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Human experimental study

'Central sensitization' in chronic neck/shoulder pain

Dagfinn Matre*, Stein Knardahl

Department of Work Psychology and Physiology, National Institute of Occupational Health, Oslo, Norway

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ABSTRACT

Background and purpose: 'Central sensitization' (CS) may play a major role in maintaining several chronic pain conditions. CS has been proposed to play a significant role in a range of musculoskeletal pain conditions, such as trapezius myalgia, fibromyalgia, temporomandibular disorders, and low back pain. Whether CS varies over time within an individual is not known. This study evaluated (1) whether there is an intra-individual association between clinical pain and signs of CS, and (2) whether there is an inter-individual association between clinical pain and signs of CS.

Methods: Twenty-seven sedentary workers (19 women, 8 men) with varying neck/shoulder pain participated in a pre-test and in two test sessions. On one of the test sessions the subjects had weak (or no) clinical pain (*weak-pain day*). On the other test session the subjects had stronger clinical pain (*strong-pain day*). As an indicator of 'central sensitization', we assessed the area of secondary pinprick hyperalgesia (tested by 84.4 g/mm^2 Von Frey hairs) in response to a first-degree burn to the volar forearm (contact heat, 46 °C, 5 min). While in the lab, the subjects' current clinical pain intensity (0–10 cm VAS) and distribution was assessed ($PINT_{lab}$ and $PDIST_{lab}$). The subjects also rated their pain intensity and distribution retrospectively from the past 30 days ($PINT_{30\,d}$ and $PDIST_{30\,d}$).

Results: $PINT_{lab}$ was lower on the weak-pain day (1.7 ± 1.5 cm) than on the strong-pain day (4.3 ± 1.6 cm). This was also the case for the other clinical pain measures ($PDIST_{lab}$, $PINT_{30\,d}$ and $PDIST_{30\,d}$) and indicated that the participants were successfully recruited at days that differed in clinical pain severity. Despite a significant intra-individual difference in clinical pain between days, the area of secondary hyperalgesia did not differ between *weak-* and *strong-pain days* (50.3 ± 13.5 cm^2 vs. 51.2 ± 12.6 cm^2). Testing the inter-individual association between clinical pain and secondary hyperalgesia, we found a positive correlation between $PINT_{lab}$ and secondary hyperalgesia on the *weak-pain day* (rho = 0.6), but not on the *strong-pain day* (rho = 0.1). Given the stable secondary hyperalgesia across weak- and strong-pain days, this implies that subjects with a small secondary hyperalgesic area exhibited a relatively large variation in clinical pain between days, whereas subjects with a large secondary hyperalgesic area exhibited relatively small variation in clinical pain.

Conclusions: When subjects are observed across days, 'central sensitization', measured as the area of secondary hyperalgesia after a first-degree burn, does not seem to be important for clinical pain intensity per se, but may be important for clinical pain variation. Subjects with indication of low 'central sensitization' seem to exhibit larger variation in pain between "good" and "bad" days than subjects with indication of high 'central sensitization'. The study indicates that 'central sensitization' does not explain intra-individual variations in clinical pain.

Implications: This study raises the question of the role of 'central sensitization' in clinical musculoskeletal pain disorders. Furthermore, a precise definition of the 'central sensitization' concept is called for.

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1. Introduction

'Central sensitization' (CS) may play a major role in maintaining several chronic pain conditions (e.g. Woolf [1]). CS is a rather broad concept of "a prolonged but reversible increase in the excitability and synaptic efficacy of neurons in central nociceptive pathways" [1] that may be homosynaptic or heterosynaptic, spinal segmental or non-segmental, dependent or independent of continuous peripheral input. The present study aimed to determine the relationship between CS and clinical neck/shoulder pain by a within-subjects design.

In conditions with clearly defined peripheral mechanisms such as osteoarthritis, successful treatment may result in normalization of signs of CS outside the painful area [2,3]. This indicates that in

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* Corresponding author at: National Institute of Occupational Health, P.O. Box 8149 Dep., N-0033 Oslo, Norway. Tel.: +47 23 19 52 15; fax: +47 23 19 52 04.
E-mail addresses: dagfinn@stami.no, dagfinn.matre@gmail.com (D. Matre).

