrictor reflex GHQ-28 10 cm VAS scale	Neck disability index (NDI)	ALL PF's measured at 2, 3 and 6 months post-injury NDI at 6 months	3 groups – Recovered, Mild, Moderate to Severe Pain and Disability at 6 months: PPT's and TPT's lower at baseline for "Moderate to Severe" group and remained low. Other groups had higher baseline thresholds and recovered to normal by 6 months. Psychological distress not found to be a predictor of altered central pain modulation. No CI's & OR's
Harkness et al. 2004	Prospective cohort	WP	Newly employed workers Subjects free of WP selected for F/u.	premorbid	Detailed questionnaire information on: Mechanical exposure Posture Physical environment PsychoSoc risk factors	Pain status questionnaire based on ACR 1990 criteria	12 and 24 months	Those who pulled heavy weights had an 80% increased, but not statistically significant, risk of symptom onset compared with those who did not perform these activities. Those who squatted for >15 minutes (OR 2.0 95%CI: 1.1-3.6)and those who thought their work was monotonous or boring (OR 1.9 95% CI: 1.1–3.2) had a significantly increased approximately double) odds of developing new-onset WP in 2 years.
Diatchenko et al. 2005	3 year prospective longitudinal	TMD	TMD free at baseline, no exclusion criteria	Pre-morbid	COMT genotyping for pain sensitivity PPT's Ischaemic pain thresholds	TMD with QST high sensitivity	3 monthly interviews and annual physical examinations for up to 3 years to identify new onset TMD	From n=170, n=15 new onset TMD were detected; in whom COMT genotypes for HPS were significantly more prevalent than the APS and LPS haplotypes. HPS haplotypes (and associated pain sensitivity in QST) predict new onset TMD. The incidence density ratio of 2.3 was significant (95% CI: 1.1–4.8), suggesting that the HPS and/or APS haplotypes represent significant risk factors for TMD onset.
Wynne- Jones et al. 2006	Prospective longitudinal	WP	Inclusion: UK residents, fluent in English. Excluded if reported WP in the period 1 month pre-MVA.	Median 23 days post MVA	General Health Q'aire Illness Attitude Q'aire Rate general health (excellent to poor) Somatic Symptom check list	WP (ACR 1990 criteria)	12 months	54 (7.8%) reported new WP. Few collision-specific factors predicted the onset of WP. In contrast, post-collision physical symptoms (rate ratio 2.5, 95% confidence interval 1.2–5.1), pre-collision health-seeking behavior (RR 3.6, 95% CI 1.6–7.9), pre-collision somatization (RR 1.7, 95% CI 0.99–2.8), and perceived initial injury

