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ORIGINAL ARTICLE

Chemosensory perception, symptoms and autonomic responses during chemical exposure in multiple chemical sensitivity

Linus Andersson[1] · Anna-Sara Claeson[2] · Thomas Meinertz Dantoft[3,4] · Sine Skovbjerg[3] · Nina Lind[2] · Steven Nordin[2]

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Abstract
Purpose Multiple chemical sensitivity (MCS) is a prevalent medically unexplained symptom characterized by symptom reactions to everyday chemical exposure below hygienic thresholds. The aim of this study was to investigate the expressions of hyper-reactivity in MCS during whole-body exposure to low concentrations of the odorant *n*-butanol.
Methods We exposed 18 participants with MCS and 18 non-ill controls to a low concentration of the odorant *n*-butanol using an exposure chamber. The first 10 min constituted blank exposure, after which the *n*-butanol concentration increased and reached a plateau at 11.5 mg/m^3.
Results MCS participants, compared with controls, reported greater perceived odor intensities, more unpleasantness to the exposure and increasing symptoms over time. MCS participants also expressed higher pulse rate and lower pulse rate variability than controls did. No group differences were found for breathing rate or tonic electrodermal activity responses.
Conclusions We conclude that MCS sufferers differ from healthy controls in terms of autonomic responses, symptoms and chemosensory perception during chemical exposure.

Keywords Multiple chemical sensitivity · Chemical intolerance · Environmental intolerance · Olfaction · Autonomic nervous system

✉ Linus Andersson
linus.andersson@psy.umu.se

Anna-Sara Claeson
anna-sara.claeson@psy.umu.se

Thomas Meinertz Dantoft
Thomas.Meinertz.Dantoft@regionh.dk

Sine Skovbjerg
sine.skovbjerg.jakobsen@regionh.dk

Nina Lind
nina.lind@psy.umu.se

Steven Nordin
steven.nordin@psy.umu.se

1 Department of Occupational and Public Health Sciences, University of Gävle, Johan Bures Väg 13, 907 36 Umeå, Sweden

2 Department of Psychology, Umeå University, 901 87 Umeå, Sweden

3 Danish Research Centre for Chemical Sensitivities, Copenhagen University Hospital Gentofte, Ledreborg Allé 40, 2, 2820 Gentofte, Denmark

4 Department of Systems Biology, Center for Biological Sequence Analysis, Technical University of Denmark, Kemitorvet, Building 208, 2800 Lyngby, Denmark

Introduction

To borrow Kreutzer et al. 's (1999) word, a *provocative* percentage of the population is adversely affected by everyday chemicals at concentrations assumed to be harmless. Between 9 and 33 % of the adult population reports some kind of chemical intolerance (CI), most often attributed to odors (Kreutzer et al. 1999; Caress and Steinemann 2003, 2004; Carlsson et al. 2005; Hausteiner et al. 2005; Johansson et al. 2005; Berg et al. 2008). An even larger percentage is found in occupational settings (Magnavita 2001). CI is commonly used as an umbrella term referring to negative reactions to everyday chemical exposure (Bell et al. 2001). A smaller but, nevertheless, substantial proportion of the population reports a severe, debilitating form of CI, with prevalence estimates ranging from 0.5 to 6.3 % (Kreutzer

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et al. 1999; Caress and Steinemann 2003, 2004; Johansson et al. 2005; Park and Knudson 2007). The most pertinent contributing factor to the large variability in estimated prevalence is the wide variety in definitions.

Multiple chemical sensitivity (MCS) is arguably the most widely used label for severe CI. According to the 1999 Consensus on MCS (1999), based on Nethercott et al. (1993) and clarified by Lacour et al. (2005), MCS is defined as a chronic condition (at least 6 months, causing significant impairment), with symptoms that recur reproducibly (in the central nervous system; CNS, associated with self-reported hypersensitivity), in multiple organ systems (obligatory in CNS and at least one in another organ system), in response to low levels of exposure to multiple unrelated chemicals, and which improve or are resolved when incitants are removed.

