International Journal of Hygiene and Environmental Health 216 (2013) 202–210

Contents lists available at SciVerse ScienceDirect

International Journal of Hygiene and Environmental Health

journal homepage: www.elsevier.com/locate/ijheh

Multiple chemical sensitivity: On the scent of central sensitization

Marie Thi Dao Tran[a,*], Lars Arendt-Nielsen[b], Ron Kupers[c,d], Jesper Elberling[a]

[a] The Danish Research Centre for Chemical Sensitivities, Department of Dermato-Allergology, Copenhagen University Hospital Gentofte, Denmark
[b] Laboratory for Experimental Pain Research, Centre for Sensory-Motor Interaction (SMI), Department of Health Science and Technology, Aalborg University, Denmark
[c] PET Unit, Rigshospitalet, Copenhagen University Hospital, Denmark
[d] Institute of Neuroscience & Pharmacology, Panum Institute, Faculty of Health Sciences, University of Copenhagen, Denmark

ARTICLE INFO

Article history:
Received 22 September 2011
Received in revised form 6 February 2012
Accepted 20 February 2012

Keywords:
Multiple chemical sensitivity
Central sensitization
Conditioning pain modulation
Quantitative sensory testing

ABSTRACT

Background: Multiple Chemical Sensitivity (MCS) is a chronic condition characterized by recurrent, non-specific symptoms in response to chemically unrelated exposures in non-toxic concentrations. Although the pathophysiology of MCS remains unknown, central sensitization may be an important factor contributing to the clinical manifestations.
Purpose: To use quantitative sensory testing (QST) to study central hyperexcitability and multiple aspects of central sensory processing in MCS patients without comorbid overlapping disorders and to compare the results with those among matched controls.
Methods: 15 MCS patients and 15 healthy matched controls underwent QST to assess the following aspects of pain: capsaicin-induced secondary punctate hyperalgesia, stimulus response function (SRF) to punctate mechanical stimuli before and after capsaicin injection, temporal summation to punctate stimuli post capsaicin injection, pressure pain thresholds, heat pain thresholds, tonic heat stimulation and conditioning pain modulation (CPM: formerly known as diffuse noxious inhibitory control or DNIC).
Results: The mean area of capsaicin-induced secondary punctate hyperalgesia was significantly larger in MCS patients than in controls at 5, 30 and 60 min post capsaicin injection ($p = 0.01$). In addition MCS patients reported higher ratings in response to punctate mechanical stimuli assessed by SRF compared with controls ($p < 0.001$). The CPM test induced significantly higher pain ratings in patients than in controls ($p = 0.002$). We found no group differences in pressure pain and heat pain thresholds, temporal summation to punctate stimuli post capsaicin injection, capsaicin and tonic heat pain ratings or CPM effect.
Conclusion: Increased capsaicin-induced secondary punctate hyperalgesia was demonstrated in MCS patients without comorbid, overlapping disorders, suggesting facilitated central sensitization in MCS.

Introduction

Multiple Chemical Sensitivity (MCS) is a chronic condition characterized by recurrent, non-specific symptoms from multiple organ systems in response to chemically unrelated exposures in low concentrations (Cullen, 1987; Nethercott et al., 1993). Symptoms from the central nervous system such as headache, fatigue and cognitive deficits are especially frequent among MCS patients (Berg et al., 2009; Lacour et al., 2005; Ross, 1992).

Since Randolph's (Randolph, 1962) first description of the condition, little progress has been made in the understanding of the pathophysiology of MCS. In the past decades, many theories have been suggested to account for MCS, biological as well as psychological or a combination of both (Graveling et al., 1999; Winder, 2002). Central sensitization has been suggested as a biopsychological explanation for MCS (Yunus, 2007; Bell et al., 1996; Sorg and Newlin, 2002; Rainville et al., 2001; Holst et al., 2011a; Ursin and Eriksen, 2001).

A symptomatic and diagnostic overlap has been observed between MCS and several other conditions of unknown aetiology such as chronic fatigue syndrome, fibromyalgia, irritable bowel syndrome and multiple functional somatic symptoms (Aaron and Buchwald, 2001; Buchwald and Garrity, 1994; Jason et al., 2000; Kuzminskyte et al., 2010). This raises the possibility that a common pathophysiological mechanism, such as central sensitization, could underlie these different clinical conditions. Central sensitization implies an increased central response to a normal sensory input (Yunus, 2008) and has been well demonstrated in fibromyalgia (Nielsen and Henriksson, 2007). In contrast, empirical support for central sensitization in MCS has remained scarce. A recent study (Holst

* Corresponding author at: The Danish Research Centre for Chemical Sensitivities, Department of Dermato-Allergology, Copenhagen University Hospital Gentofte, Ledreborg Allé 40, 2. th., DK-2820 Gentofte, Denmark. Tel.: +45 39978456; fax: +45 39978458.
E-mail address: mathtr01@geh.regionh.dk (M.T.D. Tran).

1438-4639/$ – see front matter © 2012 Elsevier GmbH. All rights reserved.
doi:10.1016/j.ijheh.2012.02.010

et al., 2011a) has provided some support for central sensitization in MCS with findings of increased capsaicin-induced secondary punctate hyperalgesia and temporal summation to punctuate mechanical stimulation.

Capsaicin has been widely used to explore sensory mechanisms of pain processing in both normal and pathological states (Morris et al., 1997; Simone et al., 1989; Arendt-Nielsen and Yarnitsky, 2009) because it induces pain, neurogenic inflammation (flare), hyperalgesia and allodynia (LaMotte et al., 1991; Simone et al., 1989). Capsaicin-induced secondary hyperalgesia is considered to be the result of sensitized central nociceptive neurons (Simone et al., 1991; Torebjork et al., 1992), in contrast to neurogenic inflammation, which mainly reflects peripheral activity (Littlejohn et al., 1987). Temporal summation of pain is an increased response to repetitive nociceptive stimulation, which may be facilitated in patients with central sensitization (Gottrup et al., 1998; Sörensen et al., 1998). However, the study by Holst et al. included MCS patients with comorbid overlapping disorders, which may question this association between MCS and central sensitization. In support of a central component in MCS, controlled brain imaging studies have demonstrated abnormal central odour processing in MCS patients (Hillert et al., 2007; Orriols et al., 2009).

Thus the purpose of this study was to study central hyperexcitability and multiple aspects of central sensory processing in MCS patients without comorbid, overlapping disorders by utilizing a variety of quantitative sensory tests (QST). These included a capsaicin pain model, a conditioning pain modulation model and a tonic heat pain model. The hypotheses of the study were that pain processing in MCS patients is facilitated compared with healthy matched controls i.e. enlarged capsaicin-induced secondary punctate hyperalgesia, increased stimulus response function (SRF) to punctate mechanical stimuli post capsaicin injection, increased temporal summation to punctate stimuli post capsaicin injection, reduced pain thresholds, increased pain intensity ratings, equal flare responses and reduced conditioning pain modulation.