					Primary care visit count in 1 year period pre MVA Collision specific factor Q'aire Symptom severity Q'aire VAS pain scale			severity (RR 1.7, 95% CI 0.9–3.3), in addition to older age (RR 3.3, 95% CI 1.5–7.1), were all independently predictive of new onset WP. In combination, these factors accounted for about a 20-fold difference in the risk of new onset WP.
Gupta et al. 2007	Prospective longitudinal	WP	Included if free of WP but who showed evidence of somatising behaviour.	Pre-morbid	Somatic symptom score Illness behaviour score Total pain threshold Tender point count (ACR 1990 criteria)	WP (ACR 1990 criteria)	15 months	In people who show somatising behaviour a high pre-morbid tender point count is associated with the onset of new WP (OR 4.1, 95% CI: 1.1 -15.5, p=0.042), a low pain threshold at baseline is not.
Ferrari 2010	Prospective Longitudinal with consecutive recruitment	Whiplash neck injury following motor vehicle accident	Included: WAD Gd 1 or 2, they were seated within the interior of a car, truck, sports/utility vehicle, or van in a collision (any of rear, frontal or side impact) No LOC Age 18+ Within 7 days accident Excluded: #'s,neuro signs, (i.e. WAD gd 3 – 4) prev WAD, non trauma pain Non MVA	Within 7 days of onset	Recovery expectation questionnaire Age Gender Initial Whiplash Disability Questionnaire score	BPPT (1- angle of elbow flexion & 2- 10cm VAS)	3 months	Those who expect 'never to get better' or 'don't know' have a much higher likelihood of developing at least one sign of central sensitisation 3 months later.
Slade et al. 2014	Nested Case control study using longitudinal data from prospective cohort study.	TMD	Included: English language fluency, intention to live in the area > 2 years. <5 HA's pcm for previous 3 months, no prior TMD symptoms / treatment, absence of 13 specific health conditions. Excluded: orofacial pain >5 days in past 30 days and/or evoked pain in >=3 muscle locations or =>1 TMJ.	Pre-morbid	PPT's Interval between visits Study site Gender Race ethnicity	TMD and PPT's	Up to 5 years	Pre-morbid PPT's measurements not useful in predicting the course of TMD (whether TMD will be transient vs persistent) but do provide insight into the mechanisms of altered central pain modulation in generalized pain in recent onset TMD.
Markkula et al. 2016	Prospective longitudinal	WP	Included if no pain nor exclusion criteria reported in 1975 and 1981. Excluded if had rheumatic diseases, malignancies, Subjects with: missing data on regional pain in 1975 & 1981;WP & likely FM in 1975 & 1981; reported frequent use of analgaesialtered central pain modulation in 1975 or 1981.	Pre-morbid In 1975	FM Q'aire, medical record data. Questions based on other predictive study results on: Regional pain Headaches Migraine Zygosity (by validated twin q'aire.) Sleep Weight BMI Smoking Physical activity leisure-time activity.	WP or FM using ACR 1990 criteria for FM	6 and 15 years: T1: 1981, T2: 1990.	The strongest non-genetic predictor was frequent headache (OR 8.6, CI 95 % 3.8–19.2), followed by persistent back pain (OR 4.7, CI 95 % 3.3–6.7) and persistent neck pain (OR 3.3, CI 95 % 1.8–6.0).

Table Glossary: *ACR – American College of Rheumatology; WP – widespread pain; FM – fibromyalgia; Q'aire - questionnaire; WAD – whiplash associated disorders; LOC – loss of consciousness; BPPT – brachial plexus provocation test; GHQ – general health questionnaire; QST –quantitative sensory testing; PPT – pressure pain threshold; TPT - temperature pain threshold. COMT- catecholamine-O-methyltransferase*

Study Characteristics

All the studies were prospective longitudinal cohort studies (table 5). All investigated prognostic factors with an outcome measure related to altered central pain modulation.

Baseline measurements of predictors were taken pre-morbidly by the majority of studies (McBeth et al., 2001; Harkness et al., 2004; Diatchenko et al., 2005; Gupta et al., 2007; Slade et al., 2014 and Markkula et al., 2016) and at the acute stage of the pain in Sterling et al., (2003), Wynne-Jones et al., (2006) and Ferrari, (2010), so that it was likely that baseline predictors were measured before the onset of altered central pain modulation. Follow-up measurements were all taken at time points beyond the normal healing time frame, ranging from 3 months (Diatchenko et al., 2005; Ferrari, 2010) to 6 months (Sterling et al., 2003), 12 months (McBeth et al., 2001; Wynne-Jones et al., 2006), 15 months (Gupta et al., 2007), 24 months (Harkness et al., 2004), 5 years (Slade et al., 2014) and 15 years (Markkula et al., 2016).

Predictors varied widely across studies and can be grouped according to sensory sensitivity, psychological and other factors. Six studies (McBeth et al., 2001; Sterling et al., 2003; Diatchenko et al, 2005; Gupta et al., 2007; Slade et al., 2014; Markkula et al., 2016) used sensory sensitivity at baseline as a predictive factor of altered central pain modulation. Diatchenko et al., (2005) specifically used a genetic marker for sensitivity, unlike the others which included quantitative sensory testing (QST) or the American College of Rheumatology (ACR; 1990) criteria as predictors. Psychological measures included Somatising Symptoms Checklist (McBeth et al., 2001; Gupta et al., 2007) and Illness Attitudes Scale (McBeth et al., 2001; Wynn-Jones et al., 2006), Illness Behaviour Score (Gupta et al., 2007), Recovery Expectation Questionnaire (Ferrari, 2010), perception of premorbid general health including psychological distress, using the General Health Questionnaire (McBeth et al., 2001; Sterling et al., 2003; Wynne-Jones et al., 2006) and work-related psychosocial risk factors (Harkness

et al., 2004). Work related physical factors (Harkness et al., 2004) and collision-specific factors (Wynne-Jones et al., 2006) were also tested as predictors.

