

This item is the archived peer-reviewed author-version of:

Hyperexcitability of the central nervous system in children with chronic pain : a systematic review

Reference:

Pas Roselien, Ickmans Kelly, Van Oosterwijck Sophie, Van der Cruyssen Kelly, Foubert Anthe, Leysen Laurence, Nijs Jo, Meeus Mira.- Hyperexcitability of the central nervous system in children with chronic pain : a systematic review
Pain medicine - ISSN 1526-4637 - 19:12(2018), p. 2504-2514
Full text (Publisher's DOI): <https://doi.org/10.1093/PMPNX320>

Hyperexcitability of the central nervous system in children with chronic pain: a systematic review

Roselien Pas^{a,b}, PT, MSc, Kelly Ickmans^{a-c}, PT, PhD, Sophie Van Oosterwijck^e, PT, MSc, Kelly Van der Cruyssen^e, PT, MSc, Anthe Foubert^e, PT, MSc, Laurence Leysen^{a,b}, PT, MSc, Jo Nijs^{a-c}, PT, PhD, Mira Meeus^{a,d,e}, PT, PhD

Affiliations: ^a Pain in Motion International Research Group, www.paininmotion.be; ^b Department of Physiotherapy, Human Physiology and Anatomy (KIMA), Faculty of Physical Education & Physiotherapy, Vrije Universiteit Brussel, Belgium; ^c Department of Physical Medicine and Physiotherapy, University Hospital Brussels, Belgium; ^d Department of Rehabilitation Sciences and Physiotherapy, Faculty of Medicine and Health Sciences, Ghent University, Belgium; ^e Department of Rehabilitation Sciences and Physiotherapy, Faculty of Medicine and Health Sciences, University of Antwerp, Belgium

Address correspondence to: Kelly Ickmans; Vrije Universiteit Brussel (VUB); Department of Physiotherapy, Human Physiology and Anatomy (KINE/KIMA); Building F; Laarbeeklaan 103; BE-1090 Brussels; Belgium; phone +32 24774489; Kelly.ickmans@vub.be

Description of potential conflicts of interest: The authors have no conflict of interest relevant to this article to disclose.

Key Words: chronic pain, child, secondary hyperalgesia, central hyperexcitability

Running title: Central hyperexcitability in children

Acknowledgements: This work is funded by a Chair the Berekuyt Academy / European College for Decongestive Lymphatic Therapy, the Netherlands. The funding source had no involvement in the study design; in the collection, analysis and interpretation of the data; in the writing of the report, nor in the decision to submit the article for publication.

Description of potential conflicts of interest: The authors have no conflict of interest relevant to this article to disclose.

Abstract

Objective: Hyperexcitability of the central nervous system plays an important role in the development and maintenance of chronic pain in adults. This knowledge led to improved treatment strategies within this population. In children, however, research on the presence of central hyperexcitability is scarce. To further investigate this topic in children with chronic pain there is need for a clear literature overview.

Design: Systematic review

Methods: The literature search was performed using the electronic databases PubMed and Web of Science. An article was considered eligible if it included children (2-12 years old) diagnosed with chronic pain. Articles had to report original research outcomes related to central hyperexcitability and a comparison with a healthy control group was necessary. Characteristics of the study sample, the assessment and conclusions regarding central hyperexcitability were extracted from each included article.

Results: Twelve case-control studies were included with moderate to good methodological quality (510 children with chronic pain and 670 healthy controls). After summarizing the articles' results on indices of central hyperexcitability, we concluded that secondary hyperalgesia might be present in children with recurrent abdominal pain, juvenile fibromyalgia and juvenile idiopathic arthritis. Preliminary evidence exists for altered cortical nociceptive processing in children with migraine and recurrent abdominal pain.

Conclusions: Based on the results of this review, central hyperexcitability might be present in in several pediatric chronic pain conditions. Further research on other manifestations of central hyperexcitability (e.g. bottom-up and top-down mechanisms and nociceptive brain

changes) are necessary to provide firm evidence about its presence in children with chronic pain.

Introduction

Chronic pain, generally defined as continuous or recurrent pain episodes lasting more than 12 weeks, or pain that persists beyond the normal expected time for tissue healing, is a common problem in children and adolescents(1). Prolonged pain can be disease-related, may occur post injury or can be idiopathic, arising spontaneously or from an obscure or unknown cause. Prevalence rates of chronic pediatric pain are generally higher in girls, increase with age and range substantially in community surveys (e.g., headache: 8-83%; abdominal pain: 4-53%; back pain: 14-24%; musculoskeletal pain: 4-40%)(1,2). Chronic pediatric pain is reported to be distressing and in severe cases prolonged pain may even severely debilitate and affect the children's overall quality of life(3). In addition, previous research reported that children with a history of childhood chronic pain show a greater predisposition to persistent pain and are more likely to develop new and different types of pain into adulthood(4,5).

The pathophysiology of chronic pain is complex and can be partly explained by an interaction between primary afferent nerves, dorsal horn neurons, spinal glia, neurotransmitters and other factors that transit and perpetuate the symptoms of chronic pain(3). Awareness is growing that central hyperexcitability may be of prime importance in the development, persistence and management of chronic pain(6). Central hyperexcitability refers to an increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input (i.e. central sensitization)(7). This process encompasses malfunctioning of descending inhibitory nociceptive pathways, increased activity of facilitatory nociceptive pathways and altered neuronal synapses in the brain(8–11).

Central hyperexcitability can manifest itself as an increased responsiveness to a variety of stimuli including mechanical pressure, chemical substances, cold temperature, heat

temperature and electrical stimuli(11–14). Since different mechanisms contribute to central hyperexcitability as mentioned above, it is challenging for researchers to measure central hyperexcitability. This may explain the absence of a true gold standard measurement for the assessment of central hyperexcitability in human subjects(15). Therefore, clinical or neurophysiological manifestations are assessed by different methods such as quantitative sensory testing, algometry, generalised hyperalgesia, wind-up, efficacy of endogenous analgesic control, etc. Outcomes are compared with healthy controls to provide information regarding the potential involvement of central hyperexcitability in chronic pain states.