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these conditions increased excitability may depend on nociceptive input from the affected peripheral region. However, CS has been proposed to play a significant role in unexplained pain conditions in which no peripheral pathogenesis has been established, such as neck/shoulder pain [4], trapezius myalgia [5], fibromyalgia [6], temporomandibular disorders [7], headache [8], unspecific low back pain [9,10], and neuropathic pain [11]. Most studies investigating the relationship between 'central sensitization' and musculoskeletal pain have been cross-sectional studies where signs of CS have been found in a patient group and not in a control group (see above). Chronic subjective musculoskeletal complaints exhibit large variations in pain over time (e.g. Steingrimsdottir et al. [12]). If CS is causally related to musculoskeletal complaints it seems reasonable that CS should exhibit variations that are temporally related to variations in pain. Comparing characteristics of pain systems in periods of weak vs. strong pain within individual subjects is a research paradigm which seems underutilized.

Participants were sedentary workers with neck/shoulder pain that varied between days. Secondary hyperalgesia was assessed on a day with weak neck/shoulder pain and on a day with stronger neck/shoulder pain. CS was assessed by a proxy: the secondary hyperalgesia induced by a first-degree burn, which depends on central dorsal horn mechanisms [13,14].

Two hypotheses were tested. First, there is an intra-individual association between clinical pain and the burn-induced area of secondary hyperalgesia; i.e. a subject will develop a larger area of secondary hyperalgesia on a day with stronger clinical pain than on a day with weak clinical pain. Second, there is an inter-individual association between clinical pain and the burn-induced area of secondary hyperalgesia; i.e. subjects developing large areas of secondary hyperalgesia will exhibit more clinical pain than subjects developing small areas of secondary hyperalgesia.

2. Methods

2.1. Design

The study design was a single-blind cross over study with two test sessions on separate days. On one of the test sessions the subject had weak (or no) clinical pain (*weak-pain day*). On the other test session the subject had stronger clinical pain (*strong-pain day*). The order of the weak- and strong-pain days followed from the spontaneous variation in the subjects' neck/shoulder pain. This resulted in 2/3 of the subjects being tested on a weak-pain day first and 1/3 of the subjects tested on a strong-pain day first. The imbalance in session order did not affect the results: a re-analysis after removing data from a random half of the subjects that had been tested on a weak-pain day first showed the same result as when all subjects were included. At least 1 week before the test sessions, the subjects participated in a pre-test session in order to be familiarized with the procedures.

2.2. Daily morning pain reported by SMS

During the days after the pre-test session, until completion of both test sessions, subjects reported their morning pain by SMS each weekday morning. They responded to this question: "On a scale from 0 to 10, what is the intensity of your neck or shoulder pain right now? 0 = no pain, 10 = worst pain imaginable". When a subject reported a morning pain intensity that corresponded to that individual's pain intensity on a common 'good' or 'bad' day (within ±1 on the 0–10 NRS), he or she was assigned to *weak-pain day* or *strong-pain day*, respectively, and asked to come to the lab for a full test session the same day.

2.3. Subjects

Eighty-two subjects responded to one of three recruitment channels: advertisement in a major newspaper, online advertisement on the institute's home page, or through the corporate health services at a large bank.

Inclusion criteria were pain in the shoulder and/or neck area (unilateral or bilateral) for at least 2–3 days per week, days without neck/shoulder pain, age between 18 and 65 years, working ≥50% of full time, sedentary work (with a computer most of the time), and being familiar with the Norwegian language. Exclusion criteria were: regular smoking, reporting having a clinically defined inflammatory or neurogenic cause of their neck/shoulder pain, having other inflammatory, metabolic or cardiac diseases, having generalized pain, or taking prescription drugs regularly.

Thirty-two subjects were included based on the inclusion/exclusion criteria. Five subjects withdrew from the study after the pre-test day. Twenty-seven subjects completed the study. Their mean (±SD) age was 45.7 ± 12.0 years (range 23–65 years) and 19 were females. One subject was left-handed and used the computer mouse with his left hand. Subjects were paid for their participation. The data were collected within a 5-month time frame. Informed consent was obtained from each subject and the experimental protocol was approved by the regional ethical committee and conducted according to the Helsinki declaration.

2.4. Measurement of secondary hyperalgesia

As an indicator of 'central sensitization', we assessed the area of secondary pinprick hyperalgesia in response to a first-degree burn [14]. Secondary hyperalgesia was measured on the forearm, away from the clinically painful neck/shoulder region.