Risk of Bias Assessment

All studies were ultimately judged as low risk of bias. Diatchenko et al., (2005) initially presented as high ROB. It was written in a style relevant to its background of genetics and according to the journal requirements in which it was published and in order to review it fairly, the supporting information was obtained from the journal website.

Table 3. Risk of Bias summary for methodological quality.

Study	Study participation (QUIPS)	Target Population (CHARMS)	Study attrition /complete follow up (QUIPS)	Prognostic Factor Measure (QUIPS)	Outcome measurement (QUIPS)	Study confounding (QUIPS)	Statistical analysis and reporting (QUIPS)	Overall Statement of Risk of Bias
	Data related to outcome may be different for participants and eligible non-participants	Description of source of participants and inclusion and exclusion criteria.	Data related to outcome may be different for completing and non-completing participants	The measurement of the PF may be different for different levels of the outcome of interest	Measurement of the outcome may be different related to the baseline level	Outcome may be distorted by another factor related to outcome	Reported results may be spurious or biased related to analysis or reporting	Based on number of low, moderate and high ratings
McBeth et al., 2001	L	L	L	L	L	L	L	Low
Sterling et al., 2003	H	L	L	L	L	M	L	Low
Harkness et al., 2004	L	L	H	L	L	L	L	Low
Diatchenko et al., 2005	L	L	H	L	L	L	L	Low
Wynne- Jones et al., 2006	L	L	H	L	L	L	L	Low
Gupta et al., 2007	L	L	L	L	L	L	L	Low
Ferrari, 2010	L	L	L	L	H	L	M	Low
Slade et al., 2014	M	L	H	L	M	L	L	Low
Markkula et al., 2016	L	L	L	L	L	L	L	Low

L= low risk of bias; M = moderate risk of bias; H = High risk of bias.
QUIPS = Quality in Prognostic Studies
CHARMS = Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies

Three main groups of predictors were identified across the studies as: 1) sensory sensitivity factors, 2) psychological factors, and 3) other factors (Table 6). According to the groups, there might be a higher risk of the patient developing altered central pain modulation, if:

1) High sensory sensitivity can be identified at baseline using QST or the ACR guidelines for tender point counts or genetic testing for sensory sensitivity;

2) Somatisation, poor illness attitudes and negative expectation of recovery can be identified at baseline, (Somatisation Checklist; Illness Attitudes questionnaire; Expectation of Recovery questionnaire);

3) Pre-morbid frequent headaches were apparent.

Table 6: Clinical interpretation of results

Author	Grouped Results	Quality of evidence and strength of recommendation (GRADE score)
Sensory Hypersensitivity at baseline		
Sterling et al., (2003)	Higher sensory sensitivity (using QST) within 4 weeks of a whiplash injury is a predictor of altered central pain modulation (low PPT) at 6 months, associated with moderate to severe pain and disability and poor recovery. High sensory sensitivity at the acute stage is apparent in all individuals who experienced a whiplash injury but sensory sensitivity is 1) less elevated at baseline and 2) returns to normal, in those who do not develop altered central pain modulation at 6 months, compared with those who do.	Moderate
Diatchenko et al., (2005)	Genetic sensitivity to pain, associated with pre-morbid pain sensitivity to QST is a predictor of altered central pain modulation (TMD with low PPT's and ischaemic pain thresholds). In this study group, healthy individuals with genetic markers for sensitivity (COMT genotyping for HPS	