As mentioned above, central hyperexcitability is a form of maladaptive neuroplasticity(16). To date, there is increasing evidence for involvement of central hyperexcitability in many adult chronic pain conditions including rheumatoid arthritis, low back pain, osteoarthritis, fibromyalgia, chronic whiplash and gastrointestinal disorders(12,17–21). However, evidence about central hyperexcitability in adults should not be generalised to children. A major concern is the child's different neuroplasticity in comparison to adults(22). Additionally, research has shown that differences in central pain modulation exist between children and adolescents(23) due to e.g. developmental changes in pain cognitions and emotions.

Therefore, this review aims to investigate the existing literature on the presence and possible role of central hyperexcitability in children with chronic pain. If central hyperexcitability is present in certain chronic pediatric pain populations, then treatment programmes should be adapted accordingly.

Methods

A systematic search of the existing literature was done using the PRISMA guidelines(24).

Eligibility Criteria

To be included in this systematic review articles had to meet the following inclusion criteria: (1) participants had to include children (aged 2-12 years), diagnosed with chronic or recurrent pain; (2) articles had to report on outcomes related to central hyperexcitability (pain thresholds, temporal summation, conditioned pain modulation, etc.), compared to a healthy control group. (3) The duration of pain was of great importance; according to the IASP definition of chronic pain, children had to have pain for at least 3 months(7). Articles involving patients with acute, postoperative or palliative pain were excluded. (4) Finally, the articles had to be full text reports or original research (no abstracts, case reports, reviews, meta-analysis, letters, expert opinions or editorials). All languages other than Dutch or English were excluded from this systematic literature search.

Information sources and search

A systematic search of the existing literature was performed using the electronic databases PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>) and Web of Science (<http://apps.webofknowledge.com>). The last search was run on 9 October 2017. The search strategy was based on a combination of keywords and MESH terms and could be divided in three groups according “PICO”: (P1) chronic pain; (P2) in children and (O) a measure of central hyperexcitability (Table 1). Limits were applied for language (Dutch and English), species (Humans) and ages (Child, Preschool child). The complete search strategy for all databases is available as supplementary material (Appendix 1).

Study selection

Eligibility assessment was performed independently in a blinded standardized manner by three reviewers. All titles and abstracts were read to identify relevant articles. In addition, we scanned the reference lists of the selected articles. In case of uncertainty regarding the

eligibility of the article based on title and abstract or absence of the abstract, the full text version of the article was retrieved and evaluated against the inclusion criteria. The full text version of all articles that met the inclusion criteria were further examined on methodological quality and data extraction.

Data collection process & data items

A data extraction sheet was developed and completed independently by three researchers. Two researchers (A.F. & S.V.O.) used a specific template in Excel to screen all articles. Another researcher (R.P) used the software Rayyan, a web app for exploring and filtering searches for eligible studies(25). Disagreements between reviewers were resolved by discussion on a consensus meeting. If no consensus could be reached, a fourth researcher was consulted (M.M.). The selected articles were imported in the reference software EndNote and checked for duplicates.

Information was extracted from each included article on: (1) characteristics of the study sample (including age, sex, disease), (2) the study sample's inclusion criteria; (3) assessment and general conclusions regarding central hyperexcitability.

Quality Assessment (Risk of bias)

Risk of bias was assessed by three independent, blinded researchers who were not acquainted with each other's evaluation of the search results before having a consensus meeting. After having rated the selected articles, the results of all researchers were compared and differences were analyzed and discussed. In case of a disagreement, another opinion was provided by a fourth researcher (M.M.). The methodological quality of the case-control studies was performed using the Newcastle-Ottawa Scale (NOS), which is recommended by the Cochrane Collaboration (<http://www.cochrane.org>). The NOS uses a star rating system to judge quality

based on three aspects of the study. A maximum of 9 stars can be awarded. No cut-off value of methodological quality was set for inclusion. Detailed information on the authors' rating method of the NOS is available as supplementary material (Appendix 2).

Results

Study selection

The selection process of the relevant papers is presented in Figure 1. The initial search using PubMed, Web of Science and hand-search of reference lists revealed 1379 papers after the removal of duplicates. The remaining articles were screened on title and abstract, resulting in 179 articles for full-text screening. After this last screening, 12 articles remained for inclusion.

Risk of bias

The three researchers agreed in most cases on scoring the selected papers on risk of bias assessment. After a second review and discussing the discrepancies, the reviewers reached a consensus on all items. The definite consensus score and detailed information on the scores of methodological quality can be found in Table 2. The methodological quality was overall acceptable (the total number of stars varied between 3 and 7), with only one study scoring a total of 3 stars(26). Criterion 9 of the NOS, concerning the non-response rate was not evaluated, since not a single study described a follow-up period. All included studies were given a level of evidence B, since only case control studies were included(27).

Study characteristics

The main characteristics of the included studies are presented in Table 3. Studies on children with recurrent abdominal pain (RAP)(28–31), juvenile idiopathic arthritis (JIA)(26,32–34), migraine (MIG)(35,36), temporomandibular disorder (TMD)(37) and juvenile fibromyalgia

(FM)(38) were selected. In total 1180 children were included in this review, of which 510 children presenting chronic pain and 670 healthy controls. More detailed information about the studies' assessments on central hyperexcitability is available as supplementary material (Appendix 3).

Indices of central hyperexcitability

1. Pain thresholds

Pressure pain thresholds (PPTs)

Nine studies performed PPTs as part of their outcome measures(26,28–30,32,34,35,38,39).

Different local and remote test sites were used, depending on the chronic pain population.

Three studies examined PPTs in children with RAP. Two studies reported significant lower PPTs at all test sites when compared to healthy controls(28,29), while another study found the opposite(30).

Five studies, assessing PPTs in children with JIA presented inconsistent findings. The majority of the studies showed significantly lower PPTs at all measured test points(26,32,34,39). Reid et al. found the opposite, showing no difference in PPTs in children with JIA when compared to healthy controls(38). The latter study also examined PPTs in children with juvenile FM and reported significantly lower PPTs at the test sites when compared to healthy controls. However, at the remote test sites only significant lower pain tolerance in children with juvenile FM could be found(38).