The burn was produced by heating the skin of the volar forearm to 46 °C for 5 min with a 25 mm × 50 mm Peltier thermode (Sense 3.1 software and Thermotest, Somedic AB, Hörby, Sweden). The thermode was held in place by a cuff inflated to 15 mmHg in order to standardize pressure on the skin. The thermode was removed at the end of the heating. Subjective heat pain was reported continuously on an electronic 10-cm visual analogue scale (VAS) during the 5-min heating (0 = no pain and 10 = worst pain imaginable). The heat pain VAS was sampled (200 Hz) and stored on computer (MP150 data acquisition and Acknowledge software, Biopac Systems Inc., California).

To determine the size of the secondary hyperalgesic area sensory testing (ST) started 1 min after the thermode was removed from the skin. The skin was touched with a Von Frey filament (84.4 g/mm^2 pressure) every 3–4 s at 5-mm intervals along eight linear radials [15,16]. Testing started 5–6 cm from the presumed hypersensitive area and did not include the primary area that had been covered by the thermode. The subject was instructed to alert the experimenter when a sensation was clearly *more* intense than the previous one. The skin was then marked. The process was repeated in the opposite direction. The subject was then instructed to alert the experimenter when a sensation was clearly *less* intense than the previous one. The two marks (inward and outward) for each radial were transferred to plastic foil and joined to form two areas for each stimulus site. The marked area was scanned to a computer and digitized (Engauge Digitizer 4.1, GNU free software, http://digitizer.souceforge.net/).

2.5. Individual variation in clinical pain

During a telephone interview at inclusion, the subject was asked to rate the neck/shoulder pain intensity of a common *weak-pain day* and *strong-pain day* on a 0–10 numerical rating scale (NRS; 0 = no pain and 10 = worst pain imaginable). Daily morning pain intensity

ratings by SMS were later compared against these weak/strong-day ratings to determine the day when the subject was to participate in the test sessions.

2.6. Clinical pain reports

The clinical pain report included two measures of clinical pain intensity and two measures of clinical pain distribution assessing clinical pain during the past 30 days and current clinical pain (in the lab).

2.6.1. Pain during the past 30 days

Subjects filled out a health-complaint report (HCR) [12] assessing several health complaints over the past 30 days. Eleven musculoskeletal complaints were analysed (head, neck, left and right shoulder, left and right forearm, left and right hand, back, chest and legs). The scores of each musculoskeletal pain complaint (0 = not troubled, 1 = a little troubled, 2 = quite troubled and 3 = seriously troubled) were summed for a total musculoskeletal pain intensity score ($PINT_{30\,d}$). Counting the number of painful body areas (between 0 and 11) produced a pain distribution score between 0 and 11 ($PDIST_{30\,d}$).

2.6.2. Current pain

Current clinical pain intensity (in the lab) was assessed on a 10-cm paper visual analogue scale ($PINT_{lab}$), whereas current distribution of pain was assessed by pain drawings on a small scale body map ($PDIST_{lab}$). The body maps were digitized and the pain area quantified (ImageJ 1.42, National Institutes of Health, USA; http://rsb.info.nih.gov/ij) in arbitrary units (A.U.).

2.7. Experimental procedures

Each test session started with a clinical pain report. This was followed by two burn stimulations with subsequent sensory testing of the area of secondary hyperalgesia; one test on each forearm (left/right order was balanced). The principal investigator was blinded with respect to the subjects' pain status (weak-pain or strong-pain).

Since the regulation of arterial pressure and heart rate seems to interact with the regulation of pain [17], mean arterial finger blood pressure (MAP) and heart rate (HR) was monitored continuously by the Penãz method with a cuff placed on the right third finger (Finapres Ohmeda 2300, Englewood, CO, USA).

2.8. Statistics

Several of the variables were non-normally distributed (Kolmogorov–Smirnov test). Thus, non-parametric statistics were applied unless otherwise is noted. The area of secondary hyperalgesia and heat pain VAS measurements was averaged across the left and right side since no side differences were found (Wilcoxon; secondary hyperalgesia: $p > 0.7$; heat pain VAS: $p > 0.35$).

To determine differences in clinical pain measurements and secondary hyperalgesia between *weak-* and *strong-pain days*, Wilcoxon paired tests were used. To determine whether secondary hyperalgesia was associated with the measures of clinical pain, Spearman's correlation analyses were performed separately for *the weak-pain day* and *strong-pain day*. The significance level was set to 0.05.

