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ABSTRACT

Background: Pain neuroscience education is effective in chronic pain management. Central sensitization (i.e. generalized hypersensitivity) is often explained as underlying mechanism for chronic pain, because of its clinical relevance and influence on pain severity, prognosis, and treatment outcome.

Objectives: To examine whether patients with more or fewer symptoms of central sensitization respond differently to pain neuroscience education.

Design: A secondary analysis of a multicentre, triple-blind randomized controlled trial

Setting: University hospital Ghent and University Hospital Brussels, Belgium.

Patients: 120 persons with chronic spinal pain with high or low self-reported symptoms of central sensitization

Interventions: Pain neuroscience education or neck/back school. Both interventions were delivered in three sessions: one group session, one online session and one individual session.

Main Outcome Measures: disability (primary), pain catastrophizing, kinesiophobia, illness perceptions and hypervigilance.

Results: Pain disability did not change in any group (p=.242). Regarding secondary outcomes: significant interaction effects were found for pain catastrophizing (p-values: p=.02 to p=.05), kinesiophobia (p=.02), and several aspects of illness perceptions (chronicity: p=.002; negative consequences: p=.02; personal control: p=.02; and cyclicity: p=.02). Bonferroni post-hoc analysis showed that only the pain neuroscience education group showed a significant improvement regarding kinesiophobia (p<.001, medium effect sizes), perceived negative consequence (p=.004 and p<.001, small to medium effect sizes) and perceived cyclicity of the illness (p=.01 and p=.01, small effect sizes).

Conclusion: Pain neuroscience education is useful in all patients with chronic spinal pain as it improves kinesiophobia and the perceived negative consequences and cyclicity of the illness regardless the self-reported signs of central sensitization. Regarding pain catastrophizing, pain neuroscience education is more effective in patients with high self-reported symptoms of central sensitization.

Level of Evidence: Therapy, Level I

Keywords: kinesiophobia, illness perceptions, therapy, education, randomized controlled trial

INTRODUCTION

In the last decade the focus of educational programs for people with chronic pain has shifted remarkably to pain neuroscience education [1–5]. Pain neuroscience education is used to increase the patients' knowledge of the underlying pain physiology, to decrease the threat value of pain, and to reconceptualise pain [6,7]. Neurophysiological mechanisms of the peripheral and central nervous system and neuroplastic changes occurring in case of chronic pain are explained in layman's terms, using photographs, drawings, metaphors, etc. Particular attention is given to the brain, and its role in pain related thoughts, attitudes and psychological distress, which influence pain perception [8]. There is some evidence to support that pain neuroscience education can improve health status, pain beliefs, illness perceptions, anxiety, kinesiophobia, and endogenous pain modulation in several chronic pain populations, including patients with chronic spinal pain [1,9–14]. Yet, others indicate the need for more studies to support the clinical utility of pain neuroscience education [3,4] or that this type of education is insufficient by itself to change perceived disability [2,15].

One of the studies indicating the insufficiency of pain neuroscience education to change perceived disability comprises the original analysis of the data presented in this paper [15]. Although there was no change in the perceived disability in response to pain neuroscience education, there was an improvement in secondary outcomes like kinesiophobia, and illness perceptions. The absence of an effect on perceived disability might relate to a heterogeneity in the population regarding symptoms of central sensitization (i.e. generalized hypersensitivity), as evidence shows more

perceived disability in subgroups that display more symptoms of central sensitization[16]. Central sensitization is one of the mechanisms explained during pain neuroscience education. Therefore, groups with more prominent symptoms of central sensitization might relate more to the content and might experience more improvement regarding perceived disability (and even other outcome measures) in response to pain neuroscience education. However, this is merely an assumption, that has not been investigated before, which is the scope of this paper.

Central sensitization is a maladaptive type of neuroplasticity which maintains nociceptive hypersensitivity long after tissue healing has occurred [17], and is characterized by generalized hypersensitivity of the somatosensory system [18,19]. Negative or maladaptive pain related thoughts can facilitate this process [20]. Yet, central sensitization is not the only explanatory model for chronic spinal pain in literature. Others suggest for example impaired movement, postural control and deconditioning as underlying mechanisms for chronic spinal pain [21–23].

Nevertheless, three lines of evidence support the clinical importance of central sensitization (i.e. generalized hypersensitivity) in chronic pain patients: 1) compared to pain patients without signs of central sensitization, patients with predominant central sensitization – objectified using experimental pain measures – report higher pain severity and lower quality of life [24,25]; 2) central sensitization relates to poorer prognosis [26–28] and 3) mediates treatment outcome after physical rehabilitation [28–30] in various chronic musculoskeletal pain populations.

One particular instrument that assesses self-reported symptoms of central sensitization (i.e. generalized hypersensitivity) is the Central Sensitization Inventory (CSI). The CSI evaluates the occurrence of hypersensitivity for senses unrelated to the musculoskeletal system (e.g. chemical substances, cold, heat, stress, electrical stimuli, etc.) [31–36], and is a reliable and valid instrument [37,38]. Still, it needs to be acknowledged that – like other behavior measures of central sensitization in humans (i.e. quantitative sensory testing) – the CSI is an indirect measure of central sensitization. Nevertheless, unlike in animal studies, there is currently no other way to assess central sensitization in humans.

The CSI (with the cut-off of >40) has an 81% sensitivity to distinguish between a central sensitivity syndrome group and a non-patient group [39,40], has a strong connection with psychological distress [41], and has strong psychometric properties and potential to be a useful clinical outcome measure [42]. As the content of pain neuroscience education relates partly on central sensitization as underlying mechanism for chronic pain and explains the influence of psychological distress on chronic pain, people suffering more from self-reported symptoms of central sensitization and related psychological distress might identify more with the specific content of the education and might therefore respond better. Identifying groups that respond better or worse to pain neuroscience education, would enable clinicians to provide better therapy to patients with chronic spinal pain.

Because of the ability of pain neuroscience education to improve several important outcomes in chronic pain (e.g. health status, illness perceptions, kinesiophobia, etc.), the clinical importance of central sensitization (i.e. generalized hypersensitivity) in

chronic pain, and the ability of the CSI to differentiate between patients with and without self-reported symptoms of central sensitization, it seems warranted to examine whether patients with more self-reported symptoms of central sensitization respond differently to pain neuroscience education than those with fewer self-reported symptoms of central sensitization. Therefore, this study aimed to investigate if the effectiveness of pain neuroscience education (vs. biomedical neck/back school) differs in patients with high and low baseline self-reported symptoms of central sensitization.

METHODS

Design overview

This multicentre, triple-blind randomized controlled trial took place in two centres: the University Hospitals of Ghent and Brussels. The trial was approved by the local ethics committees (University Hospital Brussels and University Hospital Ghent) and was conducted between January 2014 and January 2016. All participants signed the informed consent. The full study protocol is registered online (ClinicalTrials.gov NCTxxxxx) and is published elsewhere [43]. The trial is reported according to CONSORT guidelines [44].

Here we report the effects of pain neuroscience education (vs. biomedical neck/back school as the control education) on self-reported questionnaires (assessing disability, catastrophizing, kinesiophobia, illness perceptions, and hypervigilance) in groups with high and low self-reported symptoms of central sensitization (i.e. generalized hypersensitivity). Outcome measures were obtained at baseline and directly after three sessions of education.

Study population and sample size

The study population examined in this secondary analysis is the same as the study population of the original analysis, which is published elsewhere [15]. One-hundred-twenty persons with non-specific chronic spinal pain (nCSP) were recruited through different sources: flyers in the university hospitals in Ghent and Brussels and primary care practices (medical doctors), via adverts and via social media.