Materials and methods

Study population

The study comprised 30 participants: 15 MCS patients and 15 controls. Individuals with self-reported MCS were recruited through advertisements in patient organizations' newsletters and on the website of "The Danish Research Centre for Chemical Sensitivities". All patients met Lacour's criteria (Lacour et al., 2005) i.e.: (1) symptom duration of at least 6 months, (2) symptoms in response to at least 2 of 11 categories of chemical exposures, (3) at least one CNS symptom and one symptom from another organ system, (4) symptoms causing adjustments of personal lifestyle, or of social or occupational life, (5) symptoms occurring when exposed and improving or resolving when exposures are removed, (6) symptoms are triggered by exposure levels that do not induce symptoms in other individuals who are exposed to the same levels. MCS patients were included if they were at least 18 years of age and were able to rate pain reliably. Exclusion criteria comprised: drug or alcohol abuse, current use of antidepressants or anxiolytics, pregnancy, nursing, or self-reported disorders with altered pain perception (e.g. neurological, cardiovascular or psychiatric disorders except for previous depression, diabetes, overlapping disorders such as fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome or temperomandibular disorder). Controls were also recruited through advertisements and were selected to match patients by age and sex on group level. Inclusion criteria for control subjects were: ability to rate pain reliably, absence of major medical disorders, psychiatric disorders, recent surgery (<6 months), chronic pain, drug or alcohol abuse, pregnancy, nursing or use of medications. The study was approved by the local Ethics Committee (approval no: H-4-2010-015). All participants gave written informed consent and received the equivalent of 200 Euro for their participation.

Table 1
Chronological outline of performed QST procedures.

Day 1	CPM model – control bath session
	PPT at baseline
	PPTT at baseline
	Pain intensity rating of control bath (23 °C)
	PPT during control bath
	PPT 10 min post control bath
	30-min break
	Capsaicin pain model
	SRF at baseline
	Pain intensity rating of capsaicin injection
	Flare
	Secondary punctate hyperalgesia (5 min)
	SRF post injection
	Temporal summation
	Secondary punctate hyperalgesia (30 min)
	Secondary punctate hyperalgesia (60 min)
Day 2	CPM model – cold pressor bath session
	PPT at baseline
	PPTT at baseline
	Pain intensity rating of cold pressor bath (0–1 °C)
	PPT during cold pressor bath
	PPT 10 min post cold pressor bath
	30-min break
	Phasic and tonic heat pain model
	HPT at baseline
	HPTT at baseline
	Pain intensity rating of tonic heat stimulation (47 °C)

CPM, conditioning pain modulation; PPT, pressure pain threshold; PPTT, pressure pain tolerance threshold; SRF, stimulus response function; HPT, heat pain threshold; HPTT, heat pain tolerance threshold.

Study design

Before inclusion, all candidates participated in a preliminary session to determine their ability to rate pain reliably and to familiarize them with the testing conditions. The preliminary session took place in the same room as the actual testing sessions but on a different day. Pain-rating reliability was determined through heat stimuli administered to the right forearm by a Peltier element-based, computer-controlled thermal stimulator with a probe measuring 3 cm × 3 cm (TSA-II, Medoc, Israel). Four fixed predetermined temperatures (43, 45, 47 and 49 °C) were delivered to the right forearm for 6 s in a mixed sequence. Participants rated pain intensity after each temperature on an 11-point rating scale with anchor points, 0 (no pain) and 10 (worst pain imaginable). If a participant did not feel pain, he/she rated the heat intensity on an 11-point rating scale with anchor points, 0 (no warmth) and 10 (most intense warmth). If participants were able to differentiate the temperatures by proportional ratings, they were considered able to rate pain reliably. No potential participants were excluded on this basis. At the preliminary session, all participants were familiarized with the remaining devises used for QST.

To reduce test session length and to avoid the tonic stimuli influencing the subsequent test results, the actual testing procedures took place on two different days at least one week apart and on each day a fixed as opposed to randomized sequence of testing with 30-min pauses was used (Table 1). To minimize influences on pain perception, all participants were instructed to refrain from using analgesics, herbal medicine and food supplements 3 days before the day of testing and to refrain from consuming food or beverages containing caffeine and from smoking on the day of testing. If participants reported pain on the day of testing, the testing day was

rescheduled. Prior to the QST procedures, participants rested in a comfortable seated position in a quiet room for 15–20 min. Each testing day lasted approximately 3 h. All testing procedures were performed by the same investigator (MTDT).

Capsaicin pain model

Prior to injection, we outlined 8 linear vectors arranged radiating at 45° angles on the volar side of the right forearm halfway between the cubital fossa and the wrist. With the forearm placed on an armrest, each participant received an intradermal injection of 0.1 ml capsaicin in a concentration of 3.3 μM (1 μg/ml, 0.01% solution) at the meeting point of the 8 vectors using a 29-gauge disposable needle producing a circular blister with a radius of 0.5 cm.

Pain intensity. Participants rated pain intensity continuously for the first 5 min after capsaicin injection using an electronic visual analogue scale (eVAS) consisting of a 10 cm light display with a low anchor point (no pain) and a high anchor point (worst pain imaginable). The eVAS was controlled by the participant using a slide button. Pain ratings were digitized into a numerical value (0–10) and sampled at 5 s intervals. We calculated mean pain ratings (VAS_{mean}), peak pain rating (VAS_{max}) and area under the VAS-time curve (VAS_{AUC}). The latter was calculated using the trapezoidal rule of numerical integration: $VAS_{AUC} = 1/2 \cdot (x_2 - x_1) \cdot (y_0 + 2y_1 + \cdots + 2y_{n-1} + y_n)$.

Visible flare. At 5 min post injection, the area of visible flare was assessed by placing a transparent sheet of paper on the skin with visual hyperaemia and outlining the area with a marker. The outlined area was cut out, weighed in mg and converted into cm^2.

Secondary punctate hyperalgesia. We used a handheld mechanical probe (diameter 0.6 mm, weight 50.1 g, Centre for Sensory-Motor Interaction, Aalborg University) with a blunt tip that exerted the same force at each application to determine the area of secondary punctate hyperalgesia at 5, 30 and 60 min post injection. During the procedure, participants were blindfolded and the probe was applied to the skin for 1 s with an interstimulus interval (ISI) of 2 s starting from a point well outside the injection site and then sequentially reapplied to the skin moving along a vector towards the injection site in steps of 0.5 cm. The participants were instructed to report when the pricking sensation changed in intensity or character to become more intense, painful, burning or otherwise different. When the participant reported a change in sensation at two successive points, the first point was marked. This procedure was repeated along all 8 vectors (V_1–V_8). The 8 marks were connected to form an area of secondary punctate hyperalgesia. The area (A) was calculated using trigonometry by the rule of the area of a triangle, adding up and subtracting the area of the capsaicin blister: $A = 1/2 \cdot \mathrm{Sin}(45^\circ) \cdot (V_1 \cdot V_2 + V_2 \cdot V_3 + \cdots + V_7 \cdot V_8 + V_8 \cdot V_1) - (\pi \cdot 0.5^2)$. An area was calculated only when there were at least 2 neighbouring marks.

Stimulus response function (SRF). We assessed sensitivity to punctate stimuli before and after capsaicin injection. We stimulated the skin area 1 cm latero-distal to the border of the capsaicin blister with 7 handheld probes exerting a pressure of 0.8, 1.6, 3.2, 6.4, 12.8, 25.6, or 50.1 g. We applied each probe 3 times to the skin with an ISI of 10 s. The participants were blindfolded and reported an average pain rating of each weight using an 11-point numerical scale on which 5 was defined as the pain threshold, 0 as no sensation and 10 as worst pain imaginable. We started with stimuli of middle weight and decreased to the lowest weight and then ended with the highest weights. If a stimulus was rated 0, then the stimuli below this weight were automatically assigned 0.