	haplotypes) developed TMD with altered central pain modulation.	
Gupta et al., (2007)	A high pre-morbid tender point count is a predictor of altered central pain modulation (WP). In healthy pain-free individuals who show somatising behaviour (Somatisation Check list), PPT's taken at all 16 points are summed to make a total PPT score. Of those PPT's, the ones measuring <4kg/cm² are counted as tender points and totalled up per participant.	
Slade et al., (2014)	After the onset of TMD, pre-morbid low PPT's are a predictor of persistent pain and altered central pain modulation (low PPT).	
Psychological factors		
McBeth et al., (2001)	In a healthy population, those who show evidence of somatisation before pain onset are more likely to experience altered central pain modulation in the form of WP within 12 months of showing somatisation.	
Wynne- Jones et al., (2006)	A tendency towards somatisation and health seeking behaviour pre-morbidly (Somatisation check list and GHQ), increased perception of initial injury severity (Illness attitudes questionnaire) severity of initial symptoms (symptom severity questionnaire) and older age all predict altered central pain modulation (WP) after a whiplash injury.	Moderate
Ferrari, (2010)	Responses of [I expect] 'never to get better' or 'don't know' on the Recovery Expectation questionnaire are predictors of altered central pain modulation (BPPT with VAS) after whiplash by 3 months.	
Other factors		
Markkula et al., (2016)	In a healthy population, pre-morbid frequent headache, followed by subsequent persistent regional back or neck pain are predictors of altered central pain modulation (WP).	NA

NA= not applicable

None of the studies selected were specific to low back pain, therefore predictors of altered

central pain modulation in low back pain could not be determined.

Discussion

This study set out to 1) identify predictors of altered central pain modulation in adults with general musculoskeletal pain conditions and secondly, if data were to allow, 2) determine predictors for NSLBP. We found nine high quality articles, and identified three groups of predictors of altered central pain modulation, two with a moderate strength of evidence 1) sensory sensitivity factors, 2) psychological factors and one which only included one study 3) other factors.

Some overlapping themes were found, for example, across all studies the musculoskeletal pain conditions were limited to whiplash, temporomandibular disorder (TMD) and widespread pain (WP). Similarly, sensory sensitivity tests were limited to QST, the ACR guidelines (1990) and COMT (catecholamine-O-methyltransferase) genetic testing. There was more variation across psychological measures, although the Somatisation Checklist and GHQ were used three times, enabling some qualitative comparisons. In this review, we did not find any articles that had studied the predictors of altered central pain modulation in NSLBP.

Due to the relatively new concept of altered central pain modulation in the last 15 years there has been little consensus as to what predictors lead to altered central pain modulation. It is therefore perhaps not surprising that many of the predictors tested varied widely as researchers attempt to narrow down the possibilities. The heterogeneity of predictors and of outcome measures made grouping of factors and outcomes for comparisons broad and prevented meta-analysis of the results.

Definitions of altered central pain modulation

One challenge during this review was a lack of definition for altered central pain modulation. At the time of publication of many of the studies, there was a lack of clinical guidelines on

how to identify altered central pain modulation in patients. Altered central pain modulation was not directly defined but could be inferred. Some of the studies used the ACR guidelines (1990) as a validated measure of WP (McBeth et al., 2001; Harkness et al., 2004; Wynn-Jones et al., 2006; Gupta et al., 2007; Markkula et al., 2016). Although the full ACR guidelines provide diagnostic criteria for identifying fibromyalgia, a section of the guidelines specifically identify WP. WP is indicative of altered central pain modulation (Nijs et al., 2014) and is an appropriate primary outcome measure for altered central pain modulation to be included in the current review.

The musculoskeletal pain disorders studied also allowed for inference of altered central pain modulation: Whiplash grade 1 or 2 (Sterling et al., 2003; Ferrari, 2010), WP (McBeth et al., 2001; Harkness et al., 2004; Wynn-Jones et al., 2006; Gupta et al., 2007; Markkula et al., 2016) and TMD (Diatchenko et al, 2005; Slade et al., 2014). These musculoskeletal pain disorders, when chronic, have been described as being closely associated with altered central pain modulation (Yunus, 2008; Kindler et al., 2010, Mayer et al., 2012) increasing the likelihood that the study populations in the current review contain a proportion presenting with altered central pain modulation at follow-up.

Quantitative Sensory Testing (QST) was used in four studies and included PPT (Sterling et al., 2003; Diatchenko et al., 2005; Ferrari, 2010; Slade et al, 2014); Temperature Pain Thresholds (TPT; Sterling et al., 2003) and the Brachial Plexus Provocation Test (BPPT; Sterling et al.,2003; Ferrari, 2010). Whilst PPT's are a valid measure of altered central pain modulation (Shy et al., 2003), BPPT, although associated, has not been validated specifically for measuring altered central pain modulation in Ferrari (2010). Despite this, the BPPT has been accepted for use by some authors as a test to indicate central hypersensitivity in whiplash associated disorders (Sterling, 2008), enabling these two studies Sterling et al., (2003) and Ferrari, (2010) to be eligible for inclusion into the current review.