PASW statistics 18 (formerly SPSS) was used for all statistical analyses (IBM, Somers, New York, USA).

3. Results

3.1. Intra-individual variation in clinical pain and secondary hyperalgesia

$PINT_{lab}$ was lower on the *weak-pain day* compared to the *strong-pain day* (Fig. 1A and Table 1). This was also the case for the other measures of clinical pain intensity and distribution (Table 1), indicating that the participants were successfully recruited at days that differed in clinical pain severity. The mean ± SD of the individual between-days difference in $PINT_{lab}$ was 2.7 ± 2.0 cm on the VAS.

Despite a significant intra-individual difference in clinical pain between days, the area of secondary hyperalgesia did not differ between *weak-* and *strong-pain days* (Fig. 1A and Table 1). The mean ± SD of the individual between-days secondary hyperalgesia difference was 0.9 ± 10.5 cm^2 (1.8 ± 20.9%). Neither were there any gender effects on secondary hyperalgesia (Mann–Whitney *U*; *weak-pain day*: $p = 0.67$, *strong-pain day*: $p = 0.83$).

Subjective heat pain scores during burn induction (heat pain VAS) were not different between the 2 days (Table 1).

3.2. Inter-individual association between clinical pain intensity and secondary hyperalgesia

Bivariate correlation analyses tested the associations between secondary hyperalgesia and the two measures of clinical pain intensity ($PINT_{lab}$ and $PINT_{30\,d}$). A significant positive correlation was found between $PINT_{lab}$ and secondary hyperalgesia on the *weak-pain day*, whereas on the *strong-pain day* there was no correlation (Fig. 1B). Controlling for gender (partial correlation analysis) did not change these results. There was a trend towards a positive association between $PINT_{30\,d}$ and secondary hyperalgesia on both test days (Fig. 1B).

3.3. Inter-individual association between clinical pain distribution and secondary hyperalgesia

Bivariate correlation analyses tested the associations between secondary hyperalgesia and the two measures of clinical pain distribution ($PDIST_{lab}$ and $PDIST_{30\,d}$). Both pain distribution measures showed a positive association with secondary hyperalgesia, which was significant only for the *strong-pain day* (Fig. 1C). Controlling for gender (partial correlation analysis) did not change these results.

3.4. Clinical pain variation vs. secondary hyperalgesia

Since secondary hyperalgesia was stable across *weak-* and *strong-pain days*, the individual difference in clinical pain intensity between *weak-* and *strong-pain days* (Delta $PINT_{lab}$) was calculated and correlated with the mean area of secondary hyperalgesia (Fig. 2). This indicated that in subjects with large secondary hyper-

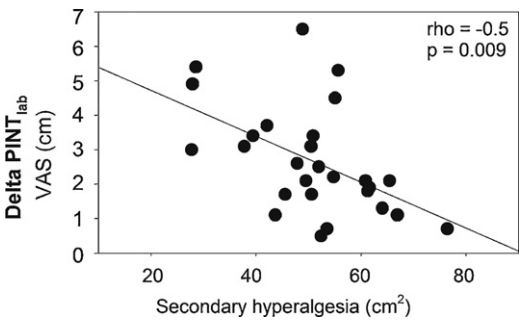

Fig. 2. The individual difference in clinical pain intensity between *strong-* and *weak-pain days* were significantly correlated with the area of secondary hyperalgesia.