Participants were found eligible for study participation is the were (1) native Dutch speaking; (2) aged between 18 and 65 years old; (3) having nCSP at least 3days/week for at least 3 months since the first symptoms: nCSP includes chronic low back pain, failed back surgery syndrome (i.e. more than three year ago, anatomically successful operation without symptom disappearance), chronic whiplash associated disorders, and chronic non-traumatic neck pain; (4) available and willing to participate in educational sessions; and (5) not continuing any other therapies (i.e. other physical therapy treatments, acupuncture, osteopathy, etc.), except for usual medication.

People were excluded in case of (1) a specific medical condition, possibly related to their pain (e.g., neuropathic pain, a history of neck/back surgery in the past three years, osteoporotic vertebral fractures, rheumatologic diseases); (2) a chronic widespread pain syndromes diagnosis (e.g. fibromyalgia, chronic fatigue syndrome); (3) having their place of residence more than 50km away from the treatment location to avoid dropout due to practical considerations; and (4) having received a form of pain neuroscience education in the past. Additionally, participants were asked not to start new medication 6 weeks prior to and during participation in this study.

Sample size calculations were performed with G*Power (Düsseldorf, Germany) based on the therapy effects on disability in the pilot study of Van Oosterwijck et al. [12] (Cohen's D= .46; usage of neck disability index in people with chronic whiplash). Calculations were based on ANOVA repeated measures (number of measurements = 2; number of groups = 4) statistics with an effect size of .15, alpha set at .05 and a desired power of .90, resulting in a total of 164 people.

169

170 ***Randomisation***

171 Participants were randomly assigned into an educational group, using a stratified
172 permuted block allocation (block size of four) with stratification factors being
173 treatment centre (Ghent or Brussels), dominant pain location (low back or neck) and
174 gender (male or female) [45,46]. Randomisation was performed at the Biostatistics
175 Unit (Ghent University) by an independent investigator using SAS 9.4.

176

177 ***Blinding***

178 The study participants and the statistician (performing the data analyses) were
179 blinded to the study hypothesis; and the outcomes assessors (collecting the data)
180 were blinded for the randomisation sequence (i.e. triple blind). Participants did not
181 know whether they received the experimental or control intervention and they did not
182 see each other in the hospital waiting rooms (no contamination between groups). The
183 therapists providing the experimental treatment were not involved in the control
184 intervention and vice versa.

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187

188 ***Subdivision of groups***

189 The baseline CSI total score was used to divide the groups based on the presence or
190 absence of self-reported symptoms of central sensitization (i.e. generalized
191 hypersensitivity). This questionnaire consists of 25 items assessing health-related
192 symptoms, rated on a Likert-scale (0= “never” to 4= “always”). The total score
193 represents the degree of self-reported symptomology (maximum score = 100). A cut-

194 off value of 40 is determined, with scores higher than 40 indicating the presence of
195 central sensitization (81% sensitivity and 75% specificity) [40]. Several studies found
196 support for the reliability and validity of the CSI, including the Dutch CSI as used here
197 [37–40].
198
199 ***Primary Outcome Measure***
200 *Pain disability Index*
201 Pain disability was chosen as primary outcome measure because of its importance in
202 people with chronic spinal pain: perceived disability relates to employment status,
203 health-related quality of life, depression, catastrophizing, anxiety and other
204 psychosocial factors related to well-being [47,48]. The Dutch version of the Pain
205 Disability Index (PDI) was used to measure the impact of pain on daily life activities.
206 The PDI is a valid measurement tool with good internal consistency and good test re-
207 test reliability [49]. Higher scores indicate a higher level of disability during activities.
208 A change in the PDI is considered clinically important when it concerns a decrease of
209 8.5 to 9.5 points[50].
210
211
212
213 ***Secondary Outcome Measures***
214 Secondary outcome measures were chosen based on their influence on levels of
215 physical activity, chronification, participation in daily life and social activities [51–54].
216 Therefore, if an intervention can improve these outcome measures, it might enhance
217 an active rehabilitation, which is crucial in the management of people with nCSP
218 [55,56].

The Dutch Version of the *Pain Catastrophizing Scale* (PCS) assesses catastrophic thoughts regarding pain in 13 statements using a 5-point Likert-scale (range: 0 to 52). Summing these scores leads to a total score of three subscales: rumination (4 statements, score range: 0 to 16), magnification (3 statements, score range: 0 to 12) and helplessness (6 statements, range: score 0 to 24). Higher scores indicate a higher degree of catastrophic thoughts regarding pain [57]. The PCS has adequate reliability in people with musculoskeletal disorders [58] and has good criterion and construct validity [58,59].

The Dutch version of the *Tampa Scale for Kinesiophobia* (TSK) contains 17 statements regarding fear of movement or (re)injury, each scored on a 4-points Likert-scale (range: 17 to 68). Higher scores indicate higher fear of movement [60,61], and the minimal clinical important difference is determined as a change of 6 points [62]. The TSK has a moderate construct validity and excellent test-retest reliability [61,63].

The Dutch version of the *Revised Illness Perception Questionnaire* (IPQr) measures several dimensions of illness perceptions: beliefs about the course of their chronic pain (score range: 0 to 25) and the time scale of illness symptoms (score range: 0 to 20), the impact of the illness on quality of life and functional capacity (score range: 0 to 30), the perceived influence of own behaviour (score range: 0 to 30) and treatment efficacy (score range: 0 to 25), the emotional responses (score range: 0 to 30) and the coherent understanding (score range: 0 to 25) of the illness [64,65]. All items are scored on a 5-point Likert scale. The IPQr has a good test-retest reliability and predictive validity in different patient populations [65].

The Dutch version of the *Pain Vigilance and Awareness Questionnaire* (PVAQ) measures the patient's awareness of and attention to pain in 16-items (range 0 to 80). Higher scores indicate a higher degree of pain vigilance and awareness. The PVAQ has good internal consistency and test-retest reliability and is shown valid and reliable in several chronic pain populations [66–68].

Intervention

All study participants received three educational sessions within two weeks. The format of administration was identical for both treatment groups. The first session was a group educational session (PowerPoint presentation, duration: 30 minutes to one hour; maximal six participants/group) led by a physical therapist with clinical experience in chronic spinal pain. The therapist delivering education in one group, did not provide education in the other group, and vice versa. Afterwards, participants received an educational booklet containing the same information to read at home. The second session was an online home-based e-learning module, containing three explanatory videos. These videos displayed the PowerPoint presentation used in the group session, with a voice-over explaining the content of the slides. After each video, the participants had to complete a questionnaire which assessed their opinion and understanding of that video. The third session comprised a 30-minute one-on-one conversation focussing on the patient's personal needs: answers from the second session's questionnaires were analysed and the application of the newly-derived knowledge into daily life was discussed. The content of the provided education (described below) rather than the format of administration differed between groups.

Experimental group

The content and pictures of the first and the second session were based on current knowledge of the neurophysiology of pain [69] and on two instructive books [6,7]. An example of a PowerPoint presentation for pain neuroscience education can be found online (http://www.paininmotion.be/storage/app/media//materials/sem-PainPhysiologyEducationEnglish.pdf).

Following topics are covered: the physiology of the 1) the neuron (receptor, axon, terminal), 2) the synapse (action potential, neurotransmitters, postsynaptic membrane potential, chemically driven ion channel), 3) descending nociceptive inhibition and facilitation (the influence of stress, emotions, thoughts, physical activity,…), 4) peripheral sensitization, and 5) central sensitization (receptor field growth, potentiation of the postsynaptic membrane, changes at cortical and subcortical level, etc.).