Temporal summation post capsaicin injection. Within the area of secondary punctate hyperalgesia, we stimulated the skin 1 cm medio-distal to the border of the capsaicin blister with a handheld probe of 50.1 g. First, we applied a single punctate stimulus followed by a train of 10 repetitive stimuli at 1.0 Hz. We applied all stimuli within an area of 1 cm^2. The participant was instructed to rate the single punctate stimulus and the perceived mean of the train of 10 stimuli on a numerical scale from 0 (no pain) to 10 (worst pain imaginable). We repeated this procedure 5 times and calculated the wind-up ratio (WUR) as the mean rating of the 5 trains divided by the mean rating of the 5 single stimuli.

Conditioning Pain Modulation (CPM) model

We assessed the CPM effect using the pressure pain threshold (PPT) as the test stimulus and ice-water hand immersion (cold pressor test) as the conditioning stimulus. We also performed a control session with a neutral water bath, which was scheduled on the first testing day to familiarize participants with the procedure.

Pressure pain thresholds. We determined pressure pain threshold (PPT) and pressure pain tolerance threshold (PPTT) by the method of limits. A handheld algometer (Somedic, Sweden) with a 1 cm^2 probe was applied to the right tibialis anterior muscle 14–18 cm proximal to the lateral malleolus, and the pressure was increased at a speed of approximately 30 kPa/s. The participants were instructed to push a button when the stimulus became painful (PPT) and when the pain became unbearable (PPTT). To train the participant, we carried out two trials of PPT assessments on the left side and then one valid trial was performed on the right side on both days of testing. We calculated mean PPT by averaging the two PPT trials from the right side. We performed one PPTT assessment on the right side on each testing day and we calculated mean PPTT by averaging the two trials. If the participant did not respond when exceeding 1600 kPa of pressure, a maximum value of 1700 kPa was assigned. We never applied the algometer on the same skin spot.

CPM testing. The participant's right hand was submerged to the wrist in a circulating water bath at a noxious temperature (0–1 °C) for 5 min (conditioning stimulus). After 4 min of cold water immersion, we assessed PPT on the ipsilateral tibialis anterior before withdrawal of the right hand from the cold pressor bath. Participants were instructed to focus their attention on the PPT assessment during conditioning stimulation to minimize the effects of distraction. If the conditioning pain stimulus became intolerable, the participant could terminate the cold pressor bath earlier than scheduled after an assessment of PPT. Ten minutes after the cold pressor bath was terminated, we assessed PPT again. Changes in PPT at baseline to PPT during conditioning stimulation were assessed within and between groups and were considered to reflect a CPM effect. For the control bath session, the procedure was replicated but with the difference that we used water of neutral (23 °C) temperature to get a measure of non-specific effects on pain perception.

Pain intensity. Participants rated pain intensity continually for 5 min on the eVAS following submersion of the hand in the cold pressor bath. We calculated the same pain measures as described for the capsaicin pain model. If the pain became intolerable, the cold pressor test was stopped and the maximum value of 10 was assigned to the missing time points.

Heat pain thresholds

We determined heat pain threshold (HPT) and heat pain tolerance threshold (HPTT) by the method of limits. When measuring HPT, we placed the thermode over the anterior side of the left thigh, 16 cm proximal to the knee. The temperature rose from an

adaptation temperature of 30 °C with a ramp rate of 3 °C/s to a maximum of 52 °C. Participants were instructed to push a button when the stimulation became painful whereupon the temperature of the probe returned to baseline. We repeated the procedure five times with an ISI of 10 s. HPT was derived by taking the average of the five trials. We measured HPTT on the same leg, 12 cm proximal to the knee. The temperature rose from an adaptation temperature of 30 °C with a ramp rate of 3 °C/s to a maximum of 53 °C. Participants were instructed to push a button when the pain became intolerable whereupon the temperature of the probe returned to baseline. We performed only a single assessment of HPTT.

Tonic heat pain model

We used the tonic heat pain model developed by Naert et al. (2008). We applied a tonic heat stimulus using the TSA-II (Medoc, Israel) with a 9 cm^2 probe placed over the anterior side of the left thigh 16 cm proximal to the knee. The temperature rose by 5 °C/s from an adaptation temperature of 30 °C to 47 °C and stayed at this level for 7 min.

Pain intensity. Participants rated pain intensity continually for 7 min on the eVAS. We calculated the same pain measures as described for the capsaicin pain model. If pain became intolerable, the tonic heat stimulus was terminated and the maximum value of 10 was assigned to the missing time points.

Questionnaire

Participants completed a questionnaire that included self-estimated health, asthma, previous doctor-diagnosed depression, symptoms of depression and anxiety and somatosensory amplification. Asthma was assessed by the criteria used by the European Community Respiratory Health Survey (ECRHS) (Pekkanen et al., 2005). Symptoms of depression and anxiety were assessed using the Symptom Check List (SCL-92) (Olsen et al., 2004). Lastly, we assessed somatosensory amplification using the Somato-Sensory Amplification Scale (SSAS) (Barsky et al., 1988). Somatosensory amplification refers to a tendency to experience physical sensations as intense, noxious and disturbing.

Statistical analyses

Statistical analyses were mainly done using PASW Statistics 18 software. For continuous data analyses between groups, we selected multiple regression analyses adjusting for the match variables sex and age with or without prior log transformation after ensuring that the model assumptions were met. We used a paired *t*-test to do within group analyses when the model assumptions for *t*-test were met. To compare the numerical VAS scores between patients and controls and the effect of the capsaicin injection in the SRF analyses, we used the McCullagh model (R software) and corrected for repeated measurements for each subject by using robust standard errors. We investigated interactions, and adjusted for sex and age differences. Finally, we analysed categorical data with Fischer's exact test. Significance levels were set at $p < 0.05$.

Table 2
Clinical characteristics of MCS patients and controls.

	MCS ($n = 15$)		Controls ($n = 15$)	
	n	%	*n*	%
Lacour's criteria for MCS	15	(100)	0	(0)
Self-estimated health				
Excellent or good	5	(33)	15	(100)
Fair, poor or bad	10	(67)	0	(0)
Asthma	2	(13)	0	(0)
Previous depression	3	(20)	0	(0)
Smoking	2	(13)	1	(7)
Hormone status				
Premenopausal	4	(33)	6	(50)
Postmenopausal	8	(67)	6	(50)
Hormone therapy[a]	5	(42)	1	(8)

[a] Hormone therapy included oral contraceptives, hormonal intrauterine devices or hormone therapy for menopausal symptoms.

Results

Table 2 shows the clinical characteristics. Average age was 52.2 (SD 8.7) years among MCS patients and 51.9 (SD 8.0) years among controls. There were 12 women and 3 men in each group. MCS patients rated their health significantly poorer ($p < 0.01$) and more frequently had asthma and a history of depression than controls did.

Psychological measures

Patients scored significantly higher than controls on symptoms of depression and anxiety and SSAS ($p < 0.01$). The mean scores for MCS patients and controls were 0.7 and 0.1 (symptoms of

Table 3
Quantitative Sensory Testing by the capsaicin pain model in MCS patients and controls.