No dose–response relationship has been identified linking exposure concentration to symptom severity in MCS (Sorg 1999). Neither do sufferers express a characteristic symptom pattern (Sorg 1999). An exposure that leads to eye irritation for one person can result in headache and nausea for another. Despite severe and widespread symptoms, there are no reliable physiological markers currently available that can be used to separate sufferers from non-ill individuals (Labarge and McCaffrey 2000; De Luca et al. 2011). Differences between CI/MCS and controls have, however, been reported in empirical studies and include alterations of CNS functions (Bell 1996; Hillert et al. 2007; Andersson et al. 2009; Hillert et al. 2013), metabolic and immunological dysregulation (De Luca et al. 2010, 2011; Dantoft et al. 2014) and an increased area of capsaicin-induced secondary hyperalgesia to painful stimuli, which could be a reflection of a neurogenic vulnerability to sensory input (Tran et al. 2013). Das-Munshi et al. (2007) concluded in a review of exposure studies that individuals with CI/MCS reacted to exposure, but only when the provocation was discernable by the chemical senses. The authors further argued that expectations play a prominent role in the CI/MCS reactions. The results and conclusions of these studies should, however, be considered tentative. The lack of reliable biomarkers categorizes MCS as a medically unexplained illness.

Somewhat surprisingly, CI and MCS do not seem to be characterized by particularly acute chemical senses. The sufferers do not differ from non-ill controls in terms of absolute odor detection thresholds (Doty et al. 1988; Papo et al. 2006; Andersson et al. 2009; Kärnekull et al. 2011). Neither do individuals with CI or MCS generally rate olfactory stimuli as more intense than do controls (Österberg et al. 2003; Papo et al. 2006; Hillert et al. 2007; Andersson et al. 2009). Some researchers have found lower trigeminal detection thresholds (Andersson et al. 2009) and stronger perceived intensities for trigeminal stimuli in CI and MCS (Nordin et al. 2005; Hillert et al. 2007; Andersson et al. 2009), whereas others have not (Papo et al. 2006). Trigeminal exposures elicit burning, cooling and stinging sensations and are mediated through the fifth, trigeminal, rather than the first, olfactory, cranial nerve.

Several theoretical models have been proposed to explain the intangible aspects of MCS. Hypothetical explanations include sensitization of limbic neurons (Bell et al. 1992, 2001), neurogenic inflammation (Meggs 1993; Bascom et al. 1997), classical conditioning (Siegel and Kreutzer 1997; Van den Bergh et al. 2001) and oxidative stress involving nitric oxide/peroxynitrate (Pall 2003). A common denominator of the models seems to be the assumption of an acquired, persistent hyper-reactivity most often developed during a period characterized by high strain on the bodily systems.

The aim of this study was to investigate expressions of hyper-reactivity in MCS during exposure to low concentrations of the odorant *n*-butanol. To mimic everyday settings, we utilized an exposure chamber for full-body exposure. Based on previous theories of CI and MCS, we hypothesized that individuals with MCS would, over an extended period of *n*-butanol exposure, (1) report stronger perceived odor intensities, lower odor valence (greater odor unpleasantness) and more symptoms and (2) express higher breathing rate, higher tonic electrodermal activity (EDA), higher pulse rate and lower pulse rate variability (PRV), compared with controls.

Method

Participants

Participants who considered themselves as either especially sensitive or relatively unaffected by chemical exposure were recruited through advertisement at public places and in the local newspaper. Smoking, pregnancy, current breast feeding, having been diagnosed with fibromyalgia, chronic fatigue or irritable bowel syndrome were exclusion criteria. Prior to the exposure, participants were screened for anosmia (also constituting an exclusion criterion) using a 0.44 % v/v (336 ppm) concentration of *n*-butanol (99 %, Merck) of the Connecticut Chemosensory Clinical Research Center Threshold Test (Cain 1989).

Thirty-eight individuals were recruited by phone after having assessed their MCS status. Eighteen individuals (16 women, 2 men) fulfilled the MCS criteria (Lacour et al. 2005) by reporting (1) symptoms from low-level chemical exposures that others generally tolerate, (2) that symptoms had been occurring during at least the previous 6 months, (3) that symptoms occur when the chemical exposure is present and subside when removed, (4) that

Table 1 Reported health conditions and scores on self-rating questionnaires in the multiple chemical sensitivity (MCS) and control group