One study investigated PPTs in children with MIG but found no differences compared with healthy controls(35).

In summary, moderate evidence was found for secondary mechanical hyperalgesia in children with RAP and JIA. Preliminary evidence has shown some potential for the presence of secondary hyperalgesia in children with juvenile FM and no evidence was found in children with MIG.

Thermal thresholds (cold and heat pain thresholds)

Three studies assessed thermal pain thresholds(26,31,36). All three studies examined those thresholds in a different population, though all used the thenar eminence as remote test site.

Zohsel et al. found no lower heat pain thresholds compared to healthy controls, neither in children with MIG(36) nor in children with RAP(31).

Another study examining both heat and cold pain thresholds in children with JIA showed the opposite. Both thresholds were lower at all test sites compared to healthy controls(26).

In contrast to the preliminary evidence in children with JIA, no evidence for secondary thermal (hot and/or cold) hyperalgesia was found in children with MIG or RAP.

Other measurements

Jedel et al. examined the pain threshold in children with TMD, giving electrical stimulation between the thumb and the index finger. No significant difference was found compared to healthy controls, indicating preliminary evidence for the absence of secondary hyperalgesia in children with TMD. Two studies investigating the mechanical pain threshold in response to a set of seven standardized pinprick punctuate probes with a blunt tip, found significant lower thresholds in children with MIG(31) and RAP(31).

2. Detection thresholds

One study examined sensory detection thresholds in children with JIA(26). Both mechanical

and thermal detection thresholds (heat and cold) were significantly different compared to healthy controls; JIA patients were hypersensitive to mechanical stimuli, but hyposensitive to thermal stimuli (heat and cold). In children with JIA, a greater temperature change was required to perceive temperature. Similarly, the vibration detection thresholds were significantly lower compared to healthy controls, indicating hyposensitivity.

Overall, preliminary evidence was found for secondary mechanical hypersensitivity in children with JIA and secondary hyposensitivity in response to thermal (heat and cold) and vibration stimuli.

3. Temporal Summation of Pain

Two studies examined the so-called “wind-up” phenomenon. Their first study was conducted in children with MIG. Nearly all participants showed signs of temporal summation at both test sites. However, no significant group differences were found(36).

Their second study in children with RAP showed different results, depending on the test site. No significantly different response to repetitive noxious stimulation was found at the local test site. Still, at the remote site, children with RAP showed significantly decreased temporal summation compared to the control group(31).

Preliminary evidence has shown some potential for the absence of increased activity of facilitatory nociceptive pathways in children with MIG and RAP.

4. Thermal habituation

Thermal habituation was examined in two studies(31,36). Less thermal habituation was seen at the remote test site in children with MIG, compared to healthy children(36). However, no

significant group differences were found. At the local test site, both groups of children showed thermal habituation, again not significantly different.

Contrasting results were found in children with RAP(31). They showed more habituation in response to tonic heat at the remote test site compared to healthy children. Still, at the local test site, no significant group differences were found(31).

In contrast to preliminary evidence in children with RAP, no explicit evidence for reduced thermal habituation was found in children with MIG.

5. Altered cortical nociceptive processing

Two studies evaluated cognitive aspects of nociceptive processing in children with RAP(30) or MIG(35), using electroencephalography. The authors concluded that chronic pain in children is associated with automatic attention to painful and potential painful stimuli, which may reflect difficulties in sufficient activation of pain-inhibiting processes(30,35). These preliminary findings suggest that altered cortical nociceptive processing, as a feature of central hyperexcitability, might be present in children with RAP and MIG.

Discussion

The goal of the present systematic literature search was to review the scientific literature addressing central hyperexcitability in children with chronic pain.

Similar to research in adults(8,18,40,41), evidence for the presence of secondary hyperalgesia was found in children with JIA(26,32–34) and juvenile FM(38). Heterogeneity within the RAP and MIG population and modality-specific alterations in somatic pain sensitivity(42,43) might explain the inconsistent results regarding secondary hyperalgesia in children with RAP and MIG(28–31,36). Despite a recent study suggesting the role of generalized

hyperexcitability in the central processing of nociceptive input in the pathophysiology of TMD(44), secondary hyperalgesia could not be found in children(37).

Besides pain and detection thresholds, advanced measurement techniques to assess descending inhibitory nociceptive pathways (conditioned pain modulation) and facilitatory nociceptive pathways (temporal summation or wind-up ratio) exist to gain clinical relevance in the evaluation of central hyperexcitability in both adults and children(45,46). This systematic review underlines the dearth of knowledge on the efficacy of these pathways in children with chronic pain(31,36). Although, inefficient endogenous nociceptive control is seen in various adult chronic pain populations(17,50–52). Moreover, research has shown that the efficiency of our descending inhibitory nociceptive pathways decreases with age(53). In light of the foregoing, the question arises how this system works in children. One study suggested that endogenous pain modulatory mechanisms of premature children are not as well developed as those of children not exposed to early pain at birth(54). However, alterations in this system might also occur in the context of chronic pain in children. One study investigated its efficacy and found deficient endogenous nociceptive control in girls with irritable bowel syndrome when comparing them to healthy controls(55). This study was not included in this systematic review because it did not meet the inclusion criteria for pain duration (pain complaints > 3 months). Future research is warranted to confirm these preliminary results and to further investigate both pain inhibition and facilitation pathways in children with other chronic pain disorders.

Additionally, research about the neuroplastic brain changes in relation to central hyperexcitability is lacking. Fortunately, multiple non-invasive structural and functional neuroimaging methods have been developed to enable rapid progress in understanding the

processing of pain in the human brain and to provide insight into the mechanisms underlying chronic pain(49).

This systematic review has some limitations. Different diseases involving chronic pain were included, leading to a heterogeneous study population. Even when using the same test device, different protocols and different local and remote test sites were used to evaluate the presence of central hyperexcitability, possibly leading to different results. Both aspects hampered the formulation of a straightforward conclusion regarding the presence of central hyperexcitability in children with chronic pain in general.