	MCS ($n = 15$)		Controls ($n = 15$)		*p*-Value
	Mean	SD	Mean	SD	
VAS_{mean}	1.8	(1.1)	1.6	(0.7)	0.54[a]
VAS_{max}	8.2	(3.1)	7.4	(2.6)	0.46[a]
VAS_{AUC} (cm x min)	8.8	(5.2)	7.8	(3.5)	0.56[a]
Flare area (cm^2)	11.8[d]	(6.3–25.1)[e]	10.4[d]	(4.7–81.4)[e]	0.56[b]
2nd hyperalgesia (cm^2)					
5 min	55.5	(33.4)	29.1	(22.6)	**0.01**[a]
30 min	55.5	(33.7)	29.0	(22.9)	**0.01**[a]
60 min	57.3	(38.3)	23.8	(20.2)	**0.01**[a]
SRF_{pre} (VAS)	2.3	(1.0)	1.4	(0.5)	**<0.01**[c]
SRF_{post} (VAS)	2.8	(1.6)	2.7	(1.4)	0.71[c]
WUR	1.3	(0.3)	1.6	(0.5)	0.11[a]

VAS_{mean}, mean pain ratings; VAS_{max}, peak pain ratings; VAS_{AUC}, area under the VAS-time curve; SRF_{pre}, mean stimulus response function pre injection; SRF_{post}, mean stimulus response function post injection; WUR, wind-up ratio.

[a] Multiple regression adjusting for sex and age.
[b] Multiple regression adjusting for sex and age with prior log transformation.
[c] McCullagh regression model.
[d] Geometric mean.
[e] Range.

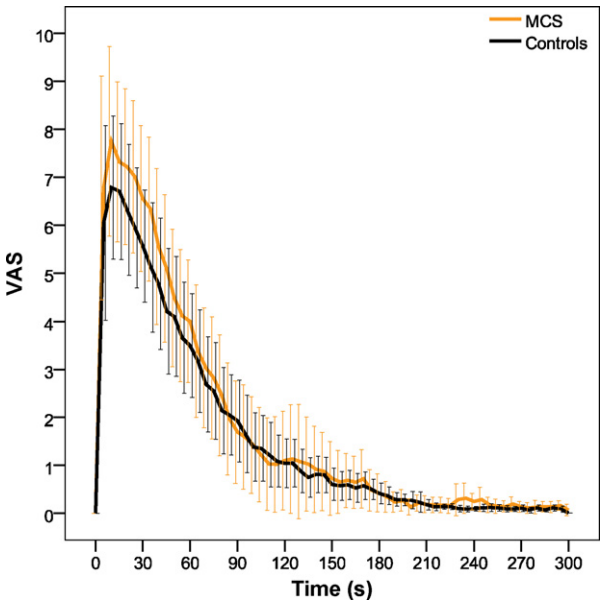

Fig. 1. Mean pain ratings during the first 5 min post capsaicin injection (I = 95% confidence intervals). No significant differences in capsaicin pain ratings were found between MCS patients and controls ($p > 0.40$).

depression), 0.4 and 0.1 (symptoms of anxiety) and 26.1 and 22.3 (SSAS), respectively.

Capsaicin pain model

Intradermal capsaicin injections evoked pain that peaked at mean 11 s (range 5–25) post injection. In all participants, pain was completely absent within 5 min of injection. No differences were observed between MCS patients and controls in any of the pain intensity measures (Table 3, Fig. 1). The mean pain scores for patients and controls were 1.8 and 1.6 (VAS_{mean}), 8.2 and 7.4 (VAS_{max}) and 8.8 and 7.8 (VAS_{AUC}), respectively.

Capsaicin injections induced visible flare in all participants. Mean flare area was 11.8 and 10.4 cm^2 for patients and controls, respectively, with no significant difference between groups ($p = 0.56$, Table 3).

The mean area of secondary punctate hyperalgesia was significantly larger in MCS patients compared with controls at all three time points of measurement ($p = 0.01$). Adjusting for depression or anxiety did not alter the results (data not shown). The area of secondary punctate hyperalgesia was 1.9–2.4 times larger in patients than in controls (Table 3). Only one participant (control) did not develop secondary punctate hyperalgesia after capsaicin injection at any of the three measurement points.

At baseline, MCS patients rated the 7 punctate stimuli significantly higher than controls did ($p < 0.001$, Fig. 2A, Table 3). In contrast, there was no group difference in pain ratings post injection (Fig. 2B, Table 3). There was a significant interaction between group and capsaicin injection ($p = 0.003$): capsaicin injection induced a significant increase in VAS ratings in controls (OR = 3.92, $p < 0.001$) but not in patients (OR = 1.20, $p = 0.43$).

Temporal summation was evoked within the area of secondary punctate hyperalgesia in 26 of 30 participants. Mean wind-up ratio (WUR) was 1.3 for patients and 1.6 for controls. The difference between groups was not significant (Table 3).

Conditioning pain modulation

Six patients could not complete the cold pressor bath. The average immersion time for these patients was 118 s (SD 13). One patient became nauseous and the remaining five found the pain intolerable.

Submersion of the right hand in the cold pressor bath caused a quick increase in pain ratings up to around 40 s after start, followed by a slow but steady increase, which stabilized after approximately 100 s for the remaining time (Fig. 3). The time profile of the VAS curves was similar in patients and controls; however, the cold pressor bath induced significantly higher pain ratings in patients than in controls ($p = 0.002$, Table 4, Fig. 3). The mean pain scores for patients and controls were 7.6 and 4.6 (VAS_{mean}), 8.9 and 5.9 (VAS_{max}) and 37.5 and 22.2 (VAS_{AUC}), respectively.

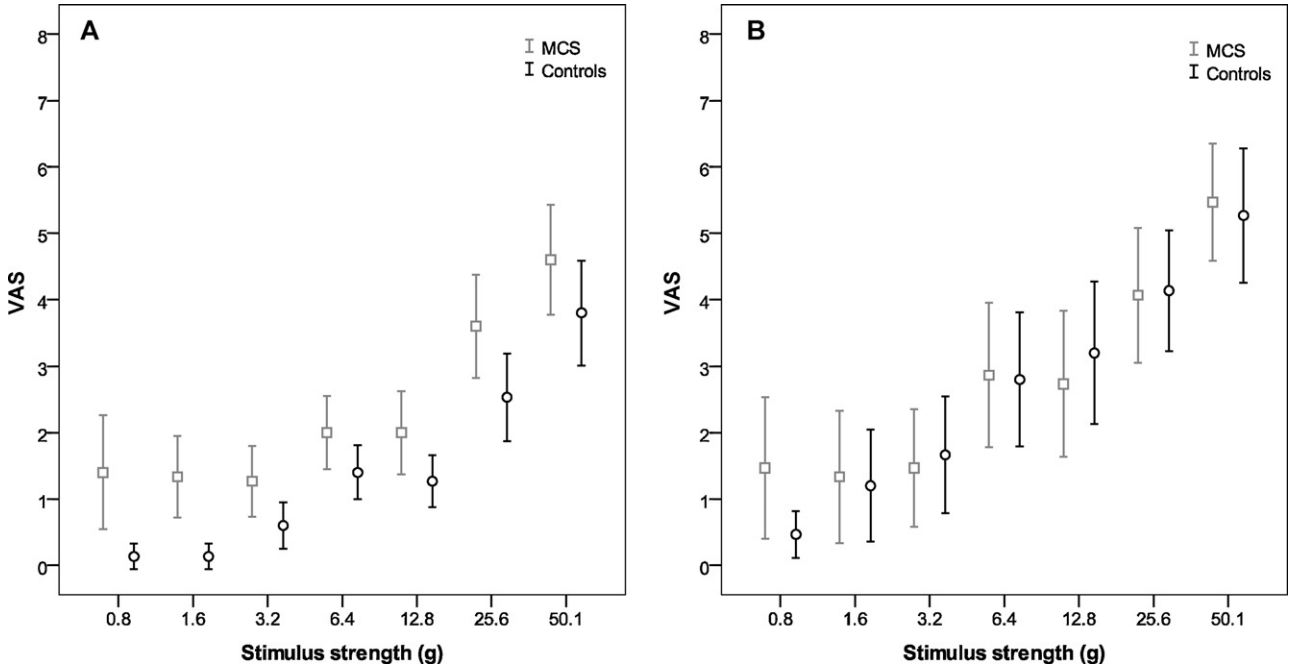

Fig. 2. Stimulus response function (SRF) pre (A) and post capsaicin (B) injection in MCS patients and controls (I = 95% confidence intervals). The difference in pain ratings between MCS patients and controls was significant pre ($p < 0.01$) but not post injection ($p = 0.71$).