	MCS	Controls	*p* value
Participants, (*n*)	18	18	
Age, mean (±SD)	44 (14)	41 (14)	Ns
Chemical sensitivity scale, mean (±SD)	96 (16)	72 (10)	<.001
Perceived stress scale, mean (±SD)	18 (6)	16 (8)	Ns
SCL-90 anxiety, mean (±SD)	0.5 (0.5)	0.5 (0.6)	Ns
SCL-90 depression, mean (±SD)	0.7 (0.6)	0.6 (0.7)	Ns
SCL-90 somatization, mean (±SD)	0.8 (0.6)	0.4 (0.4)	<.05
Somatosensory amplification scale, mean (±SD)	29 (7)	25 (6)	Ns
Women/men (*n*)	16/2	14/4	
Allergic rhinitis	1	4	
Atopic asthma	1	0	
Non-atopic asthma	3	0	
Atopic eczema	0	0	
Coronary heart disease (*n*)	1	0	
Depression (*n*)	3	0	
Diabetes (*n*)	1	0	
Disease in back/joints/muscles (*n*)	1	2	
Epilepsy (*n*)	2	0	
Fibromyalgia (*n*)	2	0	
Generalized anxiety (*n*)	1	0	
High blood pressure (*n*)	5	2	
Irritable bowel syndrome (*n*)	3	0	
Migraine, (*n*)	4	0	
Multiple sclerosis (*n*)	0	1	
Noise sensitivity (*n*)	1	1	
Panic disorder (*n*)	2	0	
Post-traumatic stress disorder (*n*)	4	1	
Rheumatoid disease (*n*)	0	2	
Sensitivity to electromagnetic fields (*n*)	0	0	
Sensory hyperreactivity (*n*)	0	1	
Smoker (*n*)	1	0	
Snuff user (*n*)	2	3	

p values refer to results of independent samples *t* tests. *Ns* not significant

symptoms are elicited by at least two different chemical substances, (5) that at least two separate kinds of symptoms are involved, one of which has to involve the CNS (e.g., headache, fatigue, dizziness, memory problems, concentration difficulties or tiredness), and (6) that the symptoms cause significant impairment in daily life, either in social, recreational, occupational, educational or economic situations (confirmed by the CSS-score in Table 1).

Eighteen individuals (14 women, 4 men) were recruited as controls. They did not fulfill the MCS criteria above and reported no avoidance behavior, annoyance or symptoms attributed to low-level chemical exposure. None of the participants in the control group reported living with or having a close relative with MCS symptoms.

Demographic information and self-reported problems

Prior to the exposure procedure, all participants filled out Swedish versions of (1) the Chemical Sensitivity Scale (Nordin et al. 2003), which is a questionnaire used to assess affective and behavioral reactions to everyday chemical exposure; (2) the anxiety, depression and somatization subscales of the SCL-90 inventory (Fridell et al. 2002), which is a widely used self-report symptom inventory (Derogatis et al. 1976); (3) the Perceived Stress Scale (Nordin and Nordin 2013), which is a scale used to assess current levels of perceived stress; and (4) the Somatosensory Amplification Scale (Barsky et al. 1988), which is a scale used to assess to what degree respondents are bothered by uncomfortable visceral and somatic sensations. An additional questionnaire about common diseases and illnesses was also administered. Descriptive data of the participants are given in Table 1. Independent samples *t* tests revealed that the MCS group scored higher on the CSS and the somatization subscale of the SCL-90. No other significant group differences were found.

Materials

Chemical exposure and chamber

Participants were exposed to *n*-butanol (99.4 % J.T. Baker) at a concentration of 11.5 mg/m^3 (3.7 ppm) while seated in a windowed exposure chamber. The odorant *n*-butanol was chosen as it is a compound that is difficult to identify, has ambiguous hedonic properties, is present in the indoor air (Uhde and Salthammer 2007), and was regarded as symptom eliciting by MCS sufferers during pilot testing. It had also been used successfully in a previous exposure paradigm that produced varied reactions in terms of perceptual ratings and symptoms (Andersson et al. 2013). The concentration was clearly detectable, but well below the threshold for sensory irritation (Ruth 1986). To ensure a consistent concentration in the exposure chamber, a known amount of the odorant was fed through a nebulizer into a feed stream of filtered air monitored by a mass flow controller. The mixture was then diluted (by another stream of filtered air) to the desired concentration before it was fed into the exposure chamber. The odorized air was introduced into the

chamber after 10 min of blank (clean air) exposure, reached a plateau after approximately 8 min, and stayed constant for 42 min. The concentration of butanol in the exposure chamber was monitored by direct injection (a syringe with 0.1 mL of air) into a GC–FID (Gas chromatography with a flame ionizing detector, HP5890) system equipped with a fused silica column (HP Ultra-2, 50 m × 0.2 mm ID coated with cross-linked 5 % phenylmethylsilicone, film thickness of 0.33 µm). The GC–FID was operated in splitless mode, with a temperature starting at 35 °C and rising 2 °C/min until reaching 200 °C. The data were recorded, integrated, and quantified by Waters Empower software (Waters, Milford, MA, USA) using calibration curves from known amounts of the compound. The concentration (11.5 mg/m^3) varied slightly (SD = 1.2 mg/m^3) when the exposure reached the plateau. The exposure chamber had a volume of 2.7 m^3 (height: 200 cm, width: 90 cm, depth: 150 cm). Air was exchanged at a rate of 7.8 times per hour. The mean temperature across participants at the end of testing was 22 °C (SD ± 1 °C), and the relative humidity was 16 % (SD ± 2 %).