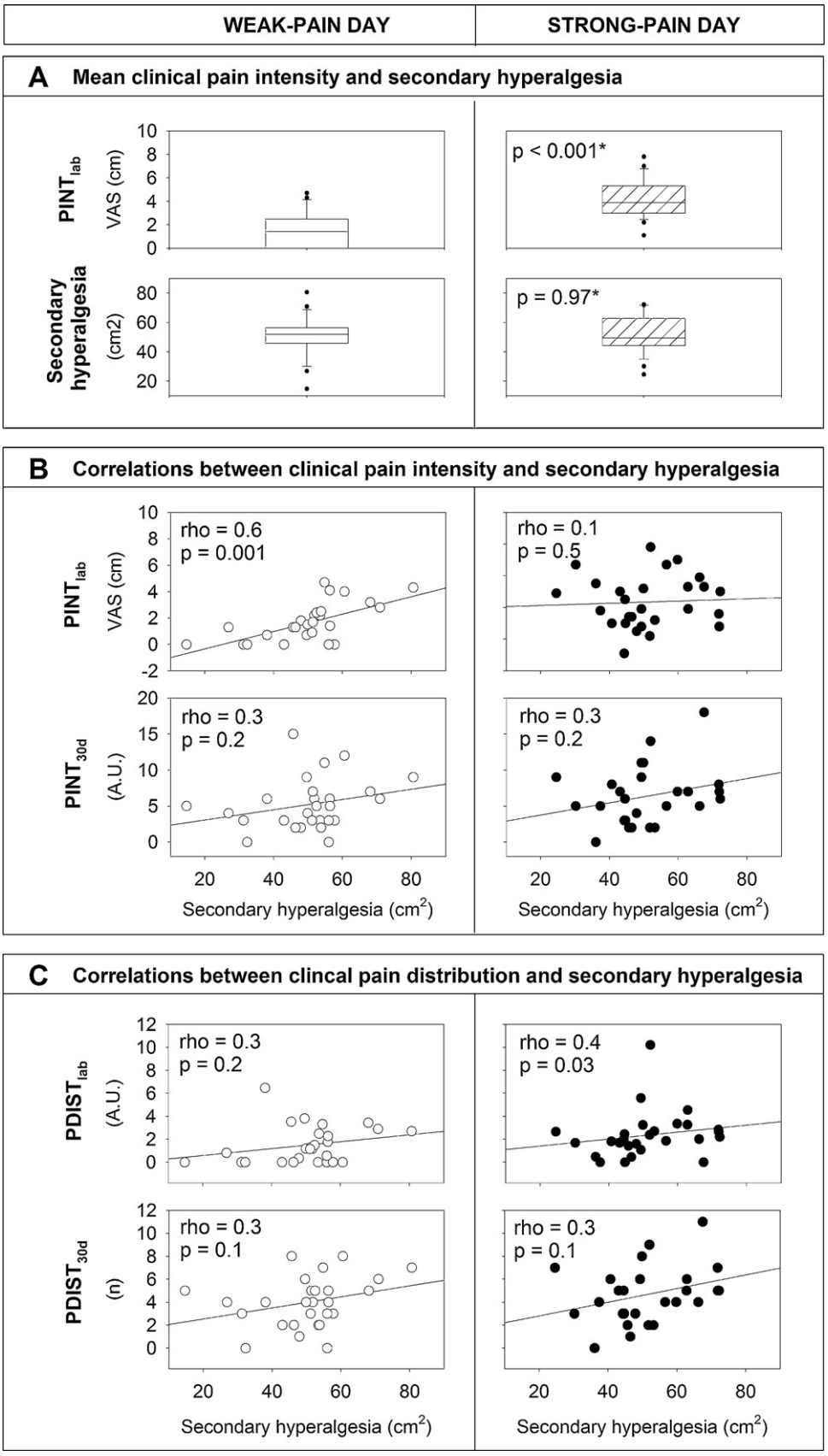

Fig. 1. (A) Subjects reported significantly higher clinical pain intensity in the lab ($PINT_{lab}$) on the strong-pain day than on the weak-pain day. No difference was found in the area of secondary hyperalgesia. Data are median, interquartile range and outliers (dots) ($n = 27$). (B) Secondary hyperalgesia was significantly correlated with $PINT_{lab}$ on the *weak-pain day* (open symbols), but not on the *strong-pain day* (filled symbols). No correlation was found between secondary hyperalgesia and $PINT_{30\,d}$. (C) Secondary hyperalgesia was positively associated with the distribution of clinical pain ($PDIST_{lab}$ and $PDIST_{30\,d}$), but the correlation was significant only for $PDIST_{lab}$ on the *strong-pain day*. A.U. = arbitrary units (see text); n = number of painful body areas.

Table 1
Descriptive statistics ($n = 27$). Measurements of clinical pain intensity, clinical pain distribution, 'central sensitization', heat pain VAS, mean arterial pressure (MAP) and heart rate (HR). Significant p-values (<0.01) are in bold.