The large differences in protocol between the included studies reflect the need for a well validated device or procedure to measure central hyperexcitability. Efforts should be made to identify subgroups within the pain conditions in order to explain inconsistent results between studies investigating the same pain condition and similar manifestations of central hyperexcitability. It should be questioned why children with chronic pain present manifestations of central hyperexcitability, such as lowered PPTs. Three of four studies(26,32,33) in children with JIA suggested that the presence of secondary hyperalgesia might be the result of long-lasting nociceptive bombardment from inflamed joints, leading to peripheral and central hyperexcitability of nociceptive afferents. Still, studies investigating this causal relationship are necessary since most of the allegations are based on adult research. Given the plasticity of the child's central nervous system, it might be hypothesized that changes in the central nervous system occur faster or more frequent in children with chronic pain when compared with adults.

The presence of central hyperexcitability implies that the brain produces pain even when there is no apparent somatic nociceptive input(56). Thus, as part of the existing multidisciplinary

treatment(2), children with chronic pain might benefit from education about the cause of their pain, relevant pain mechanisms and the integral role of psychosocial and physical factors in precipitating and maintaining their pain(57). Research in various adult chronic pain populations has shown that his main content can be given by pain neuroscience education(58–62). Future studies should investigate its positive values in children with chronic pain.

Conclusions

Based on the results of this review, central hyperexcitability might be present in children with RAP, JIA, juvenile FM and MIG. Still, substantial gaps in knowledge remain due to the varying methodologies of studies and mixed findings within disease groups. Research should further investigate whether changes in the child's brain, endogenous pain modulation and pain facilitation as manifestations of central hyperexcitability are present in children with chronic pain disorders.

Acknowledgement

This work is funded by a Chair the Berekuyil Academy / European College for Decongestive Lymphatic Therapy, the Netherlands. The funding source had no involvement in the study design; in the collection, analysis and interpretation of the data; in the writing of the report, nor in the decision to submit the article for publication. The authors have no conflict of interest relevant to this article to disclose.

References

1. King S, Chambers C, Huguet A. The epidemiology of chronic pain in children and adolescents revisited: a systematic review. *Pain*. 2011;152:2729–38.

2. Rajapakse D, Lioffi C, Howard RF. Presentation and management of chronic pain. *Arch Dis Child* [Internet]. 2014;99(5):474–80. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24554056>
3. Eccleston C, Palermo TM, Williams AC de C, Lewandowski A, Morley S, Fisher E, et al. Psychological therapies for the management of chronic and recurrent pain in children and adolescents. *Cochrane Database Syst Rev*. 2012;(12).
4. Walker LS, Dengler-Crish CM, Rippel S, Bruehl S. Functional abdominal pain in childhood and adolescence increases risk for chronic pain in adulthood. *Pain*. 2010;150(3):568–72.
5. Kashikar-Zuck S, Cunningham N, Sil S, Bromberg MH, Lynch-Jordan AM, Strotman D, et al. Long-term outcomes of adolescents with juvenile-onset fibromyalgia in early adulthood. *Pediatrics* [Internet]. 2014;133(3):e592-600. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3934334&tool=pmcentrez&rendertype=abstract>
6. Nijs J, Torres-Cueco R, van Wilgen CP, Girbes EL, Struyf F, Roussel N, et al. Applying modern pain neuroscience in clinical practice: criteria for the classification of central sensitization pain. *Pain Physician*. 2014;17(5):447–57.
7. Merskey H, Bogduk N. IASP Task Force on Taxonomy Part III: Pain Terms, A Current List with Definitions and Notes on Usage. *IASP Task Force Taxon* [Internet]. 1994;209–14. Available from: <http://www.iasp-pain.org/Content/NavigationMenu/GeneralResourceLinks/PainDefinitions/default.htm#Pain>

8. Meeus M, Nijs J. Central sensitization: A biopsychosocial explanation for chronic widespread pain in patients with fibromyalgia and chronic fatigue syndrome. *Clin Rheumatol*. 2007;26(4):465–73.
9. Seifert F, Maihöfner C. Central mechanisms of experimental and chronic neuropathic pain: Findings from functional imaging studies. *Cell Mol Life Sci*. 2009;66(3):375–90.
10. Staud R, Craggs JG, Robinson ME, Perlstein WM, Price DD. Brain activity related to temporal summation of C-fiber evoked pain. *Pain*. 2007;129(1–2):130–42.
11. Meeus M, Nijs J, Van de Wauwer N, Toeback L, Truijen S. Diffuse noxious inhibitory control is delayed in chronic fatigue syndrome: An experimental study. *Pain* [Internet]. 2008;139(2):439–48. Available from: <http://dx.doi.org/10.1016/j.pain.2008.05.018>
12. Desmeules JA, Cedraschi C, Rapiti E, Baumgartner E, Finckh A, Cohen P, et al. Neurophysiologic evidence for a central sensitization in patients with fibromyalgia. *Arthritis Rheum*. 2003;48(5):1420–9.
13. Kasch H, Qerama E, Bach FW, Jensen TS. Reduced cold pressor pain tolerance in non-recovered whiplash patients: A 1-year prospective study. *Eur J Pain*. 2005;9(5):561–9.
14. Morris VH, Cruwys SC, Kidd BL. Characterisation of capsaicin-induced mechanical hyperalgesia as a marker for altered nociceptive processing in patients with rheumatoid arthritis. *Pain*. 1997;71:149–86.
15. Woolf CJ. Central Sensitization: Implications for the diagnosis and treatment of pain. *Pain*. 2012;152(3 Supplemental):1–31.
16. Nijs J, Meeus M, Versijpt J, Moens M, Bos I, Knaepen K, et al. Brain-derived