Should baseline measures be taken pre-morbidly or during the acute stage?

In the current study, it was assumed *a priori* that taking baseline measurements in the acute stage of injury precedes the onset of altered central pain modulation. Sterling et al., (2003) argue that acute stage measures may not accurately reflect pre-morbid sensory sensitivity as alterations in central pain modulation may have already taken place. However, it could be argued acute-stage sensitivity measures do give an indication of pre-morbid sensitivity status, as in the study by Sterling et al., (2003), those who developed altered central pain modulation showed higher sensitivity at baseline than the rest of the acute-stage cohort, and remained higher at follow-up.

Pre-morbid baseline measures were taken in the population based studies reported in the current review, with the advantage that the predictors were clearly taken prior to the development of altered central pain modulation symptoms. As well as the disadvantage of longer periods needed to reach post-morbid follow-up, longer time frames may introduce confounders based on demographic and time-dependent co-morbidities. Wynne-Jones et al., (2006), possibly attempted to overcome this by measuring baseline pre-morbid predictors retrospectively using questionnaires around the time of the whiplash (acute stage). While this is commendable, a drawback might have been participant recall bias.

Negative results

Gupta et al., (2007) and Slade et al., (2014) both found pre-morbid PPT's not to be predictive of new onset altered central pain modulation-related musculoskeletal pain. The study by Gupta et al., (2007), was underpowered and did not find a significant change from baseline PPT's in order to predict first onset WP within 15 months. This may also have been related to the group being an already–at–risk group, with somatization as an inclusion criteria. These participants may have already had lower PPT's than a healthy population, making differences more difficult to detect.

Although Slade et al., (2014) specifically sought to find predictors of new onset TMD with altered central pain modulation, their results did show that at follow-up, participants with a lower baseline PPT tended to sensitise more vigorously, developing TMD with even lower PPT's post-morbidly. Those with PPT's closer to normal pre-morbidly and who experienced TMD did not develop persistent symptoms and altered central pain modulation but instead made a full recovery. Therefore, it may be interpreted that individuals with pre-morbid low PPT's may be at greater risk of developing persistent pain with altered central pain modulation, in a TMD population. This may be generalizable to other altered central pain modulation populations such as whiplash, based on Sterling et al., (2003). Sterling et al. measured baseline PPT's within the acute stage of whiplash injury and found that those with lower baseline PPT's developed persistent pain with altered central pain modulation by 6 months.

There may be a difference between insidious onsets of WP or TMD versus traumatic onset of pain following a motor vehicle accident (MVA). Unfortunately, the three studies (Sterling et al., 2003; Ferrari, 2010; Wynne-Jones et al., 2006), where the baseline was during the acute stage following a MVA, used different predictors of altered central pain modulation onset and therefore cannot be grouped to compare with studies including insidious pain onset.

Future considerations

Although sensory hyper-sensitivity has been measured as a predictor, other aspects of sensory processing alterations have not been evaluated, such as sensory hypo-sensitivity. Mailis-Gagnon and Nicholson (2010) have found sensory hypo-sensitivity to be a feature of a sub-group of fibromyalgia patients and these have not been used as predictors in prognostic studies to date. Measures of QST do not provide a full reflection of sensory alterations or differences because they only measure sensory hyper-sensitivity to particular stimuli.

Genetic markers for sensory sensitivity were discussed in two papers – Markkula et al., (2016) with regard to twins and Diatchenko et al., (2005) with regard to COMT haplotypes. Both studies discuss the likelihood of genetic predisposition to altered central pain modulation, either insidiously or after the first onset of musculoskeletal pain. It may be proposed, on the basis of the current findings, that pre-morbid trait sensory sensitivity and psychological characteristics such as coping styles, possibly of partly genetic origin, may predispose to altered central pain modulation, either insidiously or once regional pain is experienced.