In the third session, the therapist and patient discussed the answers given during the online session by relating them to the pain neuroscience education content. After these three sessions, the patients should be able to put their pain into the right perspective and to feel less threatened by the pain, leading to the willingness to perform physical activity with progression towards feared or avoided movements.

Control group

The biomedically-focused neck/back school was based on available clinical guidelines [70,71]. Participants were expected gain biomedically-oriented knowledge

on neck and low back pain during the education. The following topics were covered: 1) the normal course and mechanical causes of neck/back pain; 2) the anatomy, physiology and biomechanics of the spinal bones, joints and muscles; 3) ergonomic advice and the importance of self-care; 4) lifting techniques (using pictures of people lifting in several ways); and 5) the value of and principles behind different types of exercises (stretching; and strength, endurance and fitness training). It did not include information on the nervous system, except for the course and location of the spinal cord and spinal nerve roots. During the third session, the patient and therapist discussed the answers given during the online session by relating them to the content of the education and patients were given ergonomic advice for specific activities and were able to practice lifting techniques.

Statistical Analysis

Data were analysed using SPSS 22.0. Subjects of both educational groups were allocated into groups based on their baseline CSI scores. Subjects with a CSI score higher than 40 were allocated into the highCSI group, the others into the lowCSI group, leading to a total of four groups. Differences in response to the interventions between the four groups were first analysed using ANCOVA, with gender as covariate. As this covariate did not show significant interaction in any variable, the analysis was performed again without this covariate. The assumption of homogeneity and sphericity was checked by Levene's and Mauchly's test respectively. When the assumption of sphericity was violated, Greenhouse-Geisser corrections were used. In case of significant interaction effects (i.e. implying that the compared groups respond differently to the intervention given), Bonferroni Post Hoc analysis was carried out to investigate the specific differences within and between groups. Data

were analysed according to the intention-to-treat principle (i.e., the first-observation-carried-forward method). This method was used because of the short period (+/- two weeks) between the baseline and post-education measurements. Therefore, we believe that the baseline measurement is most representative as follow-up measurement for the people who dropped out. Also, we are aware that this method for conduction intention-to-treat analyses is rather stringent.

RESULTS

Subjects' demographic characteristics and comparability

Of the 120 persons included, nine (n=2 in the high CSI neck/back school group; n=2 in the low CSI neck/back school group; n=2 in the high CSI pain neuroscience education group; and n=3 in the low CSI pain neuroscience education group) dropped out before completion of the second round of questionnaires. Reasons for dropout are outlined in the study flow chart (figure 1). Subjects' baseline characteristics can be found in detail in table 1.

Effectiveness of pain neuroscience education in patients with nCSP with high and low self-reported symptoms of central sensitization

Regarding pain disability, no significant interaction effect was found (table 2), but differences at group level (p<.001) were found. All patients with high CSI scores had higher PDI scores than the groups with low CSI scores (p<.004 for all comparisons; see table 3).

For all pain catastrophizing items (except for helplessness) significant interaction effects were found (p-values ranging from p=.02 to p=.05; see table 2 and figure 2). Bonferroni post-hoc analysis (table 3 and figure 2) showed a significant difference at baseline between the two pain neuroscience education groups (mean difference rumination: 4.07, 95%CI: 2.06 to 6.07; mean difference magnification: 2.17, 95%CI: 1.07 to 3.26; mean difference total score: 9.67, 95%CI: 4.74 to 14.60) and that these three pain catastrophizing items decreased significantly only in the high CSI pain neuroscience education group (p<.001; small effect sizes), which was not seen in the

low CSI groups (negligible sizes). Surprisingly, PCS magnification increased in the low CSI pain neuroscience education group (p=.03; small effect size).

Regarding kinesiophobia, a significant interaction effect was found (p=.02; see table 2 and figure 3). Bonferroni post-hoc analysis showed that only in the pain neuroscience education groups kinesiophobia decreased significantly (p<.001, medium effect sizes; see table 3 and figure 3). Additional analysis of group effects showed significant higher kinesiophobia at baseline in the high CSI pain neuroscience education group compared to the low CSI group (p=.02). Post-education, there was a significant group difference between the high CSI groups (p=.03) and the low CSI groups (p=.001).

Last, several illness perceptions showed significant interaction effects (see table 2 and figures 4 and 5): acute/chronic timeline (p=.002), negative consequences (p=.02), personal control (p=.02) and timeline cyclical (p=.012). Bonferroni post-hoc analysis (table 3) showed that both pain neuroscience education groups improved significantly post-education for all subscales (p-values ranging from p<.001 to p=.01, small to large effect sizes). In the neck/back school groups, there was a significant improvement of IPQr ‘acute/chronic timeline’ (p<.001; medium effect size) in the low CSI group and a significant improvement of IPQr ‘personal control’ (p<.001; medium effect size) in the high CSI group. Bonferroni post-hoc analyses of group effects (table 3) showed significant higher IPQr consequences scores in the high CSI pain neuroscience education group compared to the low CSI pain neuroscience education group at baseline (p<.001) and post education (p<.001).

DISCUSSION

The aim of this study was to investigate if the effectiveness of pain neuroscience education – compared to biomedical neck/back school – differs between patients with high and low self-reported symptoms of central sensitization (i.e. generalized hypersensitivity). Results of the present study show that pain neuroscience education is superior over neck/back school for improving kinesiophobia and the perceived negative consequences and cyclicity of the illness in patients with nCSP regardless their baseline self-reported symptoms of central sensitization. Yet, only in patients with high self-reported symptoms of central sensitization, pain neuroscience education has the potential to reduce rumination about pain.

The use of CSI scores to subgroup the participants in this study and its relevance to measure central sensitization should be discussed. Like other behavioural measures, the CSI is an indirect tool to measure central sensitization and based on the recently proposed clinical classification system for central sensitization pain [72,73], CSI scores alone are insufficient to differentiate between self-reported symptoms of central sensitization and non-central sensitization pain. Although the CSI cannot directly objectify central sensitization, the questionnaire is related to psychological distress and widespread pain, and is therefore related to central sensitization [41]. Because of the shared variance between the CSI and psychological distress, it is possible that the latter predicts the outcome following pain neuroscience education in patients with nCSP, rather than central sensitization. Nevertheless, the CSI is an easy-to-use and clinically relevant tool and was therefore used as such in this study to generate clinically applicable results.

The a priori defined primary outcome measure – pain disability – did not change in any of the study groups, while previous studies on pain neuroscience education did report a positive effect on self-reported disability [2,12,74]. That discrepancy could be explained due to the use of a different questionnaire to objectify disability, e.g. the Roland Morris Disability Questionnaire [2,74] and the Neck Disability Index [12]. Other explanations may involve the use of an uncontrolled study design in earlier studies [12], or because the investigated patient population of this study comprises both patients with low back pain and neck pain, while previous studies focussed on either low back pain or neck pain patients.

Results regarding pain catastrophizing indicate that pain catastrophizing in general, and rumination in particular are two aspects that can be targeted primarily in patients with high baseline self-reported symptoms of central sensitization using pain neuroscience education (small effect sizes). Neck/back school is not able to alter pain rumination, but the total pain catastrophizing score did improve in the neck/back school group with high self-reported symptoms of central sensitization. This, combined with the improvement in the total score in the pain neuroscience education group, indicates that patients with high self-reported symptoms of central sensitization seem to benefit more from educational sessions than patients with low levels, regardless the information provided.

Pain magnification on the contrary, can be reduced by pain neuroscience education in patients with high self-reported symptoms of central sensitization (small effect size), while it tends to increase in patients with low self-reported symptoms of central

sensitization (small effect size). Therefore, one should be cautious while explaining pain neurophysiology to nCSP patients with low self-reported symptoms of central sensitization to make sure the information provided does not lead to magnification of the pain problem. While providing pain neuroscience education, the therapist should clearly assess the patients' thoughts on the delivered information and address inappropriate beliefs upon occurrence.