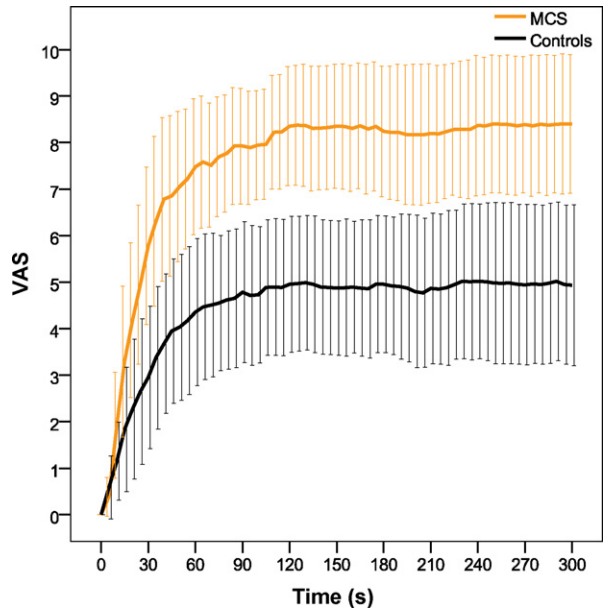

Fig. 3. Mean pain ratings during submersion of the hand in the cold pressor bath (0–1 °C) for 5 min (I = 95% confidence intervals). Pain ratings were significantly higher in MCS patients than in controls ($p < 0.01$).

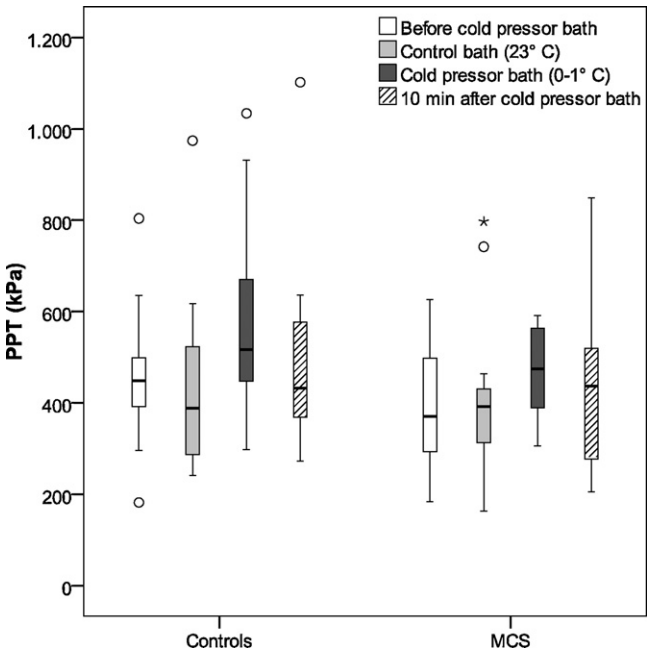

Fig. 4. Mean pressure pain threshold (PPT) before, during and 10 min after a cold pressor bath and during a neutral control bath (□ = interquartile range, I = 1.5 times the interquartile range, ○ = outliers, * = extreme values). There were no significant group differences in CPM effects ($p = 0.35$).

Mean pressure pain thresholds for patients and controls at baseline were 374.4 kPa and 415.8 kPa (PPT) and 921.8 and 997.9 kPa (PPTT), respectively, with no significant differences (Table 4).

During the cold pressor bath, mean PPT increased significantly both in patient and control groups ($p = 0.02$ and $p < 0.01$, respectively, Fig. 4). The PPT increase was 73.1 kPa for patients and 119.1 kPa for controls. The difference in PPT increase between groups was not significant ($p = 0.35$, Table 4). PPT at 10 min after the cold pressor test did not differ from the baseline value within patient ($p = 0.27$) and control groups ($p = 0.24$, Fig. 4). The control bath (23 °C) had no effect on PPT compared with baseline PPT, either within groups ($p = 0.98$ for patients and $p = 0.47$ for controls) or between groups ($p = 0.60$, Table 4).

Because six patients did not complete the cold pressor bath, we omitted these patients from a supplementary analysis of CPM effect, obtaining a mean PPT_{CPM} of 31.2 kPa (SD 101.9) for the remaining nine MCS patients. The PPT increase induced by the conditioning stimulus was no longer significant within the patient group ($p = 0.39$). However, the difference between groups did not reach statistical significance ($p = 0.11$).

Heat pain thresholds

Mean heat pain thresholds for patients and controls at baseline were 46.4 and 47.3 °C (HPT) and 50.0 and 49.9 °C (HPTT), respectively. HPT and HPTT did not differ significantly between groups (Table 5).

Tonic heat pain model

All participants completed the tonic heat stimulation apart from one MCS patient, who had to stop because of intolerable pain.

Tonic heat stimulation caused a steep increase in pain ratings up to around 20 sec after start followed by a slower increase until 125 s, whereupon the increase slowed further for the remaining time. The time profile of the mean VAS curve was again similar in patients and controls with a displacement of the patients' curve upward (Fig. 5). The differences between MCS patients and controls were not significant in any of the pain intensity measures (Table 5). The mean scores for patients and controls were 5.5 and 4.3 (VAS_{mean}), 7.1 and 6.0 (VAS_{max}) and 38.5 and 30.2 (VAS_{AUC}), respectively.

Table 4
Quantitative Sensory Testing by the CPM pain model in MCS patients and controls.

	MCS ($n = 15$)		Controls ($n = 15$)		p-Value
	Mean	SD	Mean	SD	
VAS_{mean}	7.6	(2.2)	4.5	(2.6)	**<0.01**[a]
VAS_{max}	8.9	(2.1)	5.9	(2.6)	**<0.01**[a]
VAS_{AUC} (cm × min)	37.5	(11.1)	22.2	(12.9)	**<0.01**[a]
PPT_{mean} (kPa)	374.4[c]	(170.0–603.5)[d]	415.8[c]	(229.0–800.5)[d]	0.35[b]
$PPTT_{mean}$ (kPa)	921.8	(336.2)	997.9	(294.0)	0.49[a]
PPT_{CPM} (kPa)	73.1	(104.1)	119.1	(149.3)	0.35[a]
$PPT_{Control}$ (kPa)	0.8	(152.2)	22.7	(117.0)	0.60[a]

VAS_{mean}, mean pain ratings; VAS_{max}, peak pain ratings; VAS_{AUC}, area under the VAS-time curve; PPT_{mean}, mean pressure pain threshold; $PPTT_{mean}$, mean pressure pain tolerance threshold; PPT_{CPM}, PPT during cold pressor bath – PPT before cold pressor bath; $PPT_{Control}$, PPT during control bath – PPT before control bath.