Autonomic recordings

A BIOPAC MP150 system with two wireless BioNomadix® amplifiers was used to record pulse rate, breathing rate and EDA. The wireless amplifier for pulse rate and EDA was attached to the non-dominant wrist with Velcro tape. Pulse rate was monitored using a photoplethysmographic (PPG) transducer attached to the distal phalanx of the non-dominant ring finger. EDA was recorded using reusable Ag–AgCl electrodes coated with hypoallergenic electrode gel attached to the distal phalanges of the non-dominant middle and index fingers with adhesive tape. Breathing rate was monitored by a second wireless amplifier attached to a chest-strap that recorded changes in thoracic circumference caused by respiratory movements.

Pulse rate was recorded at 1000 Hz and filtered offline with a 0.1–35 Hz band-pass filter. The first derivative of the waveform was calculated to facilitate peak identification. Motion artifacts were removed after visual inspection, after which two measures were calculated from a 5-min artifact-free recording—(1) mean interval between pulse beats and (2) mean standard deviation of the normal-to-normal pulse intervals (SDNN), which is a measure of PRV. PPG recordings have been described as a good surrogate for electrocardiography (ECG) during non-stationary recordings (Gil et al. 2010). However, the technique is susceptible to motion artifacts (Schäfer and Vagedes 2013), which was also an issue in this study. As motion artifacts occurred at random intervals, it was not possible to extract pulse rate data from several, uninterrupted 5-min intervals. We therefore aggregated the pulse rate data across the entire session.

EDA was recorded at 1000 Hz and filtered offline with a 1 Hz low-pass filter. A duplicate 0.05 Hz high-pass-filtered waveform was subtracted from the original waveform to remove phasic skin conductance responses. Mean skin conductance level (SCL) was extracted as a measure of tonic EDA from the remaining waveform, as 12 values based on 5-min blocks.

Respiration rate was recorded at 1000 Hz and filtered offline with a 0.05–1 Hz band-pass filter. Mean breathing rate was extracted from the waveform as 12 values based on 5-min blocks. Calculations of pulse rate, EDA and breathing rate data were performed in AcqKnowledge 4.2 (BIOPAC Systems, Inc.).

Tasks

Perceptual ratings

During the exposure session, participants repeatedly rated the chemosensory intensity and valence of the exposure using a Borg CR-100 scale (Borg and Borg 2002). Intensity was rated in accordance with numbers and descriptive adjectives: Nothing at all, 0; minimum, 1.5; extremely weak, 2.5; very weak, 6; weak, 12; moderate, 25; strong, 45; very strong, 70; extremely strong, 90; near maximal, 100. Numbers above 100 are not labeled, but approaches the label absolute maximum. Valence was rated using the same scale, but participants were prompted to add a plus sign before the rating if the exposure was judged as pleasant, and a minus sign before the rating if deemed unpleasant.

Symptom ratings

Ten symptoms frequently reported by persons with CI (M. J. E. Andersson et al. 2009) were also rated using the Borg CR-100 scale (Borg and Borg 2002). These constituted eye irritation, nasal mucosal irritation, skin irritation, throat irritation, shortness of breath, concentration difficulties, dizziness, tiredness, headache and nausea. The mean of these ten symptoms was used as a composite score in the statistical analysis. Both perceptual and symptom ratings were made using pen and paper, when prompted on a computer screen.

Procedure

Each participant was scheduled to an individual exposure chamber session. The chosen date was based on the date of first contact. MCS and control participants were thus interspersed throughout the data collection phase. After giving the informed consent, being shown the laboratory equipment and passing the odor detection test, each participant was sampled for blood and nasal mucosa. The blood and

mucosal sampling were repeated directly after as well as 4 h after the end of the exposure session. An analysis of the blood and mucosal samples will be published separately. After these initial tests, the participant was seated in a chair inside the chamber. The participant received a lap tray with a pen and sheet of paper on which he or she could rate the perceptual properties of the odors as well as possible symptoms. The participant was told that the concentration of the chemical inside the chamber could vary during the session. With the exposure chamber door still open, the participant rated possible baseline symptoms. After the baseline ratings, the door was closed and the participant was prompted to watch a recorded seminar on a computer screen (http://www.psy.umu.se/psykologisksalong/). The seminar was chosen to be a relatively neutral way to keep the participant preoccupied during the long exposure session. Unknown to the participant, no chemical was delivered into the chamber during the first 10 min of testing. After the 10-min period of blank exposure, the *n*-butanol was released into the chamber and reached its peak concentration after about 8 min. The concentration remained at this peak level for the rest of the session. During the session (in total 60 min), participants performed a total of 12 ratings of perceived intensity and valence, and three symptom rating blocks. Each participant was exposed once. The procedure is illustrated in Fig. 1.