Regarding kinesiophobia, medium effect sizes are found in both pain neuroscience education groups, while effect sizes remain small to negligible in the neck/back school group. This finding is consistent with previous research [2,12,74]. However, previous research did not account for the presence of self-reported symptoms of central sensitization. The results of this study indicate that for kinesiophobia, baseline self-reported symptoms of central sensitization did not influence the effect of pain neuroscience education as both groups improved equally (medium effect sizes). The decrease in kinesiophobia is a positive effect directly resulting from pain neuroscience education as this was not seen in the neck/back school group. This is an important finding as kinesiophobia is a strong predictor for chronification [75], and a decrease is shown to be related to greater improvement in pain and disability [76].

Kinesiophobia can occur from an ignorance regarding pain symptoms [77]. Patients with chronic pain may believe that their pain is related to tissue damage, while evidence shows that spinal radiological imaging findings are often unrelated to spinal pain [78]. Pain neuroscience education helps patients to understand the mechanisms underlying the pain problem by explaining that pain is the result of sensory hypersensitivity rather than a damaged spine. This knowledge may result in reduced

fear of injury or damage while moving the spine, possibly resulting in a decrease in kinesiophobia.

Also interesting findings regarding illness perceptions were found. For all aspects of illness perceptions that showed significant interaction effects, both groups with high and low baseline self-reported symptoms of central sensitization improved in response to pain neuroscience education. This implies that pain neuroscience education is able to reduce the perceived chronicity and the perceived negative impact of the illness, while it can increase the perceived fluctuations of the illness and the perceived personal control. This is not an unexpected finding as pain neuroscience education imparts a change in illness perceptions by redefining pain. Also, the increase in the aspect ‘timeline cyclical’ does not come as a surprise. This indicates that pain neuroscience education leads to stronger beliefs of unpredictability and cyclicity of the illness, which should be interpreted with respect to the content of the education. Patients learn that the normal course of chronic pain is fluctuating and unpredictable. Therefore, a significant increase in this subscale could represent the increased knowledge and acceptance.

Strengths and limitations

Study strengths include the balanced treatment arms, triple blind randomized design, use of reliable and valid outcomes and the a priori study protocol publication [43].

Also, some limitations should be mentioned. The lack of follow-up period is an important limitation of this study as information retention and delayed changes in the investigated outcome measures were not evaluated. Furthermore, one should be

cautious in extrapolating these results into the general chronic pain population given the heterogeneity of this group.

A last limitation to consider relates to the sample size calculation, which indicated the inclusion of 164 study participants (accounting for two measurements and four groups). However, as this study entails a secondary analysis of a dataset that included only 120 study participants, we failed to meet this sample size (n=164). This might explain why no effect was found for the primary outcome measure.

CONCLUSION

To conclude, results indicate that pain neuroscience education is superior to neck/back school in improving kinesiophobia and the perceived negative consequences and cyclicity of the illness in patients with nCSP regardless their baseline self-reported symptoms of central sensitization (i.e. generalized hypersensitivity). Only in patients with high self-reported symptoms of central sensitization, pain neuroscience eduacation has the potential to reduce rumination about pain, a result that is not seen in patients with low self-reported symptoms of central sensitization. In general, these results imply the use of pain neuroscience education over neck/back school in clinical practice in patients with nCSP regardless their baseline levels of self-reported symptoms of central sensitization.

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TABLE 1. Demographics and baseline characteristics of patients with nCSP with high and low self-reported signs of central sensitization

Demographic characteristics	**Pain Neuroscience Education**		**Neck/Back School**	
	High CSI (n=24)	Low CSI (n=36)	High CSI (n=30)	Low CSI (n=30)
Demographics				
Dominant pain problem[a] (NP/LBP)	13/11	19/17	17/13	15/15
Sex (F/M)	17/7	21/15	22/8	13/17
Duration of Pain[b] (months)	111 (128.3)	88 (156.5)	66.5 (96.5)	70.5 (141.5)
Educational Level[a] No degr – Lower second. – Higher second. – Higher Edu	0 – 1 – 7 – 16	0 – 3 – 4 – 29	0 – 5 – 7 – 18	0 – 3 – 6 – 21
Working Hours per week[b]	40 (12.50)	39 (15.75)	38 (23.75)	40 (12.50)
Age (y)[c]	36.58±11.03	40.47±12.49	40.13±14.91	42.10±11.10
Age (y) min-max	20 - 56	20 - 65	19 - 65	19 - 64
Baseline characteristics				
PDI (/70)	30.13±14.92	16.25±11.59	26.03±15.06	17.13±9.94
PCS Rumination (/16)	8.96±3.37	4.89±3.78	7.63±4.26	5.37±3.85
PCS Magnification (/12)	3.75±2.25	1.58±1.70	3.23±2.40	2.27±2.08
PCS Helplessness (/24)	9.63±4.39	6.19±4.33	8.73±5.98	6.47±4.31
PCS Total (/52)	22.33±8.50	12.67±8.62	19.60±11.33	14.10±9.05
TSK (/68)	37.00±6.76	32.61±6.84	37.97±6.71	35.47±6.86
IPQr acute/chronic timeline (/25)	24.63±4.13	23.33±4.19	23.13±3.58	23.33±3.70
IPQr Consequences (/20)	19.50±4.29	14.53±4.33	18.00±3.94	15.30±4.77
IPQr personal control (/30)	19.33±4.01	20.75±4.13	19.43±4.35	22.27±3.61
IPQr treatment control (/30)	16.42±2.34	17.11±2.69	16.63±3.43	17.83±2.25
IPQr illness coherence (/25)	16.88±1.96	17.17±2.79	15.63±2.71	17.27±2.15
IPQr timeline cyclical (/30)	12.83±3.05	13.28±3.64	12.53±2.62	13.80±3.25
IPQr emotional representations (/25)	17.21±3.88	13.42±3.87	15.67±4.77	13.40±5.44
PVAQ (/60)	40.88±9.18	34.25±12.88	36.10±10.45	35.43±14.72

[a]Categorical data presented as frequencies; [b] Values are presented as median (Interquartile range) for continuous data that were observed as not normally distributed; [c] Values are presented as mean±SD for continuous normal distributed data.

Abbreviations: CSI= Central Sensitization Inventory; NP= Neck Pain; LBP= Low Back Pain; F= Female; M= Male; No degr= no degree, Lower second= lower secondary, Higher second= higher secondary, Higher edu= higher education; PDI= Pain Disability index; PCS= Pain Catastrophizing Scale; TSK= Tamps Scale for Kinesiophobia; IPQr= Illness Perception Questionnaire revised; PVAQ= Pain Vigilance and Awareness Questionnaire.

TABLE 2. Effectiveness of pain neuroscience education in patients with nCSP with high and low self-reported signs of central sensitization (n=120).