[a] Multiple regression adjusting for sex and age.
[b] Multiple regression adjusting for sex and age with prior log transformation.
[c] Geometric mean.
[d] Range.

Table 5
Quantitative Sensory Testing by the phasic and tonic heat pain model in MCS patients and controls.

	MCS ($n = 15$)		Controls ($n = 15$)		p-Value
	Mean	SD	Mean	SD	
HPT_{mean} (°C)	46.4	(2.7)	47.3	(2.4)	0.32[a]
HPTT (°C)	50.0	(1.3)	49.9	(1.7)	0.88[a]
VAS_{mean}	5.5	(2.9)	4.3	(2.2)	0.23[a]
VAS_{max}	7.1	(2.9)	6.0	(2.6)	0.29[a]
VAS_{AUC} (cm × min)	38.5	(20.0)	30.2	(15.3)	0.36[a]

HPT_{mean}, mean heat pain threshold; HPTT, heat pain tolerance threshold; VAS_{mean}, mean pain ratings; VAS_{max}, peak pain ratings; VAS_{AUC}, area under the VAS-time curve.

[a] Multiple regression adjusting for sex and age.

Discussion

This study demonstrated altered sensory processing of various somatosensory stimuli in MCS patients without comorbid overlapping disorders. Compared with controls, capsaicin-induced secondary punctate hyperalgesia was increased in MCS patients, as was baseline sensitivity to punctuate mechanical stimuli and cold pain ratings. We found no group differences in pressure pain and heat pain thresholds, temporal summation to punctate stimuli post capsaicin injection, capsaicin and tonic heat pain ratings or CPM effect.

Patients in the present study scored higher on symptoms of depression and anxiety than controls did; nevertheless, these symptoms were within the normal ranges of the general population (Olsen et al., 2006).

The basic state of the nervous system

A psychophysical measurement is a reflection of the entire sensory neuraxis from the periphery to the brain. Sensory processing of external stimuli is thus a combination of physiological and psychological processes. Our findings of normal pressure pain and heat pain thresholds are in line with findings of normal thresholds of olfaction and chemosensory perception in MCS (Das-Munshi et al., 2006; Hummel et al., 1996). In contrast, patients showed increased baseline sensitivity to punctate stimuli suggesting that the baseline state of the nervous system in MCS is hyperexcitated. Interestingly, an attenuated response to punctate stimuli post capsaicin injection was observed in MCS patients and not in controls. A possible explanation for this could be a ceiling effect of the capsaicin dose that we used i.e. the capsaicin injection did not further sensitize the nervous system in patients as it was already excited. In support of this, a study by Witting et al. (2000) showed that repetitive intradermal capsaicin injections resulted in decreased or unchanged pain intensity in the hyperalgesic zone depending on the time between injections. Since increased baseline sensitivity has not been reported previously in MCS patients and the results of the pain thresholds point in the opposite direction, it will require further studies to establish whether a hyperexcitability of the basal nervous system exists.

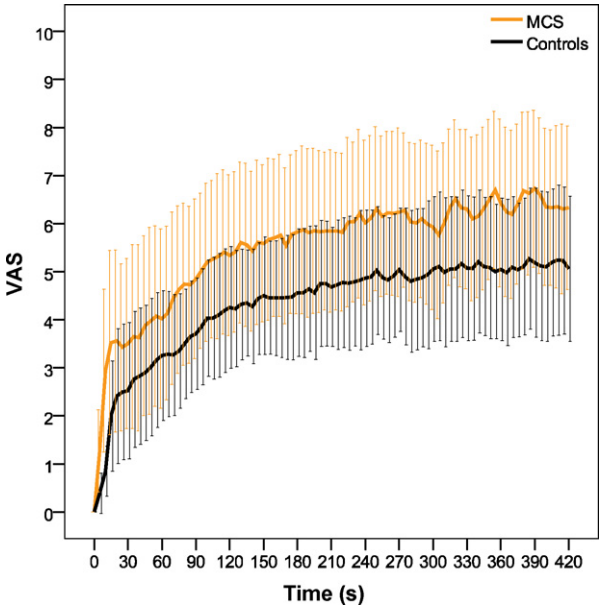

Fig. 5. Mean pain ratings during tonic heat stimulation with 47 °C for 7 min ($I = 95\%$ confidence intervals). Pain ratings of MCS patients and controls did not differ significantly ($p > 0.10$).

Central sensitization

The processing of suprathreshold nociceptive stimuli is reflected in pain intensity ratings. The ratings of capsaicin-induced pain in this study are in line with the study by Holst et al. (2011a), who reported normal pain intensity ratings at a provocational dose of capsaicin similar to ours but increased pain intensity ratings at a tenfold higher capsaicin dose than ours in MCS patients compared with in controls. We also found increased pain intensity ratings to cold pain in patients compared with controls, but on the other hand, the tonic heat pain ratings and tolerance thresholds were normal. Thus there is seemingly no clear pattern in MCS patients regarding nociceptive stimuli above threshold.

Capsaicin is a vanilloid receptor agonist that elicits ongoing discharge in nociceptive C-fibres and induces primary hyperalgesia at the injection site and secondary hyperalgesia in the unaffected area surrounding the injection site. Primary hyperalgesia is considered to be the result of sensitization of peripheral nociceptors, in contrast with secondary hyperalgesia which is a central phenomenon (Cervero et al., 2003). Two types of secondary mechanical sensory abnormality following capsaicin injection have been demonstrated: a punctate hyperalgesia and a brush-evoked pain area (allodynia) mediated by Aδ- and Aβ-fibres, respectively (LaMotte et al., 1991).

An enlarged area of capsaicin-induced secondary punctate hyperalgesia has also been demonstrated in other clinical conditions, such as rheumatoid arthritis, fibromyalgia, and vulvodynia and is thought to reflect enhanced central mechanisms (Foster et al., 2005; Morris et al., 1997, 1998). It could be argued that psychological factors may have contributed to the increased capsaicin-induced punctate hyperalgesia. Although the possibility of psychological factors having a moderating influence cannot completely be eliminated, we consider this unlikely. Firstly, participants were unaware that the purpose was to determine the area. Secondly, participants were blindfolded to prevent them from seeing the marks and yet the area of secondary hyperalgesia was significantly increased at three different time points. It thus seems probable that the increased response reflects altered peripheral or central neurogenic responses in MCS. The lack of a difference in capsaicin-induced flare response between patients and controls argues against an altered peripheral sensory response in MCS and is in accordance with a study by Holst et al. (2011b). The flare response is caused by an axon reflex that releases vasodilating substances and has been suggested to be an indirect measure of peripheral sensory activity (Jolliffe et al., 1995). In addition, accumulating evidence provides strong support for the dependence of capsaicin-induced secondary punctate hyperalgesia upon central mechanisms (Kilo et al., 1994; LaMotte et al., 1991; Torebjork et al., 1992).

It might seem inconsistent that the MCS patients had an attenuated response to capsaicin regarding the punctate mechanical intensity ratings but had an increased response to capsaicin regarding secondary punctate hyperalgesia. This could be due to differential central mechanisms underlying perceived intensity and the area of secondary punctate hyperalgesia. This is supported by the study of Witting et al. (2000), which reported no correlation between pain intensity in the hyperalgesic zone and area of secondary punctate hyperalgesia during repetitive capsaicin injections.