Statistical analysis

Analyses were performed using full factorial mixed model analyses of variance (ANOVAs) and independent samples *t* tests in IBM SPSS Statistics 20. The α was set to 0.05. Only effects associated with the factor Group are reported. Greenhouse–Geisser correction was applied in cases where $df > 1$. In such cases, uncorrected *df*s are reported. Effect sizes are reported as eta squared (η^2) and were calculated using Microsoft Office Excel 2010.

Results

Intensity and valence ratings

A 13 × 2 ANOVA on rated intensities with Time (thirteen ratings) as a within-subjects factor and Group (MCS, controls) as a between-subjects factor revealed a main effect of Group, $F(1, 34) = 4.5$, $p = .042$, $\eta^2 = .12$. As shown in

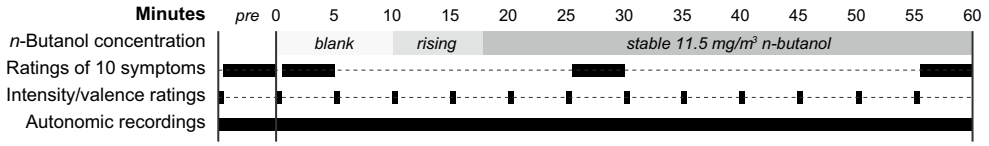

Fig. 1 Overview of the exposure chamber procedure. During the *pre* condition, participants were seated in the exposure chamber with the door open. The door was thereafter closed, and the chamber session began at minute 0

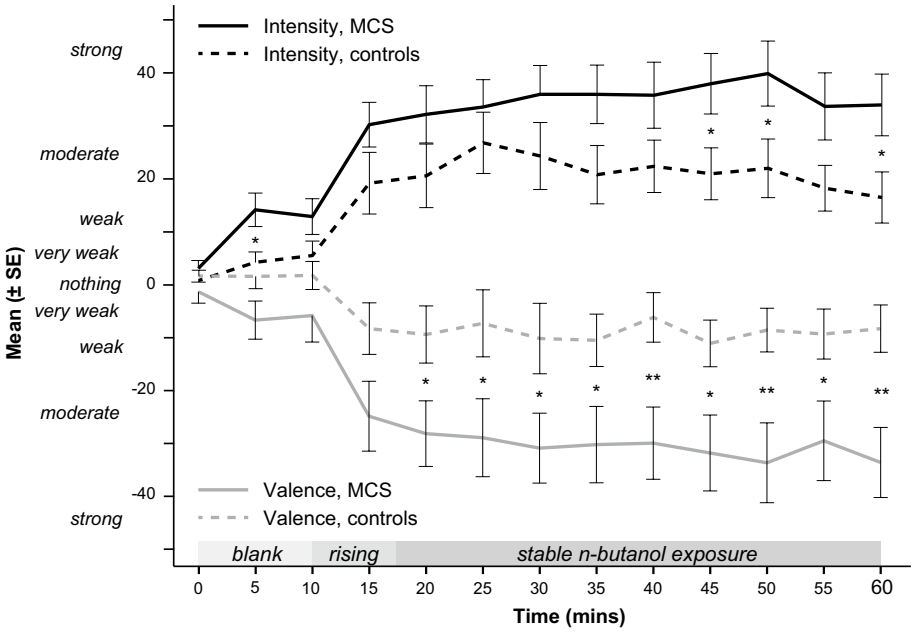

Fig. 2 Intensity and valence ratings during the blank and *n*-butanol exposure in the MCS and control group. Pleasantness was rated using positive numbers, and unpleasantness as negative numbers. *Asterisks* refer to parameter estimates (*$p < .05$, **$p < .01$)

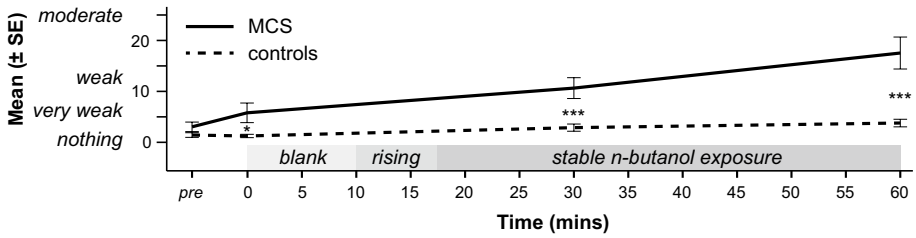

Fig. 3 Symptom ratings before the session and during the blank and *n*-butanol exposure in the MCS and control group. *Asterisks* refer to parameter estimates (*$p < .05$, ***$p < .001$)