Questionnaire	Time of measurement	Pain Neuroscience Education		Mean difference [95%CI]	Neck/Back School		Mean difference [95%CI]	ANOVA Analysis	
		High CSI levels Mean(SE) (n=24)	Low CSI levels Mean(SE) (n=36)		High CSI levels Mean(SE) (n=30)	Low CSI levels Mean(SE) (n=30)		Interaction effect	Main effect of group
Primary Outcome Measure									
PDI (/70)	Baseline	30.09(2.70)	16.25(2.16)	13.84 [6.99;20.68]	26.03(2.16)	17.13(2.36)	8.90 [2.28;15.52]	F=1.414 p=.24	F=9.580 **p<.001**
	Post Edu	27.65(2.41)	16.58(1.93)	11.07 [4.96;17.18]	28.53(2.11)	16.93(2.11)	11.60 [5.69;17.51]		
	ES Cohen's D	.19	.03	-	.21	.02	-		
Secondary Outcome Measures									
PCS Rumination (/16)	Baseline	8.96(.79)	4.89(.64)	4.07 [2.06;6.07]	7.63(.70)	5.37(.70)	2.27 [.30;4.23]	F=2.759 **p=.05**	N/A
	Post Edu	7.21(.78)	5.33(.64)	1.88 [-.11;3.86]	6.67(.70)	4.77(.70)	1.90 [-.05;3.85]		
	ES Cohen's D	.46	.11	-	<.01	.16	-		
PCS Magnification (/12)	Baseline	3.75(.43)	1.58(.35)	2.17 [1.07;3.26]	3.23(.38)	2.27(.38)	.97 [-.11;2.04]	F=3.349 **p=.02**	N/A
	Post Edu	2.83(.43)	2.36(.35)	.47 [-.63;1.58]	2.87(.39)	1.93(.39)	.93 [-.15;2.02]		
	ES Cohen's D	.44	.37	-	.17	.16	-		
PCS Helplessness (/24)	Baseline	9.63(.98)	6.19(.80)	3.43 [.92;5.94]	8.73(.88)	6.47(.88)	2.27 [-.19;4.72]	F=1.189 p=.32	F=2.633 p=.05
	Post Edu	7.96(.99)	5.92(.80)	2.04 [-.48;4.56]	7.47(.88)	5.87(.88)	1.60 [-.87;4.07]		
	ES Cohen's D	.35	.06	-	.26	.12	-		

PCS Total Score (/52)	Baseline	22.33(1.93)	12.37(1.58)	9.67 [4.74;14.60]	19.60(1.73)	14.10(1.73)	5.50 [.67;10.33]	F=3.487 **p=.02**	N/A
	Post Edu	18.00(1.93)	13.61(1.57)	4.39 [-.54;9.31]	17.00(1.72)	12.57(1.72)	4.43 [-.39;9.26]		
	ES Cohen's D	.46	.13	-	.28	.16	-		
TSK (/68)	Baseline	37.00(1.39)	32.61(1.13)	4.39 [.84;7.34]	37.97(1.24)	35.47(1.24)	2.50 [-.98;5.98]	F=3.651 **p=.02**	N/A
	Post Edu	32.25(1.43)	29.03(1.17)	3.22 [-.43;6.88]	36.53(1.28)	34.93(1.28)	1.60 [-1.98;5.18]		
	ES Cohen's D	.69	.52	-	.21	.08	-		
IPQr Acute/chronic Timeline (/25)	Baseline	24.63(.80)	23.33(.65)	1.29 [-.75;3.33]	23.13(.71)	23.33(.71)	-.20 [-2.20;1.80]	F=5.207 **p=.002**	N/A
	Post Edu	20.58(.93)	19.47(.76)	1.11 [-1.26;3.49]	22.17(.83)	21.00(.83)	1.17 [-1.16;3.49]		
	ES Cohen's D	**.95**	**.91**	-	.23	.55	-		
IPQr Consequence (/20)	Baseline	19.50(.89)	14.53(.72)	4.97 [2.70;7.24]	18.00(.79)	15.30(.79)	2.70 [.48;4.92]	F=3.429 **p=.02**	N/A
	Post Edu	16.96(.84)	12.94(.69)	4.01 [1.87;6.16]	17.90(.75)	15.00(.75)	2.90 [.80;5.00]		
	ES Cohen's D	.60	.38	-	.02	.07	-		
IPQr Personal Control (/30)	Baseline	19.33(.83)	20.75(.67)	-1.42 [-3.53;.69]	19.43(.74)	22.27(.74)	-2.83 [-4.90;-.77]	F=3.577 **p=.02**	N/A
	Post Edu	22.50(.63)	22.39(.51)	.11 [-1.49;1.72]	21.87(.56)	22.43(.56)	-.57 [-2.14;1.01]		
	ES Cohen's D	**.88**	.46	-	.68	.04	-		
IPQr Treatment control (/30)	Baseline	16.42(.56)	17.11(.46)	-.69 [-2.12;.73]	16.63(.50)	17.83(.50)	-1.20 [-2.60;.20]	F=.739 p=.53	F=1.916 p=.13
	Post Edu	17.75(.45)	18.03(.37)	-.28 [-1.42;.87]	17.07(.40)	18.30(.40)	-1.23 [-2.35;-.11]		
	ES Cohen's D	.53	.37	-	.18	.19	-		
IPQr Illness	Baseline	16.88(.50)	17.17(.41)	-.29 [-1.58;1.00]	15.63(.45)	17.27(.45)	-1.63 [-2.90;-.37]	F=1.518 p=.21	F=3.544 **p=.02**

Coherence (/25)	Post Edu	18.17(.52)	17.19(.42)	.97 [-.35;2.30]	16.30(.46)	18.07(.46)	-1.77 [-3.07;-.47]		
	ES Cohen's D	.52	.01	-	.27	.32	-		
IPQr Timeline Cyclical (/30)	Baseline	12.83(.65)	13.28(.53)	-.44 [-2.11;1.22]	12.53(.58)	13.80(.58)	-1.27 [-2.90;.37]	F=3.585 **p=.02**	N/A
	Post Edu	14.17(.67)	14.42(.54)	-.25 [-1.95;1.45]	12.77(.60)	13.13(.60)	-.37 [-2.04;1.30]		
	ES Cohen's D	.41	.36	-	.07	.21	-		
IPQr Emotional Representations (/25)	Baseline	17.21(.93)	13.42(.76)	3.79 [1.42;6.16]	15.67(.83)	13.40(.83)	2.27 [-.05;4.59]	F=.336 p=.78	F=4.330 **p=.006**
	Post Edu	17.04(.95)	14.19(.77)	2.85 [.43;5.27]	16.00(.85)	13.93(.85)	2.07 [-.31;4.44]		
	ES Cohen's D	.04	.17	-	.07	.12	-		
PVAQ (/60)	Baseline	40.88(2.49)	34.25(2.03)	6.63 [.27;12.98]	36.10(2.22)	35.43(2.22)	.67 [-5.56;6.89]	F=1.272 p=.29	F=.930 p=.43
	Post Edu	35.38(2.50)	32.61(2.04)	2.76 [-3.62;9.15]	34.97(2.23)	32.60(2.23)	2.37 [-3.89;8.62]		
	ES Cohen's D	.45	.13	-	.09	.23	-		

ANOVA repeated measures analysis. Significant results and large effect sizes were printed in **bold**. Effect Sizes were calculated as Cohen's D. Cohen's D is interpreted as 'very large' (>1.3), 'large' (.80-1.29), 'medium' (.50-.79), 'small' (.20-.49), 'negligible' (<.20).
Abbreviations: CSI: Central Sensitization Inventory; Post Edu: Post Education; PDI: Pain Disability Index; PCS: Pain Catastrophizing Scale; TSK: Tampa Scale for Kinesiophobia; IPQr: Illness Perception Questionnaire Reversed; PVAQ: Pain Vigilance and Awareness Questionnaire;

TABLE 3. Results of Bonferroni Post-Hoc analysis of the significant interaction effects after pain neuroscience education (PNE) vs. neck/back school (NBS) in patients with chronic spinal pain (n=120) with high and low scores on the Central Sensitization Inventory.