Psychological predisposition

Ferrari (2010) used a one-question questionnaire as a predictor in which expectation of recovery predicted altered central pain modulation in a whiplash group. This is a psychological variable and no baseline physical examination was performed to assess for altered central pain modulation for longitudinal comparison. Three studies (Gupta et al., 2007, Wynne-Jones et al., 2006 and McBeth et al., 2004) found that a tendency towards somatisation pre-morbidly was a predictor of altered central pain modulation. Somatisation is said to be a measure of distress and anxiety, manifesting as physical symptoms (Kroenke et al., 1998). Pre-morbid anxiety was not assessed in any of the studies; it may be useful to assess for pre-morbid trait anxiety characteristics in future studies. Distress is a measure of coping styles, none of which were assessed as predictors in any of the studies in the current review. Trait anxiety and coping styles may be an important element in the aetiology of altered central pain modulation based on somatisation being a predictor in the current review.

Predisposition requires a trigger before altered central pain modulation develops

It is suggested that if a person is predisposed to altered central pain modulation, there requires a trigger, such as an injury or trauma, to start the transition to altered central pain

modulation (Diatchenko et al., 2007; Markkula et al., 2016). This echoes the observations by Latremolier and Woolf (2009) that it is not known why some people tend to sensitise more vigorously after an injury. Markkula et al., (2016) found that if there was initially some regional pain (back or neck) or headaches, this predicted the transition to altered central pain modulation in the form of WP. What is unknown from Markkula et al., (2016) is whether the regional pain was predominantly nociceptive, which might be an important distinction to make in predicting altered central pain modulation.

Methodological Strengths

The strengths of this review are based around the methodological rigour and the use of altered central pain modulation-specific inclusion / exclusion criteria. Two independent reviewers carried out the searches and a third reviewer was available for discussion. Search terms were piloted on advice from previous authors on searching for prognostic or predictive studies.

Methodological guidelines were followed according to more than one source (David et al., 2009, Dretzke et al., 2014 and Moons et al., 2014). The search strategy included relevant databases without filter limitations, extensive hand searching and the contacting of a large number of pain researchers in order to include any potential studies. *A priori* registration of the review was done.

Valid risk of bias and data extraction tools were used (Hayden et al., 2013; Moons et al., 2014) and strict inclusion / exclusion criteria were developed from current guidelines and literature specific to altered central pain modulation enabling close adherence to the research question.

Methodological Limitations

Only papers published in English were included, to the exclusion of two in German. One paper could not be retrieved. Altered central pain modulation had to be inferred due to the lack of definitions available at the times of publication. Interpretation of the reporting of each study where altered central pain modulation was only inferred presented as a challenge at review level. This careful interpretation was done in order to extract altered central pain modulation-specific information and, despite adhering closely to current altered central pain modulation guidelines, may present as a limitation.

Conclusion

Nine studies were included in the review to identify predictors of altered central pain modulation in adults with general musculoskeletal pain conditions. We found moderate strength of evidence to suggest that sensory hypersensitivity and somatisation pre-morbidly, or higher sensory sensitivity and low expectation of recovery at the acute stage of pain are predictors of altered central pain modulation in some musculoskeletal pain conditions. The implications for this review are that pre-morbid traits of sensory sensitivity and anxiety (somatisation) might play a role in the development of altered central pain modulation. Further investigations into pre-morbid characteristics of individuals with altered central pain modulation is warranted. This may help identify risk factors likely to predispose a person with acute musculoskeletal pain to the development of chronic pain with altered central pain modulation.

References

Baert, I. A. C., Lluch, E., Mulder, T., Nijs, J., Noten, S. and Meeus, M. (2015) 'Does pre-surgical central modulation of pain influence outcome after total knee replacement? A systematic review.' *Osteoarthritis and Cartilage*,

David, M., Alessandro, L., Jennifer, M. T. and Douglas, G. A. (2009) 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA Statement.' *Open Medicine; Vol 3, No 3 (2009)*,

Diatchenko, L., Slade, G. D., Nackley, A. G., Bhalang, K., Sigurdsson, A., Belfer, I., Goldman, D., Xu, K., Shabalina, S. A., Shagin, D., Max, M. B., Makarov, S. S. and Maixner, W. (2005) 'Genetic basis for individual variations in pain perception and the development of a chronic pain condition.' *Human Molecular Genetialtered central pain modulation*, 14(1) pp. 135-143.