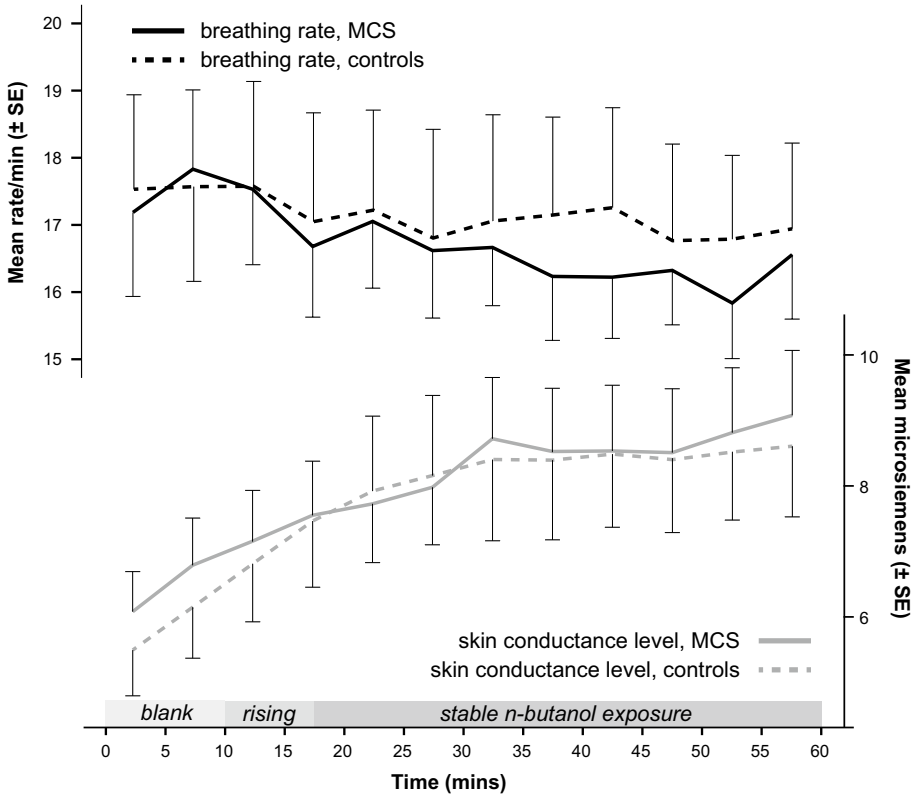

Fig. 4 Breathing rate and skin conductance level during blank and *n*-butanol exposure in the MCS and control group

Fig. 2, participants with MCS generally rated the *n*-butanol as more intense than the controls did. As suggested by the significant parameter estimates (Fig. 2), the largest difference between groups were found both during blank exposure and at the end of the session. A 13 × 2 ANOVA on valence ratings with the same factors as above revealed that the MCS group rated the exposure as more unpleasant than controls, as seen by a main effect of Group, $F(1, 34) = 7.6$, $p = .009$, $\eta^2 = .18$. The parameter estimates seen in Fig. 2 suggest that the valence ratings were significantly lower in the MCS group during exposure only.

Symptom ratings

A 4 × 2 ANOVA on the mean ratings of the ten symptoms with Time (four ratings) as a within-subjects factor and Group (MCS, controls) as a between-subjects factor revealed a Time × Group interaction, $F(3, 102) = 9{,}5$, $p < .001$, $\eta^2 = .15$. The parameter estimates in Fig. 3 reveal that the MCS participants did not report greater symptoms than controls before the chamber session, but did so during blank exposure and subsequent *n*-butanol exposure.

Breathing rate

A 12 × 2 ANOVA on the mean breathing rate during 5-min blocks with Time (12 blocks) as a within-subjects factor and Group (MCS, controls) as a between-subjects factor revealed no significant effects involving Group as a factor, all $F > .6$. The breathing rate for the two groups is illustrated in Fig. 4.