Questionnaire	Effect of Group						Effect of Time	
	High CSI PNE vs. Low CSI PNE		High CSI PNE vs. High CSI NBS		Low CSI PNE vs. Low CSI NBS			
PCS Rumination	Baseline	**p<.001**	Baseline	p=.21	Baseline	p=.62	PNE	**p=.005**[a]; p=.38[b]
	Post Edu	p=.06	Post Edu	p=.60	Post Edu	p=.55	NBS	p=.08[c]; p=.28[d]
PCS Magnification	Baseline	**p<.001**	Baseline	p=.37	Baseline	p=.19	PNE	**p=.04**[a]; **p=.03**[b]
	Post Edu	p=.40	Post Edu	p=.95	Post Edu	p=42	NBS	p=.36[c]; p=.40[d]
PCS Total Score	Baseline	**p<.001**	Baseline	p=.29	Baseline	p=.54	PNE	**p<.001**[a]; p=.39[b]
	Post Edu	p=.08	Post Edu	p=.70	Post Edu	p=66	NBS	**p=.03**[c]; p=.20[d]
TSK	Baseline	**p=.02**	Baseline	p=.61	Baseline	p=.09	PNE	**p<.001**[a]; **p<.001**[b]
	Post Edu	p=.08	Post Edu	**p=.03**	Post Edu	**p=.001**	NBS	p=.15[c]; p=.59[d]
IPQr Acute/chronic Timeline	Baseline	p=.21	Baseline	p=.17	Baseline	p=.99	PNE	**p<.001**[a]; **p<.001**[b]
	Post Edu	p=.36	Post Edu	p=.21	Post Edu	p=.18	NBS	p=.13[c]; **p<.001**[d]
IPQr Consequence	Baseline	**p<.001**	Baseline	p=.21	Baseline	p=.47	PNE	**p<.001**[a]; **p=.004**[b]
	Post Edu	**p<.001**	Post Edu	p=.40	Post Edu	**p=.05**	NBS	p=.87[c]; p=.61[d]
IPQr Personal Control	Baseline	p=.19	Baseline	p=.93	Baseline	p=.13	PNE	**p<.001**[a]; **p=.007**[b]
	Post Edu	p=.891	Post Edu	p=.454	Post Edu	p=.953	NBS	**p<.001**[c]; p=.80[d]
IPQr Timeline Cyclical	Baseline	p=.598	Baseline	p=.732	Baseline	p=.510	PNE	**p=.01**[a]; **p=.01**[b]
	Post Edu	p=.772	Post Edu	p=.120	Post Edu	p=.114	NBS	p=.63[c]; p=.17[d]

Bonferroni post-hoc analysis of significant interaction effects.
[a]Effect of Time in the Pain Neuroscience Education group with high CSI levels; [b]Effect of Time in the Pain Neuroscience Education group with low CSI levels; [c]Effect of Time in the Neck/Back School Group with high CSI levels; [d]Effect of Time in the

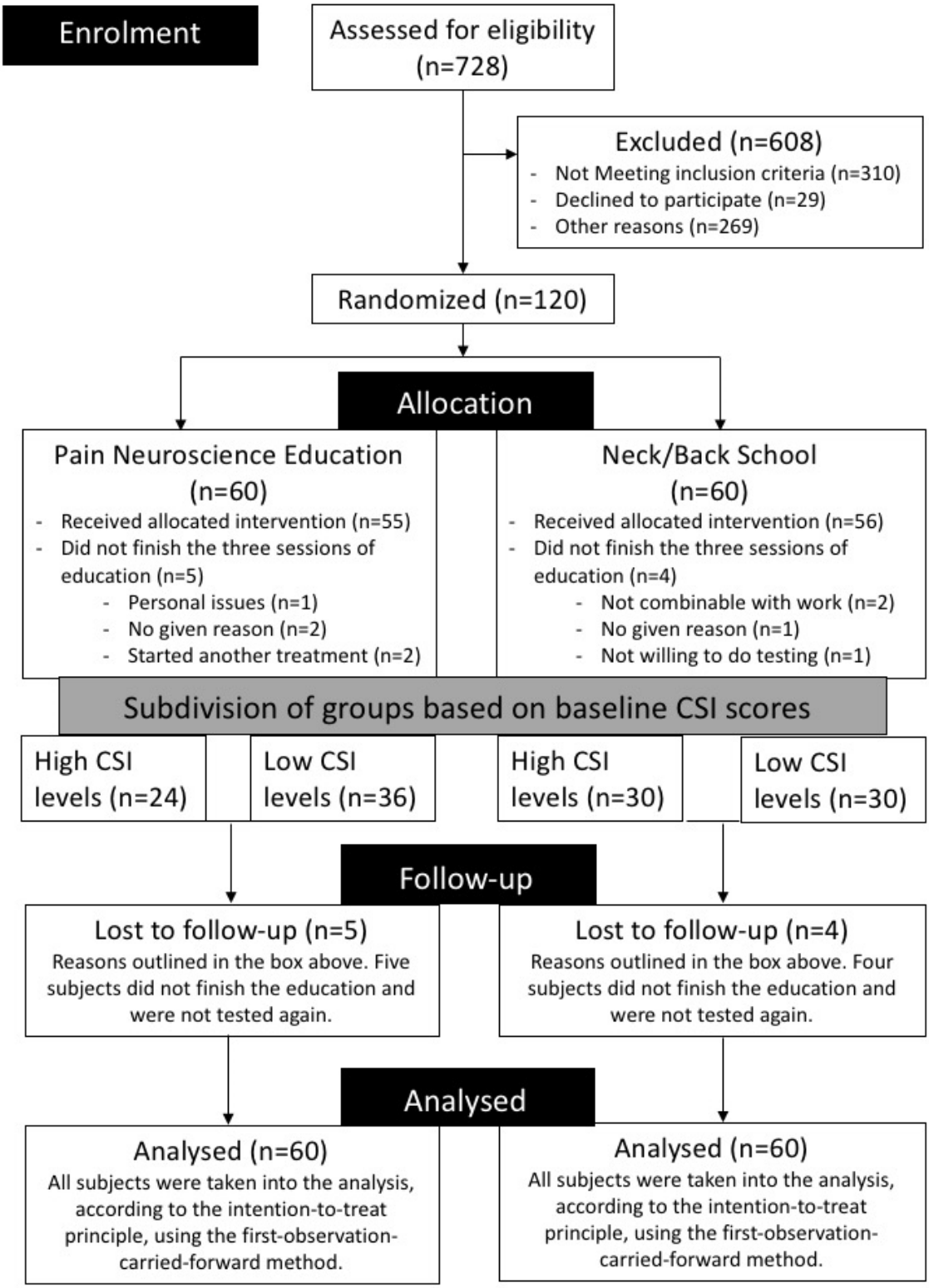
Neck/Back School Group with low CSI levels
Abbreviations: CSI= Central Sensitization Inventory; PNE= Pain Neuroscience Education; NBS= Neck/Back School; Post Edu= Post Education; PCS= Pain Catastrophizing Scale; TSK= Tampa Scale for Kinesiophobia; IPQr= Illness Perception Questionnaire revised.