- neurotrophic factor as a driving force behind neuroplasticity in neuropathic and central sensitization pain : a new therapeutic target ? 2014;1–12.
17. Van Oosterwijck J, Nijs J, Meeus M, Paul L. Evidence for central sensitization in chronic whiplash: A systematic literature review. *Eur J Pain (United Kingdom)*. 2013;17(3):299–312.
 18. Meeus M, Vervisch S, De Clerck LS, Moorkens G, Hans G, Nijs J. Central sensitization in patients with rheumatoid arthritis: A systematic literature review. *Semin Arthritis Rheum [Internet]*. 2012;41(4):556–67. Available from: <http://dx.doi.org/10.1016/j.semarthrit.2011.08.001>
 19. Lluch E, Torres R, Nijs J, Van Oosterwijck J. Evidence for central sensitization in patients with osteoarthritis pain: A systematic literature review. *Eur J Pain (United Kingdom)*. 2014;18(10):1367–75.
 20. O'Neill S, Manniche C, Graven-Nielsen T, Arendt-Nielsen L. Generalized deep-tissue hyperalgesia in patients with chronic low-back pain. *Eur J Pain*. 2007;11(4):415–20.
 21. Moshiree B, Zhou Q, Price DD, Verne GN. Central sensitisation in visceral pain disorders. *Gut*. 2006;55(7):905–8.
 22. Fine JG, Sung C. Neuroscience of child and adolescent health development. *J Couns Psychol [Internet]*. 2014;61(4):521–7. Available from: <http://search.proquest.com/docview/1586105602?accountid=166133>
 23. Tsao JCI, Seidman LC, Evans S, Lung KC, Zeltzer LK, Naliboff BD. Conditioned Pain Modulation in Children and Adolescents: Effects of Sex and Age. *J Pain [Internet]*.

- 2013;14(6):558–67. Available from: <http://dx.doi.org/10.1016/j.jpain.2013.01.010>
24. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol*. 2009;62(10):e1-34.
 25. Elmagarmid A, Fedorowicz Z, Hammady H, Ilyas I, Khabsa M, Ouzzani M. Rayyan: a systematic reviews web app for exploring and filtering searches for eligible studies for Cochrane Reviews. In: Abstracts of the 22nd Cochrane Colloquium. John Wiley & Sons; 2014. p. 9.
 26. Cornelissen L, Donado C, Kim J, Chiel L, Zurakowski D, Logan DE, et al. Pain hypersensitivity in juvenile idiopathic arthritis: a quantitative sensory testing study. *Pediatr Rheumatol Online J*. 2014;12:39.
 27. CBO K voor gezondheidszorg. Evidence-based Richtlijnontwikkeling Handleiding voor werkgroepleden. [Www.Cbo.Nl](http://www.cbo.nl). 2007. 1-80 p.
 28. Alfvén G. The pressure pain threshold (PPTs) of certain muscles in children suffering from recurrent abdominal pain of non-organic origin. An algometric study. *Acta Paediatr*. 1993;82:481–3.
 29. Duarte M a, Goulart EM, Penna FJ. Pressure pain threshold in children with recurrent abdominal pain. *J Pediatr Gastroenterol Nutr* [Internet]. 2000;31(3):280–5. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10997373>
 30. Hermann C, Zohsel K, Hohmeister J, Flor H. Cortical correlates of an attentional bias

- to painful and innocuous somatic stimuli in children with recurrent abdominal pain. *Pain*. 2008;136(3):397–406.
31. Zohsel K, Hohmeister J, Flor H, Hermann C. Somatic pain sensitivity in children with recurrent abdominal pain. *Am J Gastroenterol* [Internet]. 2008;103(6):1517–23. Available from: <http://dx.doi.org/10.1111/j.1572-0241.2008.01911.x>
 32. Hogeweg JA, Kuis W, Oostendorp RAB, Helders PJM. General and segmental reduced pain thresholds in juvenile chronic arthritis. *Pain*. 1995;62(1):11–7.
 33. Hogeweg JA, Kuis W, Huygen ACJ, De Jong- De Vos Van Steenwijk C, Bernardis ATM, Oostendorp RAB, et al. The pain threshold in juvenile chronic arthritis. *Br J Rheumatol*. 1995;61–7.
 34. Leegaard A, Lomholt JJ, Thastum M, Herlin T. Decreased pain threshold in juvenile idiopathic arthritis: A cross-sectional study. *J Rheumatol* [Internet]. 2013;40(7):1212–7. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23637324>
 35. Zohsel K, Hohmeister J, Flor H, Hermann C. Altered pain processing in children with migraine: An evoked potential study. *Eur J Pain*. 2008;12(8):1090–101.
 36. Zohsel K, Hohmeister J, Oelkers-Ax R, Flor H, Hermann C. Quantitative sensory testing in children with migraine: Preliminary evidence for enhanced sensitivity to painful stimuli especially in girls. *Pain*. 2006;123(1–2):10–8.
 37. Jedel E, Carlsson J, Stener-Victorin E. Health-related quality of life in child patients with temporomandibular disorder pain. *Eur J Pain*. 2007;11(5):557–63.
 38. Reid GJ, Lang BA, McGrath PJ. Primary juvenile fibromyalgia: Psychological

- adjustment, family functioning, coping, and functional disability. *Arthritis Rheum.* 1997;40(4):752–60.
39. Kuis W, Heijnen CJ, Hogeweg JA, Sinnema G, Helders PJM. How painful is juvenile chronic arthritis? *Arch Dis Child* [Internet]. 1997;77(5):451–3. Available from: <http://adc.bmj.com/cgi/doi/10.1136/adc.77.5.451>
40. Clauw DJ. Fibromyalgia: An Overview. *Am J Med* [Internet]. 2009;122(12 SUPPL.):S3–13. Available from: <http://dx.doi.org/10.1016/j.amjmed.2009.09.006>
41. Cagnie B, Coppieters I, Denecker S, Six J, Danneels L, Meeus M. Central sensitization in fibromyalgia? A systematic review on structural and functional brain MRI. *Semin Arthritis Rheum* [Internet]. 2014;44(1):68–75. Available from: <http://dx.doi.org/10.1016/j.semarthrit.2014.01.001>
42. Zbinden a M, Fischer M. The Effect of N-Methyl-D-aspartate Single and Repeated Nociceptive Controlled Experimental Human. *J Neurophysiol.* 1995;
43. Curatolo M, Petersen-Felix S, Arendt-Nielsen L, Giani C, Zbinden a M, Radanov BP. Central hypersensitivity in chronic pain after whiplash injury. *Clin J Pain* [Internet]. 2001;17(4):306–15. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15563322>
44. Sarlani E, Greenspan J. Evidence for generalized hyperalgesia in temporomandibular disorders patients. *Pain.* 2003;102:221–6.
45. Arendt-Nielsen L. Central sensitization in humans: assessment and pharmacology. In: *Handb Exp Pharmacol.* 2015. p. 79–102.
46. Birnie KA, Caes L, Wilson AC, Williams SE, Chambers CT. A practical guide and