		Weak-pain day		Strong-pain day		Weak vs. strong
		Mean	SD	Mean	SD	p-Value[a]
Clinical pain intensity						
$PINT_{lab}$	(cm)	1.7	1.5	4.3	1.6	**<0.001**
$PINT_{30\,d}$	(A.U.)	5.2	3.6	6.4	4	**0.012**
Clinical pain distribution						
$PDIST_{lab}$	(A.U.)	1.5	1.6	2.4	2	**0.001**
$PDIST_{30\,d}$	(n)	4	2.2	4.7	2.5	**0.027**
'*Central sensitization*'						
Secondary hyperalgesia	(cm^2)	50.3	13.5	51.2	12.6	0.97
Heat pain VAS	(cm)	6	2.6	6.1	2.5	0.37
Cardiovascular parameters						
MAP_{rest}	(mmHg)	78.5	16.6	82.1	18.5	0.1
MAP_{burn}	(mmHg)	87.6	15.9	89.4	17.7	0.36
HR_{rest}	(bpm)	64.9	13.2	63.3	11.7	0.46
HR_{burn}	(bpm)	64.7	10.5	65.4	9.8	0.71

A.U. = arbitrary units (see text); n = number of painful body areas.
[a] Wilcoxon paired non-parametric tests.

algesia, the difference between *weak-* and *strong-pain days* was small compared to subjects with small secondary hyperalgesia, who exhibited a relatively large difference in clinical pain between *weak-* and *strong-pain days*. This association was significant (Spearman's two-tailed test; rho = −0.50, $p = 0.009$). Controlling for gender (partial correlation analysis) did not change these results.

3.5. Cardiovascular measurements and associations with clinical pain measurements and secondary hyperalgesia

Continuous recordings of mean arterial finger pressure (MAP) and heart rate (HR) were averaged across a 1-min resting period before the first burn (MAP_{rest} and HR_{rest}) and during each 5-min burn period (MAP_{burn} and HR_{burn}). No differences were observed in any MAP or HR measurements between the *weak-pain day* and the *strong-pain day* (Table 1).

MAP_{burn} was not associated with any of the clinical pain measurements or with secondary hyperalgesia (Spearman's rho < 0.27, $p > 0.17$). Similarly, HR_{burn} was not associated with any of the clinical pain measurements or with secondary hyperalgesia (rho < 0.40, $p > 0.05$).

4. Discussion

The present results indicate that provoked secondary hyperalgesia in a clinically non-afflicted part of the body varies little across days despite a significant difference in the intensity and distribution of clinical pain. Subjects with large areas of secondary hyperalgesia tended to report a higher intensity of clinical pain than subjects with small areas of secondary hyperalgesia. Subjects with small areas of secondary hyperalgesia exhibited larger variation in pain intensity between "good" and "bad" days than subjects with large areas of secondary hyperalgesia.

4.1. Association between secondary hyperalgesia and clinical pain

The present study tested the hypothesis that a proxy of 'central sensitization', the area of secondary hyperalgesia, is associated with the intensity of the neck/shoulder pain as it varies spontaneously across days in the same subjects: are there signs of more pronounced 'central sensitization' on a day with strong clinical pain than on a day with weak (or no) clinical pain in a given subject? Several studies have found a positive association between indicators of 'central sensitization' and clinical pain in patients [4,5,9,7,18], but the authors have not found confirmation of this effect by multiple measurements within subjects.

The proxy of 'central sensitization' measured in the present study (secondary hyperalgesia) seems to be a rather stable phenomenon that does not vary despite significantly different levels of clinical pain intensity and distribution. The hypothesis that a general CS maintains both clinical pain and the experimentally induced secondary hyperalgesia is not supported. The present data did not find larger areas of secondary hyperalgesia on the day with strong pain than on the day with weak pain. A second hypothesis maintains that nociceptive input from the periphery maintains a state of CS (that is normalized when the nociceptive input is treated successfully). This has been reported in several clinical [2,3,19] as well as experimental [20] pain conditions. The present data does not support this hypothesis since there was no reduction in secondary hyperalgesia on the weak-pain day. If peripheral nociceptive input drives CS, one would expect reduced secondary hyperalgesia. A third explanation may be that the observed variation in clinical pain is due to variation in nociceptive input from the periphery that acts only locally and does not maintain CS. Thus, based on the present data it does not seem likely that spontaneous between-days variation in clinical neck/shoulder pain intensity and distribution is determined by between-days variation in 'central sensitization'. Variation in nociceptive input from the periphery may be the most likely explanation.