Dretzke, J., Ensor, J., Bayliss, S., Hodgkinson, J., Lordkipanidzé, M., Riley, R. D., Fitzmaurice, D. and Moore, D. (2014) 'Methodological issues and recommendations for systematic reviews of prognostic studies: an example from cardiovascular disease.' *Systematic Reviews*, 3, 12/03
08/12/received
11/13/accepted, p. 140.

Ferrari, R. (2010) 'Predicting central sensitisation - whiplash patients.' *Australian Family Physician*, 39(11) pp. 863-866 864p.

Gupta, A., Silman, A. J., Ray, D., Morriss, R., Dickens, C., MacFarlane, G. J., Chiu, Y. H., Nicholl, B. and McBeth, J. (2007) 'The role of psychosocial factors in predicting the onset of chronic widespread pain: results from a prospective population-based study.' *Rheumatology*, 46(4) pp. 666-671.

Guyatt, G. H., Oxman, A. D., Kunz, R., Falck-Ytter, Y., Vist, G. E., Liberati, A., Schünemann, H. J. (2008) Going from evidence to recommendations. *BMJ*;336:1049

Harkness, E. F., Macfarlane, G. J., Nahit, E., Silman, A. J. and McBeth, J. (2004) 'Mechanical injury and psychosocial factors in the work place predict the onset of widespread body pain: A two-year prospective study among cohorts of newly employed workers.' *Arthritis & Rheumatism*, 50(5) pp. 1655-1664.

Hayden, J. A., van der Windt, D. A., Cartwright, J. L., Côté, P. and Bombardier, C. (2013) 'Assessing Bias in Studies of Prognostic Factors.' *Annals of Internal Medicine*, 158(4) pp. 280-286.

Iles, R. A., Davidson, M. and Taylor, N. F. (2008) 'Psychosocial predictors of failure to return to work in non-chronic non-specific low back pain: a systematic review.' *Occupational & Environmental Medicine*, 65(8) pp. 507-517.

Iles, R. A., Davidson, M., Taylor, N. F. and O'Halloran, P. (2009) 'Systematic review of the ability of recovery expectations to predict outcomes in non-chronic non-specific low back pain.' *Journal of Occupational Rehabilitation*, 19(1) pp. 25-40.

Kindler, L. L., Jones, K. D., Perrin, N. and Bennett, R. M. (2010) 'Risk factors predicting the development of widespread pain from chronic back or neck pain.' *Journal of Pain*, 11(12) pp. 1320-1328.

Kroenke, K., Spitzer, R. L., deGruy Iii, F. V. and Swindle, R. (1998) 'A Symptom Checklist to Screen for Somatoform Disorders in Primary Care.' *Psychosomatialtered central pain modulation*, 39(3), 5//, pp. 263-272.

Malfliet, A., Kregel, J., Cagnie, B., Kuipers, M., Dolphens, M., Roussel, N., Meeus, M., Danneels, L., Bramer, W. M. and Nijs, J. (2015) 'Lack of evidence for central sensitization in idiopathic, non-traumatic neck pain: A systematic review.' *Pain Physician*, 18(3) pp. 223-235.

Markkula, R. A., Kalso, E. A. and Kaprio, J. A. (2016) 'Predictors of fibromyalgia: a population-based twin cohort study.' *BMC Musculoskeletal Disorders*, 17, 01/15
07/02/received
01/05/accepted, p. 29.

Mayer, T. G., Neblett, R., Cohen, H., Howard, K. J., Choi, Y. H., Williams, M. J., Perez, Y. and Gatchel, R. J. (2012) 'The Development and Psychometric Validation of the Central Sensitization Inventory.' *Pain Practice*, 12(4) pp. 276-285.

McBeth, J., Macfarlane, G. J., Benjamin, S. and Silman, A. J. (2001) 'Features of somatization predict the onset of chronic widespread pain: Results of a large population-based study.' *Arthritis & Rheumatism*, 44(4) pp. 940-946.

Mogil, J. S. (2012) 'Pain genetialtered central pain modulation: past, present and future.' *Trends in Genetialtered central pain modulation*, 28(6), 6//, pp. 258-266.

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Murphy, K. A. and Cornish, R. D. (1984) 'Prediction of chronicity in acute low back pain.' *Archives of Physical Medicine and Rehabilitation*, 65(6) pp. 334-337.