In contrast to the study by Holst et al., we found no group difference in temporal summation of pain. This could be due to differences in methodology as Holst et al. studied temporal summation by assessing the area under the pain rating curve (VAS_{AUC}) of repetitive punctate stimulations within the area of secondary punctate hyperalgesia for 1 min. This procedure seems to measure pain intensity more than temporal summation. We investigated temporal summation of pain by comparing pain ratings following a single stimulus and a train of 10 stimuli in order to derive a wind-up ratio, as recommended by the German Research Network on Neuropathic Pain (Rolke et al., 2006). An alternative explanation for the different finding of the present study is that the study population differed, as Holst et al. included patients with comorbidities of fibromyalgia, chronic fatigue syndrome and chronic pain. This might have biased the results as fibromyalgia and chronic pain have been associated with enhanced temporal summation (George et al., 2007; Staud et al., 2001; Weissman-Fogel et al., 2003). The absence of enhanced temporal summation in MCS patients does not argue against central sensitization, as temporal summation might be related to central sensitization but is not a necessity, i.e., central sensitization may be present with or without abnormal temporal summation of pain (Eide, 2000). Temporal summation reflects only some of the complex mechanisms behind central sensitization (Eide, 2000) and appears to depend on mechanisms different from those of secondary hyperalgesia (Magerl et al., 1998). This suggests that the neural circuits causing secondary hyperalgesia are hyperresponsive in MCS while the neural basis underlying temporal summation is unaffected.

Conditioning pain modulation

CPM is regarded as the net result of descending facilitatory and inhibitory modulation of spinal nociceptive processing (Arendt-Nielsen and Yarnitsky, 2009). In this study patients and controls both showed increased PPT during conditioning pain stimulation, suggesting normal functioning descending inhibition. However, six patients were unable to complete the cold pressor bath because of intolerable pain. This may have affected the results, which is supported by the supplementary analysis showing a reduced and non-significant PPT increase among patients, who completed the cold pressor test. Larger studies with modified methodology are required to determine whether a disturbance of descending modulation in MCS exists. In favour of this, a deficient CPM has been demonstrated in some of the overlapping disorders such as fibromyalgia, temporomandibular disorder and irritable bowel syndrome (Arendt-Nielsen and Yarnitsky, 2009).

Study limitations

There are some possible limitations in the present study. Firstly, the small sample size makes the study vulnerable to selection bias. This could be accommodated by examining a larger study population. However, the association between altered central sensory processing and MCS is supported by a previous similar finding in another patient sample (Holst et al., 2011a). Secondly, the presence of psychiatric comorbidity was based on self-reports which could be unreliable. In future studies, this could be accommodated by a more standardized psychiatric interview. Lastly, the high drop-out rate during the cold pressor test may have affected the results. Thus CPM in MCS patients should be examined in larger studies or with modified methodology e.g. reducing the submersion time in the cold pressor bath.

Sensitization of the olfactory circuits

Our findings of enhanced processing within parts of the nociceptive system provide evidence for increased processing of sensory inputs other than olfactory. Although central sensitization is not specific for MCS, it seems obvious to speculate whether enhanced cerebral processing might contribute to the multisystem symptom experiences of MCS patients when exposed to odours. Evidence from controlled brain imaging studies supports this as these studies demonstrated abnormal central odour processing in MCS patients showing hypoperfusion in odour processing brain regions during olfactory stimulation (Hillert et al., 2007; Orriols et al., 2009). Orriols et al. (2009) suggested that the cerebral hypoperfusion reflects reduced activity in inhibitory neuronal circuits producing increased excitability and facilitation. In support of this hypothesis, it has been shown that normal olfactory processing in animals is associated with widespread inhibition and sparse excitation in the primary olfactory cortex in contrast to visual, auditory and somatosensory processing, which is more balanced regarding inhibition and excitation (Poo and Isaacson, 2009; Schoppa, 2009).

Conclusion

Increased capsaicin-induced secondary punctate hyperalgesia was demonstrated in MCS patients without comorbid, overlapping disorders, suggesting central hyperexcitability in MCS.

Acknowledgement

This study was supported by a research grant from Aage Bang's Foundation.

References

Aaron, L.A., Buchwald, D., 2001. A review of the evidence for overlap among unexplained clinical conditions. Ann. Intern. Med. 134, 868–881.
Arendt-Nielsen, L., Yarnitsky, D., 2009. Experimental and clinical applications of quantitative sensory testing applied to skin, muscles and viscera. J. Pain 10, 556–572.
Barsky, A.J., Goodson, J.D., Lane, R.S., Cleary, P.D., 1988. The amplification of somatic symptoms. Psychosom. Med. 50, 510–519.
Bell, I.R., Schwartz, G.E., Baldwin, C.M., Hardin, E.E., 1996. Neural sensitization and physiological markers in multiple chemical sensitivity. Regul. Toxicol. Pharmacol. 24, S39–S47.
Berg, N.D., Linneberg, A., Dirksen, A., Elberling, J., 2009. Phenotypes of individuals affected by airborne chemicals in the general population. Int. Arch. Occup. Environ. Health 82 (4), 509–517.
Buchwald, D., Garrity, D., 1994. Comparison of patients with chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivities. Arch. Intern. Med. 154, 2049–2053.
Cervero, F., Laird, J.M., Garcia-Nicas, E., 2003. Secondary hyperalgesia and presynaptic inhibition: an update. Eur. J. Pain 7, 345–351.
Cullen, M.R., 1987. The worker with multiple chemical sensitivities: an overview. Occup. Med. 2, 655–661.
Das-Munshi, J., Rubin, G.J., Wessely, S., 2006. Multiple chemical sensitivities: a systematic review of provocation studies. J. Allergy Clin. Immunol. 118, 1257–1264.
Eide, P.K., 2000. Wind-up and the NMDA receptor complex from a clinical perspective. Eur. J. Pain 4, 5–15.
Foster, D.C., Dworkin, R.H., Wood, R.W., 2005. Effects of intradermal foot and forearm capsaicin injections in normal and vulvodynia-afflicted women. Pain 117, 128–136.
George, S.Z., Wittmer, V.T., Fillingim, R.B., Robinson, M.E., 2007. Sex and pain-related psychological variables are associated with thermal pain sensitivity for patients with chronic low back pain. J. Pain 8, 2–10.