A second hypothesis tested was that there is an inter-individual association between clinical pain and the burn-induced area of secondary hyperalgesia. In other words, are there signs of stronger 'central sensitization' in subjects with strong levels of clinical pain and larger painful areas compared to subjects with weaker clinical pain and smaller painful areas? Bivariate correlation analyses tested secondary hyperalgesia against the four measures of clinical pain intensity and distribution. A positive association was found between secondary hyperalgesia and clinical pain intensity measured in the lab ($PINT_{lab}$) on the weak-pain day, indicating some support for the hypothesis. This association was, however, not significant on the *strong-pain* day. The associations between secondary hyperalgesia and retrospective clinical pain reports (past 30 days) were relatively weak. The positive association between secondary hyperalgesia and clinical pain intensity is in accordance with several studies on neck/shoulder pain [4,5] and back pain [9,21]. The positive association between secondary hyperalgesia and spread of pain is also supported in the literature [22,23]. Thus, the positive inter-individual association between clinical and experi-

mental pain on the *weak-pain day* may reflect a general variability in somatosensory sensitivity between individuals.

The positive association between secondary hyperalgesia and clinical pain intensity during the *weak-pain day* was not present during the *strong-pain day*. This may be interpreted in several ways. Since no associations are found during the *strong-pain day*, one interpretation is that 'central sensitization' does not play a role for clinical pain intensity *per se*. This explanation was also supported above. An alternative, or complementary, interpretation rests on the stable secondary hyperalgesia measurements across *weak-* and *strong-pain days*. Thus, subjects with small hyperalgesic areas exhibit a relatively larger variation in clinical pain intensity between days, whereas subjects with large hyperalgesic areas exhibit smaller variation in clinical pain intensity between days (Fig. 2). Thus, while 'central sensitization' may not be important for strong clinical pain, subjects with signs of high 'central sensitization' seem to exhibit smaller variation in pain between "good" and "bad" days than subjects with indication of weak 'central sensitization'. Further studies investigating this relationship between 'central sensitization' and clinical pain are needed to elucidate this finding.

4.2. Methodological considerations

Acknowledging that subjective pain is multi-factorial, a test battery assessing several aspects of pain (intensity and distribution) evaluated the participants' clinical pain. In addition, we combined current clinical pain (reported in the lab during the test sessions) and retrospective pain (evaluation of clinical pain 30 days before the test sessions). Although the subjects were recruited on the basis of their neck/shoulder pain, clinical pain assessment was not restricted to the neck/shoulder region, since musculoskeletal pain frequently spreads to other body sites [24,25].

The health-complaint report of the present study asked the subjects' to recall the intensity and duration of 30 complaints from the preceding 30 days. At least two limitations may have affected these reports. First, retrospective measurements of pain may be influenced by recall bias [26]. Second, the retrospective questionnaire allowed intensity and duration ratings on ordinal scales with relatively low resolution.

4.3. Conclusion

'Central sensitization', measured as the area of secondary hyperalgesia after a first-degree burn, varies little across days, despite a significant difference in the intensity and distribution of clinical pain. This indicates that variation in nociceptive input from the periphery may be the most likely explanation for the between-day variation in clinical neck/shoulder pain in the present data.

Subjects with indication of weak 'central sensitization' seem to exhibit larger variation in pain between "good" and "bad" days than subjects with indication of strong 'central sensitization'. This raises the question of the role of 'central sensitization' in clinical musculoskeletal pain disorders. Furthermore, a precise definition of the 'central sensitization' concept is called for.

Conflict of interest statement

The authors declare that they have no competing interests.