Neblett, R., Cohen, H., Choi, Y., Hartzell, M. M., Williams, M., Mayer, T. G. and Gatchel, R. J. (2013) 'The central sensitization inventory (altered central pain modulationI): Establishing clinically significant values for identifying central sensitivity syndromes in an outpatient chronic pain sample.' *Journal of Pain*, 14(5) pp. 438-445.

Nijs, J., Van Houdenhove, B. and Oostendorp, R. A. B. (2010) 'Recognition of central sensitization in patients with musculoskeletal pain: Application of pain neurophysiology in manual therapy practice.' *Manual Therapy*, 15(2), 4//, pp. 135-141.

Nijs, J., Torres-Cueco, R., van Wilgen, C. P., Girbes, E. L., Struyf, F., Roussel, N., van Oosterwijck, J., Daenen, L., Kuppens, K., Vanwerweeen, L., Hermans, L., Beckwee, D., Voogt, L., Clark, J., Moloney, N. and Meeus, M. (2014) 'Applying modern pain neuroscience in clinical practice: criteria for the classification of central sensitization pain.' *Pain physician*, 17(5), 2014 Sep-Oct, pp. 447-457.

Roussel, N. A., Nijs, J., Meeus, M., Mylius, V., Fayt, C. and Oostendorp, R. (2013) 'Central sensitization and altered central pain processing in chronic low back pain: fact or myth?' *Clin J Pain*, 29(7), Jul, pp. 625-638.

Shy, M. E., Frohman Em Fau - So, Y. T., So Yt Fau - Arezzo, J. C., Arezzo Jc Fau - Cornblath, D. R., Cornblath Dr Fau - Giuliani, M. J., Giuliani Mj Fau - Kincaid, J. C., Kincaid Jc Fau - Ochoa, J. L., Ochoa Jl

Fau - Parry, G. J., Parry Gj Fau - Weimer, L. H. and Weimer, L. H. 'Quantitative sensory testing: report of the Therapeutialtered central pain modulation and Technology Assessment Subcommittee of the American Academy of Neurology.' (1526-632X (Electronic)), 20030325 DCOM- 20040112,

Slade, G. D., Sanders, A. E., Ohrbach, R., Fillingim, R. B., Dubner, R., Gracely, R. H., Bair, E., Maixner, W. and Greenspan, J. D. (2014) 'Pressure pain thresholds fluctuate with, but do not usefully predict, the clinical course of painful temporomandibular disorder.' *Pain*, 155(10), Oct, pp. 2134-2143.

Smart, K. M., Blake, C., Staines, A., Thacker, M. and Doody, C. (2012) 'Mechanisms-based classifications of musculoskeletal pain: Part 1 of 3: Symptoms and signs of central sensitisation in patients with low back (±leg) pain.' *Manual Therapy*, 17(4), 8//, pp. 336-344.

Sterling, M. (2006) 'Identifying those at risk of developing persistent pain following a motor vehicle collision.' *The Journal of Rheumatology*, 33(5) pp. 838-839.

Sterling, M., Jull, G., Vicenzino, B. and Kenardy, J. (2003) 'Sensory hypersensitivity occurs soon after whiplash injury and is associated with poor recovery.' *Pain*, 104(3), Aug, pp. 509-517.

Vlaeyen, J. W. S. and Linton, S. J. (2000) 'Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art.' *Pain*, 85(3), 4/1/, pp. 317-332.

Walton, D., Macdermid, J., Nielson, W., Teasell, R., Reese, H. and Levesque, L. (2011) 'Pressure pain threshold testing demonstrates predictive ability in people with acute whiplash.' *Journal of Orthopaedic and Sports Physical Therapy*, 41(9) pp. 658-665.

Wynne-Jones, G., Jones, G. T., Wiles, N. J., Silman, A. J. and Macfarlane, G. J. (2006) 'Predicting new onset of widespread pain following a motor vehicle collision.' *The Journal of rheumatology*, 33(5), 2006/05//, pp. 968-974.

Yunus, M. B. (2008) 'Central Sensitivity Syndromes: A New Paradigm and Group Nosology for Fibromyalgia and Overlapping Conditions, and the Related Issue of Disease versus Illness.' *Seminars in Arthritis and Rheumatism*, 37(6), 6//, pp. 339-352.

1.