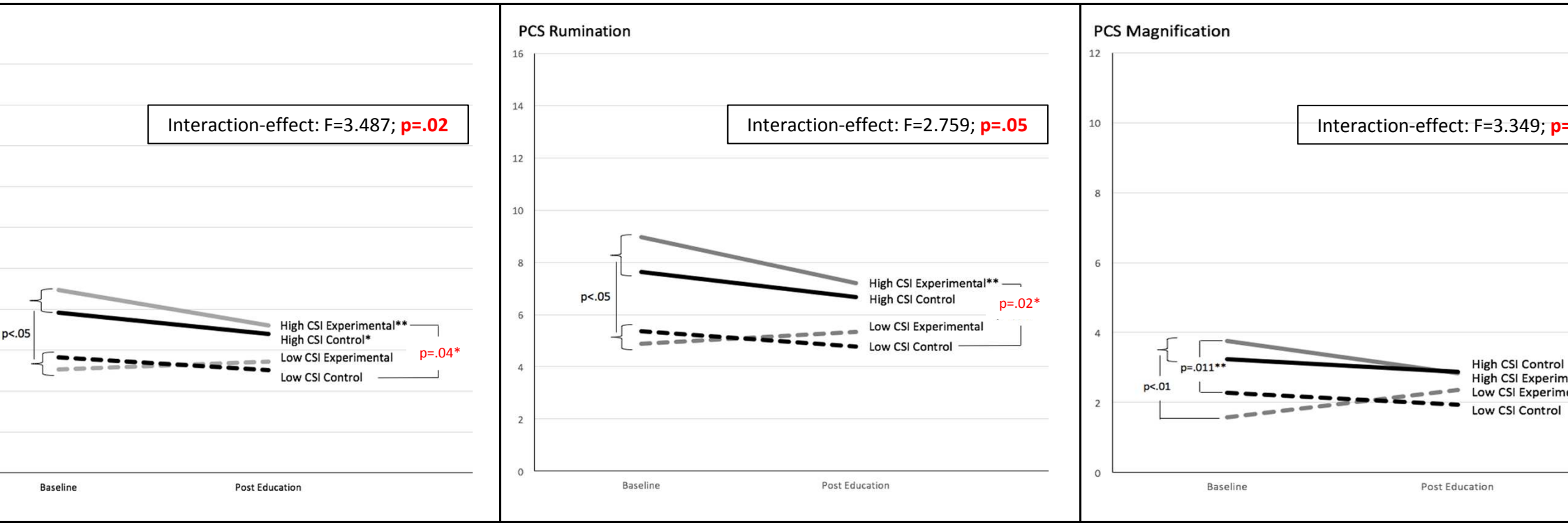
Supplementary online table S1. Post-Hoc analysis of significant Main effects of Group.

Questionnaires	**Group Differences**					
	High CSI PNE vs. Low CSI PNE	High CSI PNE vs. High CSI NBS	High CSI PNE vs. Low CSI NBS	Low CSI PNE vs. High CSI NBS	Low CSI PNE vs. Low CSI NBS	High CSI NBS vs. Low CSI NBS
PDI	**p=.001**	p>.99	**p=.002**	**p=.001**	p>.99	**p=.004**
IPQr Illness Coherence	p=.10	p=.07	p>.99	p=.18	p>.99	**p=.02**
IPQr Emotional Representations	**p=.002**	p>.99	**p=.02**	p=.33	p>.99	p=.30

Bonferroni Post-Hoc analysis of significant Main effects of Group. Significant p-values are printed in **bold**.
Abbreviations: CSI= Central Sensitization Inventory; PNE= Pain Neuroscience Education; NBS= Neck/Back School; PDI= Pain Disability Index; IPQr= Illness Perception Questionnaire revised.