Tonic EDA

A 12 × 2 ANOVA on the mean SCL during 5-min blocks with Time (12 blocks) as a within-subjects factor and

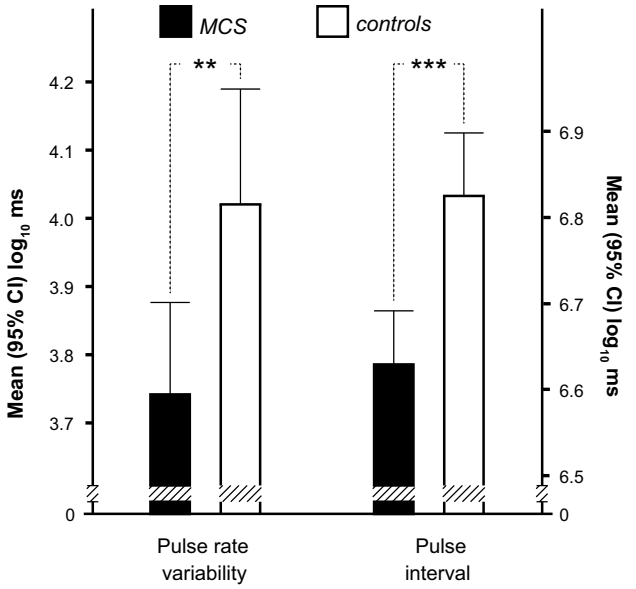

Fig. 5 Pulse rate variability and pulse interval during *n*-butanol exposure in the MCS and control group. *Asterisks* refer to the results of independent samples *t* tests (**$p < .01$, ***$p < .001$)

Group (MCS, controls) as a between-subjects factor revealed no significant effects involving Group as a factor, all $F > .5$. The Tonic EDA for the two groups is illustrated in Fig. 4.

Pulse rate and PRV

An independent samples *t* test on log-transformed intervals between pulse beats revealed that the participants with MCS had significantly higher pulse rate (i.e., lower interval between pulse beats) than controls, $t(30) = 4.4$, $p < .001$, $\eta^2 = .39$. Another independent samples *t* test on log-transformed SDNN revealed that the MCS group had significantly lower PRV than controls, $t(30) = 2.8$, $p = .009$, $\eta^2 = .20$. The pulse rate and PRV results are illustrated in Fig. 5.

Discussion

The aim of this study was to investigate how individuals with MCS and non-ill controls react to low, non-toxic concentrations of *n*-butanol. Our first hypothesis was that individuals with MCS would rate the exposure as more intense, more unpleasant and as eliciting more symptoms than did the controls. This hypothesis was corroborated by the current results, as illustrated in Fig. 2 and 3. We would like to disseminate two important aspects of these results—the reactions during blank exposure and greater group differences over time.

The MCS group reported greater symptoms during blank exposure than did controls. Parameter estimates also suggest that participants with MCS rated the blank exposure as more intense (but not more unpleasant) than controls. We argue that this effect on ratings of chemosensory perception and symptoms is due to expectancies, and not differences in rating behavior between the two groups—the MCS and control groups did not differ in their initial ratings when the exposure chamber door was open. The argument that MCS/CI reactions are associated with expectancies or an attention bias toward symptom-eliciting chemical exposures has been put forward before (Bascom et al. 1997) and has to some degree been corroborated empirically (Witthöft et al. 2006; Das-Munshi et al. 2007; Andersson et al. 2009). The observation that expectancies shape reactions should, however, not be interpreted as implying that MCS symptoms only exist on a cognitive level, or that MCS symptoms are imagined. In general, acting in accordance with predictions allows the organism to anticipate and meet the demands of a changed environment (Sterling 2004). Expectation of exposure or contextual cues (e.g., being inside the chamber, or predicting a negative outcome) can in this context be seen as a way of swiftly initiating a response to anticipated harm.

The MCS group rated greater symptoms over the course of the exposure, compared with controls, as seen by the significant Group × Time interaction. There was no such interaction for the chemosensory ratings. Nevertheless, parameter estimates suggested that the differences between groups, at least in terms of intensity ratings, tended to be larger at the end of the exposure session. The rating of symptoms, and to some degree intensity and valence, can thus be interpreted as an indication of sensitization in the MCS (Bell et al. 1992; Bascom et al. 1997; Sullivan et al. 2001; Andersson et al. 2009). A sensitized state is in some cases adaptive, constituting a defense against environmental threats. Prolonged, severe or reoccurring sensitization may, however, result in a pathological state where the heightened reactions do not subside after the deleterious exposure is removed (McEwen 2007). It is possible that the increased reactivity in the MCS group reflects such an acquired state, in which reactions may be triggered by both expectations (i.e., the reactions to the blank exposure), and low levels of chemicals that others find unproblematic (i.e., the *n*-butanol).

The greater intensity ratings in the MCS group seem to be at odds with results from previous studies, where no or only minor effects on intensity ratings have been found (Österberg et al. 2003; Papo et al. 2006; Hillert et al. 2007; Andersson et al. 2009). We suggest that MCS is indeed paralleled by stronger perceived intensities of chemosensory stimuli, and that such an effect is present, or at least most pronounced, at relatively low concentrations.