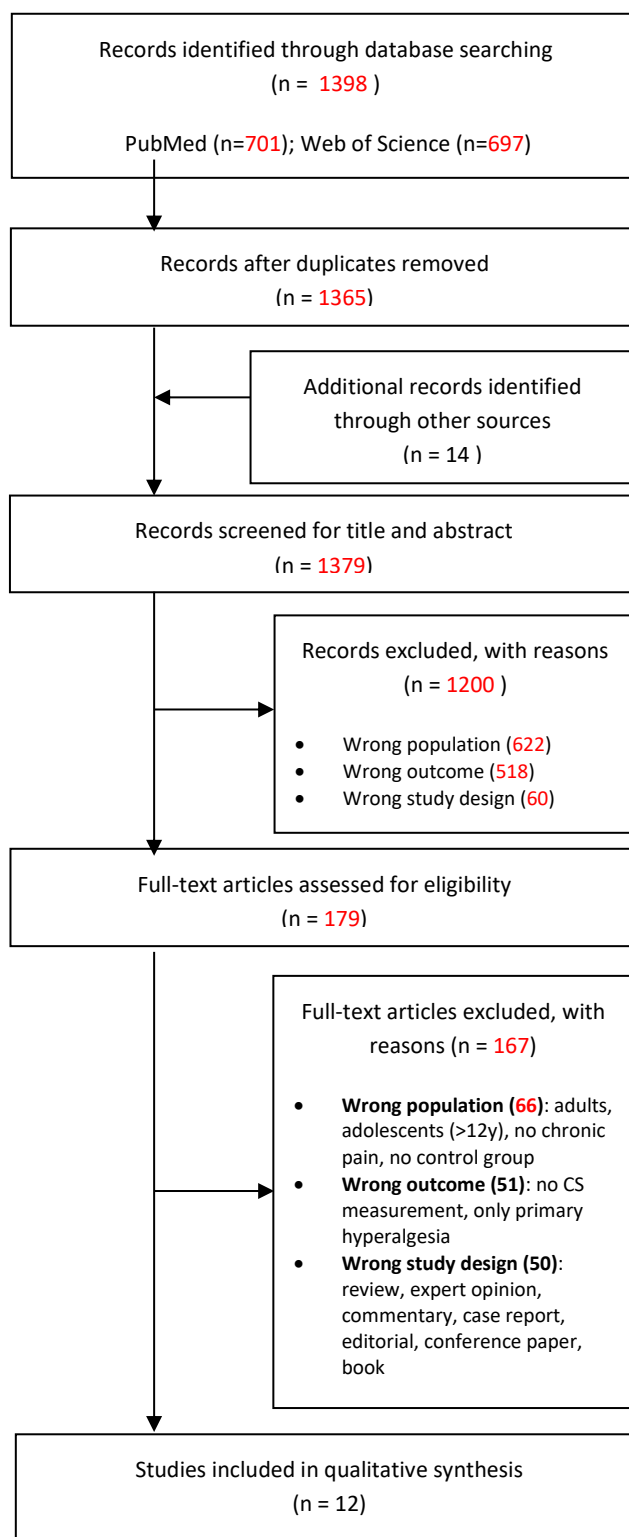
- perspectives on the use of experimental pain modalities with children and adolescents. *Pain Manag* [Internet]. 2014;4(2):97–111. Available from:
[http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4110966&tool=pmcentrez
&rendertype=abstract](http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4110966&tool=pmcentrez&rendertype=abstract)
47. Jepma M, Jones M, Wager TD. The dynamics of pain: Evidence for simultaneous site-specific habituation and site-nonspecific sensitization in thermal pain. *J Pain*. 2014;734–746.
 48. Weissman-Fogel I, Sprecher E, Granovsky Y, Yarnitsky D. Repeated noxious stimulation of the skin enhances cutaneous pain perception of migraine patients in-between attacks: Clinical evidence for continuous sub-threshold increase in membrane excitability of central trigeminovascular neurons. *Pain*. 2003;104(3):693–700.
 49. Apkarian A. The brain in chronic pain: clinical implications. *Pain Manag*. 2011;1(6):577–86.
 50. Mlekusch S, Neziri AY, Limacher A, Jüni P, Arendt-Nielsen L, Curatolo M. Conditioned Pain Modulation in Patients With Acute and Chronic Low Back Pain. *Clin J Pain* [Internet]. 2016;32(2):116–21. Available from:
<http://www.ncbi.nlm.nih.gov/pubmed/26741741>
 51. Sandrini G, Rossi P, Milanov I, Serrao M, Cecchini AP, Nappi G. Abnormal modulatory influence of diffuse noxious inhibitory controls in migraine and chronic tension-type headache patients. *Cephalalgia*. 2006;26(7):782–9.
 52. Kosek E, Hansson P. Modulatory influence on somatosensory perception from vibration and heterotopic noxious conditioning stimulation (HNCS) in fibromyalgia

- patients and healthy subjects. *Pain*. 1997;70(1):41–51.
53. Hermans L, Van Oosterwijck J, Goubert D, Goudman L, Crombez G, Calders P, et al. Inventory of Personal Factors Influencing Conditioned Pain Modulation in Healthy People: A Systematic Literature Review. 2016;0:1–12.
54. Goffaux P, Lafrenaye S, Morin M, Patural H, Demers G, Marchand S. Preterm births: Can neonatal pain alter the development of endogenous gating systems? *Eur J Pain*. 2008;12(7):945–51.
55. Williams AE, Heitkemper M, Self MM, Czyzewski DI, Shulman RJ. Endogenous inhibition of somatic pain is impaired in girls with irritable bowel syndrome compared with healthy girls. *J Pain [Internet]*. 2013;14(9):921–30. Available from: <http://dx.doi.org/10.1016/j.jpain.2013.03.003>
56. Nijs J, Malfliet A, Ickmans K, Baert I, Meeus M. Treatment of central sensitization in patients with “unexplained” chronic pain: an update. *Expert Opin Pharmacother [Internet]*. 2014;15(12):1671–83. Available from: http://www.researchgate.net/publication/263129681_Treatment_of_central_sensitization_in_patients_with_'unexplained'_chronic_pain_An_update
57. Robins H, Perron V, Heathcote L, Simons L. Pain Neuroscience Education: State of the Art and Application in Pediatrics. *Children [Internet]*. 2016;3(4):43. Available from: <http://www.mdpi.com/2227-9067/3/4/43>
58. Louw A, Diener I, Butler DS, Puentedura EJ. The effect of neuroscience education on pain, disability, anxiety, and stress in chronic musculoskeletal pain. *Arch Phys Med Rehabil [Internet]*. 2011;92(12):2041–56. Available from:

<http://dx.doi.org/10.1016/j.apmr.2011.07.198>

59. Van Oosterwijck J, Meeus M, Paul L, Schryver M, Pascal A, Lambrecht L, et al. Pain physiology education improves health status and endogenous pain inhibition in fibromyalgia: A double-blind randomized controlled trial. *Clin J Pain* [Internet]. 2013;29(10):873–82. Available from:
<http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/198/CN-00915198/frame.html>
60. Nijs J, Paul van Wilgen C, Van Oosterwijck J, van Ittersum M, Meeus M. How to explain central sensitization to patients with “unexplained” chronic musculoskeletal pain: Practice guidelines. *Man Ther* [Internet]. 2011;16(5):413–8. Available from:
<http://dx.doi.org/10.1016/j.math.2011.04.005>
61. Van Oosterwijck J, Nijs J, Meeus M, Truijzen S, Craps J, Van den Keybus N, et al. Pain neurophysiology education improves cognitions, pain thresholds, and movement performance in people with chronic whiplash: a pilot study. *J Rehabil Res Dev*. 2011;48(1):43–58.
62. Moseley GL. Evidence for a direct relationship between cognitive and physical change during an education intervention in people with chronic low back pain. *Eur J Pain*. 2004;8(1):39–45.

Figure 1. Flow chart of study selection according PRISMA guidelines



From: 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

Table 1. Keywords used to build the search strategy

Database	Keywords			Additional filters
	(P1) Patient	(P2) Problem	(O) Outcome	
Pubmed	Children Child Kid Infant Preschool	Chronic pain Idiopathic pain Intractable pain	Central nervous system sensitization Allodynia Hypersensitivity Hyperexcitability Hyperalgesia Pain facilitation Wind-up Temporal summation Long term potentiation Spatial summation Conditioned pain modulation Diffuse noxious inhibitory control Algometry Quantitative sensory testing Pain tolerance Pain threshold Pain perception Pain intensity Pain mechanism Pain dampening	Humans Dutch English Child: 6-12y Preschool child: 2-5y
Web of Science	No keywords			

Table 2. Assessment of methodological quality with Newcastle-Ottawa Scale

Study	Year	Selection				Comparability		Exposure		No. of stars
		1	2	3	4	5	6	7	8	
Alfven et al.	1993		★	★	★	★		★	★	6
Cornelissen et al.	2014	★	★			★				3
Duarte et al.	2000	★	★		★	★	★		★	6
Hermann et al.	2008			★	★	★	★		★	5
Hogeweg et al.	1995	★				★		★	★	4
Hogeweg et al.	1995	★	★			★	★	★	★	6
Jedel et al.	2007		★	★	★	★	★		★	6
Leegaard et al.	2013	★	★	★	★	★	★		★	7
Reid et al.	1997	★	★	★		★	★		★	6
Zohsel et al.	2006			★	★	★	★		★	5
Zohsel et al.	2008			★	★	★	★		★	5
Zohsel et al.	2008			★	★	★	★		★	5

0: criterion not fulfilled; 1: criterion fulfilled,

NOS: Newcastle-Ottawa Scale: Case-control studies

Criterion 1: Is the case definition adequate

Criterion 2: Representativeness of the cases

Criterion 3: Selection of controls

Criterion 4: Definition of controls

Criterion 5: Study controls for age/gender

Criterion 6: Study controls for any additional factor

Criterion 7: Ascertainment of exposure

Criterion 8: Same method of ascertainment for cases and controls

Table 3. Evidence table of the included studies

References	Sample	Inclusion criteria	Mean age (y; M ± SD)	Assessment regarding CH	Results RAP ↔ CON
Alfven et al. (1993)	49 RAP 50 CON (Total: 69♂, 71♀)	RAP: pain during >3 months, at least 1x/month CON: no pain symptoms	11	Algometer: PPT m. temporalis, m. trapezius, m. subclavius, pectoralis major (lateral insertion), m. rectus abdominus (near umbilicus), m. quadriceps	RAP: ↓ PPTs ($p<0.05$)* for all muscles except m. quadriceps ($p=0.22$)
Duarte et al. (2000)	100 RAP (45♂,55♀) 100 CON (45♂,55♀)	RAP: history of pain, at least lasting 1year CON: no previous history of recurrent or chronic pain	RAP: 9.2 CON: 9.0	Algometer: PPT m. trapezius, m. deltoideus, supraspinous muscles, nine areas of the abdominal wall, median part of tibias	RAP: ↓ PPTs ($p=0.0000$)* for all body regions
Hermann et al. (2008)	14 RAP (6♂,8♀) 15 CON (7♂,8♀)	RAP: modified Apley-criteria CON: pain episode <1/month	RAP: 12.1 ± 1.7 CON: 12.3 ± 1.5	Impact stimulating device: PPT pad of the distal phalanx of the left finger EEG: AEP, SEP forehead, right eye, right and left outer canthi of eyes	RAP: ↑ P3 component for non- and painful stimuli ($p=0.002$)*, ↑ P3 amplitude for non- and painful stimuli ($p=0.006$ and $p=0.002$)*, ↓ P3 latency for non- and painful stimuli ($p=0.001$)*
Zohsel et al. (2008)	20 RAP (9♂,11♀)	RAP: Apley- criteria, Rome III-criteria, VAS >3, pain during >3 months, at least	RAP: 10.7 ± 1.7	QST: HPT, TPS, MPT, MPS	RAP: ↑ TPS ($p<0.05$)* at the thenar,