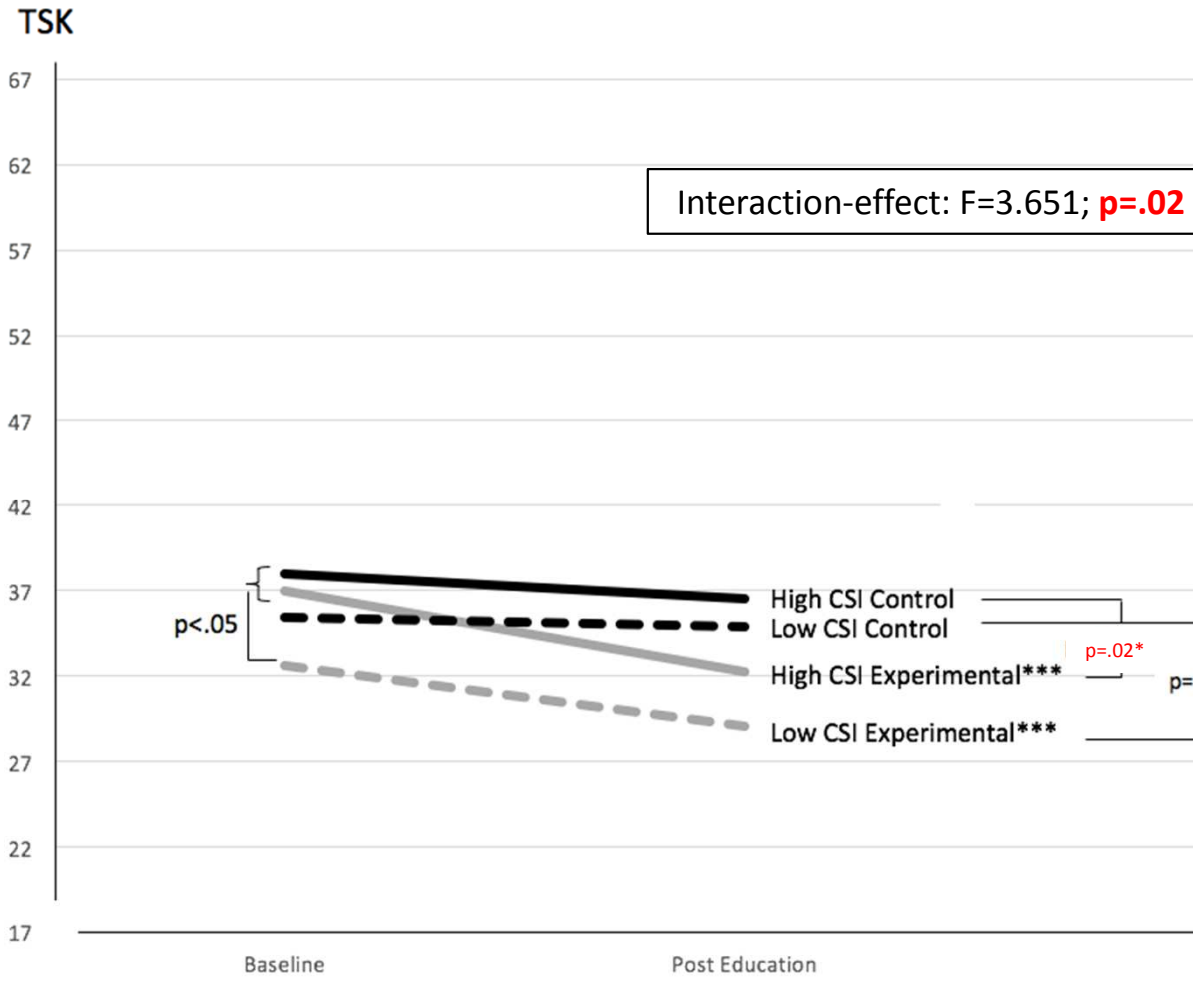
Figure 1. Study flow chart

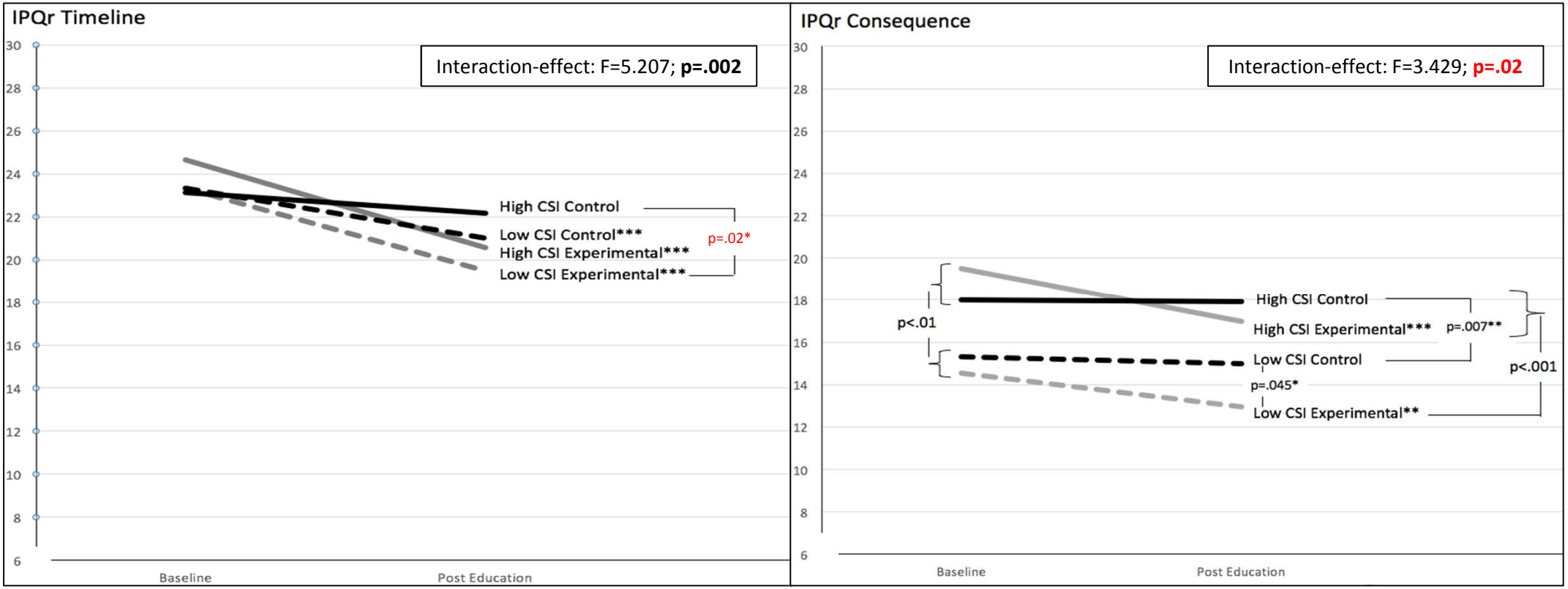




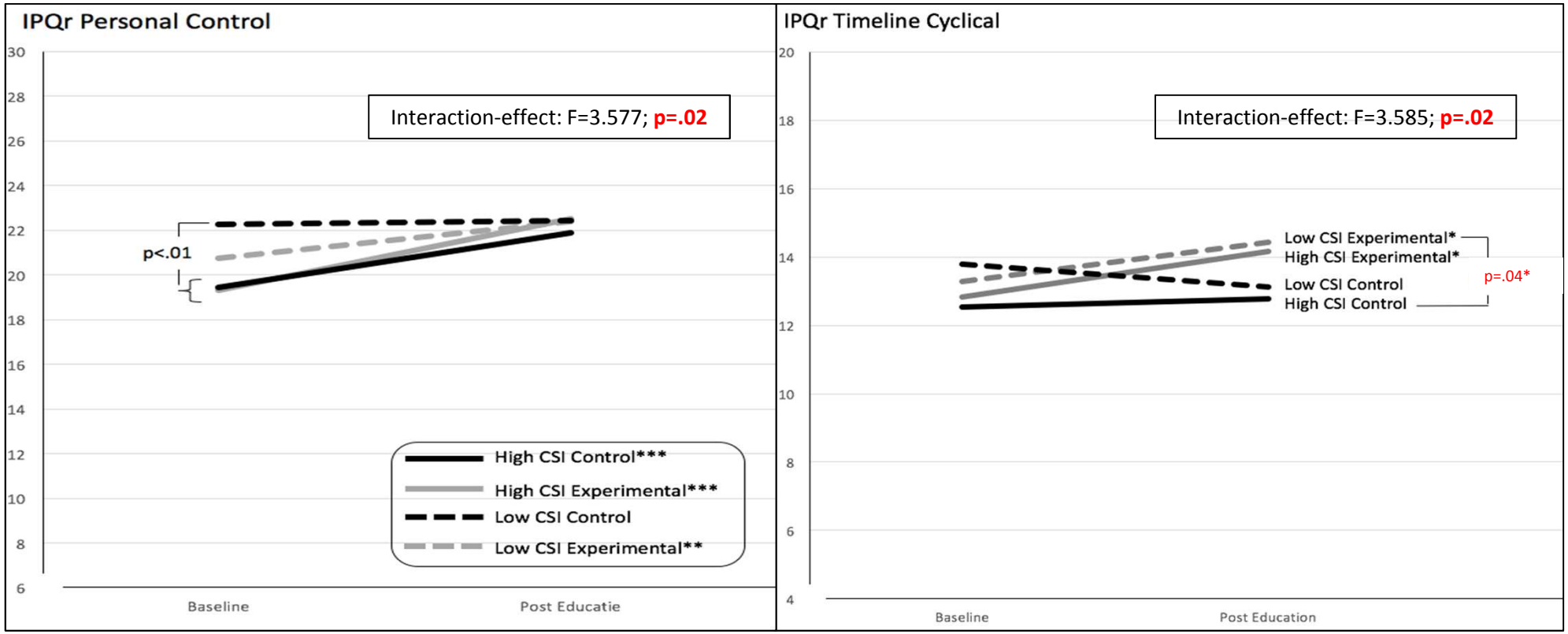
RE 2. The effect of pain neuroscience education versus neck/back school on pain catastrophizing in patients with nic spinal pain with high and low baseline CSI levels (n=120).
all significant interaction effects are displayed on the figure using a box. Significant within group effects (post-hoc erroni) are displayed behind the respective groups using an asterisk (*p<.05, **p<.01, ***p<.001). Significant betwe p effects (post-hoc bonferroni) are displayed as p-values.
eviations: PCS=Pain Catastrophizing Scale, CSI=Central Sensitization Inventory

RE 3. Pain neuroscience education is effective for easing kinesiophobia regardless self-reported signs ntral sensitization, compared to neck/back school, tients with chronic spinal pain (n=120).
all significant interaction effects are displayed on igure using a box. Significant within group effects t-hoc bonferroni) are displayed behind the ective groups using an asterisk (*p<.05, **p<.01, <.001). Significant between group effects (post-hoc erroni) are displayed as p-values.
reviations: TSK=Tampa Scale for Kinesiophobia, Central Sensitization Inventory





URE 4. The effect of pain neuroscience education and neck/back school on the perceived chronicity and negative equences of the illness in patients with chronic spinal pain with high and low baseline CSI levels (n=120). all significant interaction effects are displayed on the figure using a box. Significant within group effects (post-hoc erroni) are displayed behind the respective groups using an asterisk (*p<.05, **p<.01, ***p<.001). Significant betwe p effects (post-hoc bonferroni) are displayed as p-values.
reviations: IPQr=Illness Perception Questionnaire revised, CSI=Central Sensitization Inventory



URE 5. The effect of pain neuroscience education and neck/back school on the perceived personal control on and the city of the illness in patients with chronic spinal pain with high and low baseline CSI levels (n=120).
rall significant interaction effects are displayed on the figure using a box. Significant within group effects (post-hoc erroni) are displayed behind the respective groups using an asterisk (*p<.05, **p<.01, ***p<.001). Significant betwe p effects (post-hoc bonferroni) are displayed as p-values.
reviations: IPQr=Illness Perception Questionnaire revised, CSI=Central Sensitization Inventory