Gottrup, H., Nielsen, J., Arendt-Nielsen, L., Jensen, T.S., 1998. The relationship between sensory thresholds and mechanical hyperalgesia in nerve injury. Pain 75, 321–329.
Graveling, R.A., Pilkington, A., George, J.P., Butler, M.P., Tannahill, S.N., 1999. A review of multiple chemical sensitivity. Occup. Environ. Med. 56, 73–85.
Hillert, L., Musabasic, V., Berglund, H., Ciumas, C., Savic, I., 2007. Odor processing in multiple chemical sensitivity. Hum. Brain Mapp. 28, 172–182.
Holst, H., Arendt-Nielsen, L., Mosbech, H., Elberling, J., 2011a. Increased capsaicin-induced secondary hyperalgesia in patients with multiple chemical sensitivity. Clin. J. Pain 27, 156–162.
Holst, H., Arendt-Nielsen, L., Mosbech, H., Serup, J., Elberling, J., 2011b. Capsaicin-induced neurogenic inflammation in the skin in patients with symptoms induced by odorous chemicals. Skin Res. Technol. 17, 82–90.
Hummel, T., Roscher, S., Jaumann, M.P., Kobal, G., 1996. Intranasal chemoreception in patients with multiple chemical sensitivities: a double-blind investigation. Regul. Toxicol. Pharmacol. 24, S79–S86.
Jason, L.A., Taylor, R.R., Kennedy, C.L., 2000. Chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivities in a community-based sample of persons with chronic fatigue syndrome-like symptoms. Psychosom. Med. 62, 655–663.
Jolliffe, V.A., Anand, P., Kidd, B.L., 1995. Assessment of cutaneous sensory and autonomic axon reflexes in rheumatoid arthritis. Ann. Rheum. Dis. 54, 251–255.
Kilo, S., Schmelz, M., Koltzenburg, M., Handwerker, H.O., 1994. Different patterns of hyperalgesia induced by experimental inflammation in human skin. Brain 117 (Pt. 2), 385–396.
Kuzminskyte, R., Kupers, R., Videbech, P., Gjedde, A., Fink, P., 2010. Increased sensitivity to supra-threshold painful stimuli in patients with multiple functional somatic symptoms (MFS). Brain Res. Bull. 82, 135–140.
Lacour, M., Zunder, T., Schmidtke, K., Vaith, P., Scheidt, C., 2005. Multiple chemical sensitivity syndrome (MCS) – suggestions for an extension of the U.S. MCS-case definition. Int. J. Hyg. Environ. Health 208, 141–151.
LaMotte, R.H., Shain, C.N., Simone, D.A., Tsai, E.F., 1991. Neurogenic hyperalgesia: psychophysical studies of underlying mechanisms. J. Neurophysiol. 66, 190–211.
Littlejohn, G.O., Weinstein, C., Helme, R.D., 1987. Increased neurogenic inflammation in fibrositis syndrome. J. Rheumatol. 14, 1022–1025.
Magerl, W., Wilk, S.H., Treede, R.D., 1998. Secondary hyperalgesia and perceptual wind-up following intradermal injection of capsaicin in humans. Pain 74, 257–268.
Morris, V., Cruwys, S., Kidd, B., 1998. Increased capsaicin-induced secondary hyperalgesia as a marker of abnormal sensory activity in patients with fibromyalgia. Neurosci. Lett. 250, 205–207.
Morris, V.H., Cruwys, S.C., Kidd, B.L., 1997. Characterisation of capsaicin-induced mechanical hyperalgesia as a marker for altered nociceptive processing in patients with rheumatoid arthritis. Pain 71, 179–186.
Naert, A.L., Kehlet, H., Kupers, R., 2008. Characterization of a novel model of tonic heat pain stimulation in healthy volunteers. Pain 138, 163–171.
Nethercott, J.R., Davidoff, L.L., Curbow, B., Abbey, H., 1993. Multiple chemical sensitivities syndrome: toward a working case definition. Arch. Environ. Health 48, 19–26.
Nielsen, L.A., Henriksson, K.G., 2007. Pathophysiological mechanisms in chronic musculoskeletal pain (fibromyalgia): the role of central and peripheral sensitization and pain disinhibition. Best Pract. Res. Clin. Rheumatol. 21, 465–480.
Olsen, L.R., Mortensen, E.L., Bech, P., 2004. The SCL-90 and SCL-90R versions validated by item response models in a Danish community sample. Acta Psychiatr. Scand. 110, 225–229.
Olsen, L.R., Mortensen, E.L., Bech, P., 2006. Mental distress in the Danish general population. Acta Psychiatr. Scand. 113, 477–484.
Orriols, R., Costa, R., Cuberas, G., Jacas, C., Castell, J., Sunyer, J., 2009. Brain dysfunction in multiple chemical sensitivity. J. Neurol. Sci. 287, 72–78.
Pekkanen, J., Sunyer, J., Anto, J.M., Burney, P., 2005. Operational definitions of asthma in studies on its aetiology. Eur. Respir. J. 26, 28–35.
Poo, C., Isaacson, J.S., 2009. Odor representations in olfactory cortex: sparse coding, global inhibition, and oscillations. Neuron 62, 850–861.
Rainville, P., Bushnell, M.C., Duncan, G.H., 2001. Representation of acute and persistent pain in the human CNS: potential implications for chemical intolerance. Ann. N.Y. Acad. Sci. 933, 130–141.
Randolph, T.G., 1962. Human Ecology and Susceptibility to the Chemical Environment. Charles C. Thomas, Springfield, IL, U.S.A.
Rolke, R., Baron, R., Maier, C., Tolle, T.R., Treede, R.D., Beyer, A., Binder, A., Birbaumer, N., Birklein, F., Botefur, I.C., Braune, S., Flor, H., Huge, V., Klug, R., Landwehrmeyer, G.B., Magerl, W., Maihofner, C., Rolko, C., Schaub, C., Scherens, A., Sprenger, T., Valet, M., Wasserka, B., 2006. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. Pain 123, 231–243.
Ross, G.H., 1992. History and clinical presentation of the chemically sensitive patient. Toxicol. Ind. Health 8, 21–28.
Schoppa, N.E., 2009. Inhibition acts globally to shape olfactory cortical tuning. Neuron 62, 750–752.
Simone, D.A., Baumann, T.K., LaMotte, R.H., 1989. Dose-dependent pain and mechanical hyperalgesia in humans after intradermal injection of capsaicin. Pain 38, 99–107.
Simone, D.A., Sorkin, L.S., Oh, U., Chung, J.M., Owens, C., LaMotte, R.H., Willis, W.D., 1991. Neurogenic hyperalgesia: central neural correlates in responses of spinothalamic tract neurons. J. Neurophysiol. 66, 228–246.
Sörensen, J., Graven-Nielsen, T., Henriksson, K.G., Bengtsson, M., Arendt-Nielsen, L., 1998. Hyperexcitability in fibromyalgia. J. Rheumatol. 25, 152–155.
Sorg, B.A., Newlin, D.B., 2002. Sensitization as a mechanism for multiple chemical sensitivity: relationship to evolutionary theory. Scand. J. Psychol. 43, 161–167.
Staud, R., Vierck, C.J., Cannon, R.L., Mauderli, A.P., Price, D.D., 2001. Abnormal sensitization and temporal summation of second pain (wind-up) in patients with fibromyalgia syndrome. Pain 91, 165–175.
Torebjork, H.E., Lundberg, L.E., LaMotte, R.H., 1992. Central changes in processing of mechanoreceptive input in capsaicin-induced secondary hyperalgesia in humans. J. Physiol. 448, 765–780.
Ursin, H., Eriksen, H.R., 2001. Sensitization, subjective health complaints, and sustained arousal. Ann. N.Y. Acad. Sci. 933, 119–129.
Weissman-Fogel, I., Sprecher, E., Granovsky, Y., Yarnitsky, D., 2003. 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 104, 693–700.
Winder, C., 2002. Mechanisms of multiple chemical sensitivity. Toxicol. Lett. 128, 85–97.
Witting, N., Svensson, P., Arendt-Nielsen, L., Jensen, T.S., 2000. Repetitive intradermal capsaicin: differential effect on pain and areas of allodynia and punctate hyperalgesia. Somatosens. Mot. Res. 17, 5–12.
Yunus, M.B., 2007. Fibromyalgia and overlapping disorders: the unifying concept of central sensitivity syndromes. Semin. Arthritis Rheum. 36, 339–356.
Yunus, M.B., 2008. Central sensitivity syndromes: a new paradigm and group nosology for fibromyalgia and overlapping conditions, and the related issue of disease versus illness. Semin. Arthritis Rheum. 37, 339–352.