	23 CON (13♂,10♀)	2x/month CON: pain episode <1/month	CON: 11.0 ± 1.5	m. abdominus near umbilicus, thenar eminence nondominant hand	↓ MPS ($p=0.05$)* at the thenar
References	Sample	Inclusion criteria	Mean age (y; M ± SD)	Assessment regarding CH	Results JIA ↔ CON
Cornelissen et al. (2014)	60 JIA (16♂,44♀) 92 US CON (46♂,46♀) 151 EU CON (75♂,76♀)	JIA: clear diagnosis of JIA US CON: healthy children, no neurological disorders EU CON: healthy children	JIA: 13.0 US CON: 13.0 EU CON: 11.0	QST: MDT, VDT, CDT, CPT, HPT, MPT, Algometer: PPT affected joint, contralateral thenar eminence	JIA: ↓ PPT vs. EU CON ($p<0.001$)* at thenar eminence, ↓CPT vs. EU CON ($p<0.01$)*, vs. US CON ($p<0.001$)* at thenar eminence, ↓HPT vs. EU CON ($p<0.05$), vs. US CON ($p<0.001$)* at thenar eminence
Hogeweg et al. (1994)	33 JIA (11♂,22♀) 69 CON (33♂,36♀)	JIA: EULAR-criteria CON: healthy children	JIA: ♂11.3 ± 1.5 ♀12.1 ± 2.1 CON: 11.5 ± 3.1	Algometer: PPT joints capsules of knees, ankles, soft paravertebral tissues	JIA: ↓ PPT ($p<0.01$)* at all regions
Hogeweg et al. (1995)	57 JIA (18♂,39♀) 69 CON (33♂,36♀)	JIA: EULAR-criteria CON: healthy children	JIA: ♂12.2 ± 2.6 ♀11.8 ± 3.2 CON: 11.5 ± 3.1	Algometer: PPT joints capsules of wrists, elbows, knees, ankles, paravertebral soft tissues	JIA: ↓ PPT ($p<0.001$)* at all regions

Leegaard et al. (2013)	85 JIA (56♂,42♀) 91 CON (36♂,55♀)	JIA: ILAR-criteria CON: no comorbidity associated with pain	JIA: 11.9 ± 1.8 CON: 12.2 ± 1.9	Algometer: PPT 17 symmetric anatomically predefined joint-related or bone-related areas	JIA: ↓ total mean PPT ($p<0.001$)*
References	Sample	Inclusion criteria	Mean age (y; M ± SD)	Assessment regarding CH	Results MIG ↔ CON
Zohsel et al. (2006)	25 MIG (14♂,11♀) 28 CON (12♂,16♀)	MIG: IHS-criteria adapted for pediatric MIG CON: pain episode <1/month	MIG: 11.0 ± 1.8 CON: 11.0 ± 1.8	QST: HPT, TPS, MPT, MPS trigeminal and thenar sites	MIG: ↓ MPT ($p<0.05$)* at both trigeminal and thenar site
Zohsel et al. (2008)	16 MIG (8♂,7♀) 15 CON (7♂,8♀)	MIG: IHS-criteria adapted for pediatric MIG CON: pain episode <1/month	MIG: 12.0 ± 1.5 CON: 12.3 ± 1.5	Impact stimulating device: PPT pad of the distal phalanx of the left finger EEG: AEP, SEP forehead, right eye, right and left outer canthi of eyes	MIG: ↑ P3 component for non- and painful stimuli ($p<0.05$)*, ↑ P3 amplitude for non- and painful stimuli ($p<0.001$)*, ↓ P3 latency for painful stimuli ($p<0.001$)*
References	Sample	Inclusion criteria	Mean age (y; M ± SD)	Assessment regarding CH	Results TMD ↔ CON
Jedel et al. (2007)	21 TMD (6♂,15♀) 21 CON (6♂,15♀)	TMD: >1/week TMD pain, during >3months CON: no JIA, Ehles Danlos syndrome, myositis ossificans, diabetes, CTTH, MIG, TMD	TMD: 16 CON: 16	Pain matcher: PT between thumb and index finger left hand	TMD: no significantly ↓ mean PT

References	Sample	Inclusion criteria	Mean age (y; M \pm SD)	Assessment regarding CH	Results FM/JIA \leftrightarrow CON
Reid et al. (1997)	15 FM (2♂,13♀) 15 JRA (2♂,13♀) 15 CON (2♂,13♀)	FM: diagnosed within previous 2y JIA: polyarticular or systemic onset CON: healthy, no organic underlying organic illness	FM: 14.5 \pm 1.88 JRA: 14.5 \pm 1.95 CON: 14.6 \pm 1.89	Algometer: PPT (tender and control points), PPT ₂ (control points) right occiput, left and right trapezius, right supraspinatus, right lateral condyle, right greater trochanter, left and right knee, right low cervical	FM: \downarrow mean PPT ($p<0.05$)* at tender points, \downarrow mean PPT ₂ ($p<0.05$)* at control points
<p>RAP: recurrent abdominal pain, CON: Control group, y: Year, m.: Musculus, SD: Standard deviation, PPT: Pressure pain threshold, M: mean, EEG: Electroencephalography, AEP: Auditory Evoked Potentials, SEP: Somatosensory evoked potentials, VAS: Visual analogue scale, QST: Quantitative sensory testing, HPT: Heat pain threshold, TPS: Thermal perceptual sensitization, MPT: Mechanical pain threshold, MPS: Mechanical perceptual sensitization, JIA: Juvenile idiopathic arthritis, US: United States, EU: Europe, MDT: Mechanical detection threshold, VDT: Vibration detection threshold, CPT: Cold pain threshold, EULAR: European league against rheumatism, ILAR: International league of associations for rheumatology, MIG: Migraine, CH: Central hyperexcitability, IHS: International headache society, TMD: Temporomandibular disorder, CTTD: Chronic tension-type headache, PT₁: Pain threshold, FM: Fibromyalgia, PT₂: Pain tolerance, * Significance level $p<0.05$</p>					