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References

[1] Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain 2010.
[2] Verne GN, Robinson ME, Vase L, Price DD. Reversal of visceral and cutaneous hyperalgesia by local rectal anesthesia in irritable bowel syndrome (IBS) patients. Pain 2003;105:223–30.
[3] Kosek E, Ordeberg G. Abnormalities of somatosensory perception in patients with painful osteoarthritis normalize following successful treatment. Eur J Pain 2000;4:229–38.
[4] Johnston V, Jimmieson NL, Jull G, Souvlis T. Quantitative sensory measures distinguish office workers with varying levels of neck pain and disability. Pain 2008;137:257–65.
[5] Leffler AS, Hansson P, Kosek E. Somatosensory perception in patients suffering from long-term trapezius myalgia at the site overlying the most painful part of the muscle and in an area of pain referral. Eur J Pain 2003;7:267–76.
[6] Desmeules JA, Cedraschi C, Rapiti E, Baumgartner E, Finckh A, Cohen P, Dayer P, Vischer TL. Neurophysiologic evidence for a 'central sensitization' in patients with fibromyalgia. Arthritis Rheum 2003;48:1420–9.
[7] Fernandez-de-Las-Penas C, Galan-Del-Rio F, Fernandez-Carnero J, Pesquera J, Arendt-Nielsen L, Svensson P. Bilateral widespread mechanical pain sensitivity in women with myofascial temporomandibular disorder: evidence of impairment in central nociceptive processing. J Pain 2009;10:1170–8.
[8] Jensen R. Mechanisms of spontaneous tension-type headaches: an analysis of tenderness, pain thresholds and EMG. Pain 1996;64:251–6.
[9] O'Neill S, Manniche C, Graven-Nielsen T, Rendt-Nielsen L. Generalized deep-tissue hyperalgesia in patients with chronic low-back pain. Eur J Pain 2007;11:415–20.
[10] Giesecke T, Gracely RH, Grant MA, Nachemson A, Petzke F, Williams DA, Clauw DJ. Evidence of augmented central pain processing in idiopathic chronic low back pain. Arthritis Rheum 2004;50:613–23.
[11] Campbell JN, Raja SN, Meyer RA, Mackinnon SE. Myelinated afferents signal the hyperalgesia associated with nerve injury. Pain 1988;32:89–94.
[12] Steingrimsdottir OA, Vollestad NK, Roe C, Knardahl S. Variation in reporting of pain and other subjective health complaints in a working population and limitations of single sample measurements. Pain 2004;110:130–9.
[13] Cervero F, Gilbert R, Hammond RG, Tanner J. Development of secondary hyperalgesia following non-painful thermal stimulation of the skin: a psychophysical study in man. Pain 1993;54:181–9.
[14] LaMotte RH, Shain CN, Simone DA, Tsai EF. Neurogenic hyperalgesia: psychophysical studies of underlying mechanisms. J Neurophysiol 1991;66:190–211.
[15] Matre D, Casey KL, Knardahl S. Placebo-induced changes in spinal cord pain processing. J Neurosci 2006;26:559–63.
[16] Warncke T, Stubhaug A, Jorum E. Preinjury treatment with morphine or ketamine inhibits the development of experimentally induced secondary hyperalgesia in man. Pain 2000;86:293–303.
[17] Hagen K, Zwart JA, Holmen J, Svebak S, Bovim G, Stovner LJ. Does hypertension protect against chronic musculoskeletal complaints? The Nord-Trondelag Health Study. Arch Inter Med 2005;165:916–22.
[18] Staud R, Bovee CE, Robinson ME, Price DD. Cutaneous C-fiber pain abnormalities of fibromyalgia patients are specifically related to temporal summation. Pain 2008;139:315–23.
[19] Staud R, Nagel S, Robinson ME, Price DD. Enhanced central pain processing of fibromyalgia patients is maintained by muscle afferent input: a randomized, double-blind, placebo-controlled study. Pain 2009;145:96–104.
[20] Koltzenburg M, Torebjork HE, Wahren LK. Nociceptor modulated 'central sensitization' causes mechanical hyperalgesia in acute chemogenic and chronic neuropathic pain. Brain 1994;117(Pt 3):579–91.
[21] Diers M, Koeppe C, Diesch E, Stolle AM, Holzl R, Schiltenwolf M, van AK, Flor H. Central processing of acute muscle pain in chronic low back pain patients: an EEG mapping study. J Clin Neurophysiol 2007;24:76–83.
[22] Koelbaek JM, Graven-Nielsen T, Schou OA, Arendt-Nielsen L. Generalised muscular hyperalgesia in chronic whiplash syndrome. Pain 1999;83:229–34.
[23] Sorensen J, Graven-Nielsen T, Henriksson KG, Bengtsson M, Arendt-Nielsen L. Hyperexcitability in fibromyalgia. J Rheumatol 1998;25:152–5.
[24] Graven-Nielsen T, Arendt-Nielsen L. Peripheral and 'central sensitization' in musculoskeletal pain disorders: an experimental approach. Curr Rheumatol Rep 2002;4:313–21.
[25] DeSantana JM, Sluka KA. Central mechanisms in the maintenance of chronic widespread noninflammatory muscle pain. Curr Pain Headache Rep 2008;12:338–43.
[26] Gendreau M, Hufford MR, Stone AA. Measuring clinical pain in chronic widespread pain: selected methodological issues. Best Pract Res Clin Rheumatol 2003;17:575–92.