We emphasize that MCS/CI is characterized by adverse reactions to levels of exposure that indeed are low (Sorg 1999) and argue that stronger chemical exposure results in adverse effects in most individuals, regardless of MCS/CI.

A final note about the ratings regards the scale labels used to describe the exposures and reactions. At the end of the session, the mean rated intensity and unpleasantness was somewhere between "moderate" and "strong" in the MCS group. The control group rated the intensity at the end of the session as being between "weak" and "moderate", and unpleasantness as between "very weak" and "weak". The ratings thus reveal large discrepancies between the groups in terms of perceptual judgments of identical exposures. An exposure bordering the "strong" in terms of rated intensity and unpleasantness is arguably more bothersome and salient than an exposure weak in intensity. The controls neither ascribed the exposure much hedonic value, as seen by the valence ratings. This could be seen as an indication that the controls were relatively indifferent to the exposure. For them, it may not have constituted a particularly salient feature of the environment. The ratings thus reveal noteworthy perceptual differences in how individuals with and without MCS experience their chemical surroundings. The reactions to low, odorous exposure thus seem to vary greatly. Applied to occupational settings, the results highlight the need to consider the large inter-individual variation to even seemingly negligible exposures when setting exposure limits (Dalton and Jaén 2010; Brüning et al. 2014).

The second hypothesis was that individuals with MCS would express higher breathing rate, higher tonic EDA, higher pulse rate and lower PRV compared with controls. Neither breathing rate nor SCL differed between groups (Fig. 4). Individuals with MCS did, however, have higher pulse rate and lower PRV compared with controls (Fig. 5). The PRV result is of special interest. A low beat-to-beat variance is considered to be the result of disinhibition of the sympathetic branch of the autonomic nervous system and has been associated with prefrontal cortex hypoactivity, disturbed energy regulation and higher levels of pro-inflammatory cytokines such as interleukin 1 and 6 and tumor necrosis factor (Thayer and Sternberg 2006). These inflammatory markers have also previously been implicated in MCS (Dantoft et al. 2014). A prefrontal hypoactivity also seems to be a characteristic feature of CI (Andersson et al. 2014). According to Cohen's (1988) rule of thumb for effect sizes, the difference in PRV between groups was considerable. The lower PRV in the MCS group could thus be interpreted as a marker of deviating or exhausted organ system reactions and is reasonable given the chemosensory and symptom ratings.

The PRV measurement is, however, also a result that deserves a special call for caution. First of all, the PPG method used in this study does not always provide results that correspond to ECG recordings. Short-term variability of the PRV is often higher than the corresponding heart rate variability measure (i.e., variability based on ECG) and is more prone to motion artifacts (Schäfer and Vagedes 2013). Motion artifacts were indeed a problem in this study and precluded analyses over time. As the motion artifacts occurred at different time-points for each individual, we extracted only one PRV measure per person. This measure was based on 5-min PPG data at the end of the exposure session, with slight individual differences in time-points caused by different patterns of artifacts. Overall, the PRV result is interesting as the group effect is surprisingly large. Because of methodological limitations, the results should, however, be considered tentative and in need of future replication with more reliable cardiac measures (e.g., ECG). Moreover, it is not possible to tie the pulse measurements to the exposure itself—it is possible that the MCS group had higher pulse rate and lower PRV before the exposure session began, either because of expectations or in the form of a more long-term autonomic deviation. The second hypothesis was thus partially corroborated, albeit with cautionary notes.

In conclusion, the results from this study suggest that a continuous low-level *n*-butanol exposure elicits more symptoms and is perceived as more intense and unpleasant by individuals with MCS compared with persons without MCS. Symptoms were found to increase over time in the MCS group, and parameter estimates suggest that time may be a relevant factor for perceived odor intensity and valence as well. These results are important as ratings of the chemical exposure seldom provide differences between MCS and control groups, despite the fact that MCS is characterized by heightened reactions to such stimuli (Österberg et al. 2003; Papo et al. 2006; Hillert et al. 2007; Andersson et al. 2009). The current study setup and chemical exposure seem to produce the expected group differences and further suggest that effects are more easily discerned over time. An important issue that should be investigated in future studies regards the reaction to blank exposure. To what degree do individuals with MCS react to sham exposure? Additionally, an aim for future studies should be to investigate whether persons with MCS react similarly to other chemical compounds. In addition to deviating chemosensory perception, the results suggest lower PRV and higher pulse rate in MCS, compared with the case in controls. Although the pulse measurements come with caveats, they do, especially in combination with the ratings, constitute results that are in accordance with theoretical accounts of MCS (Bell et al. 1992; Siegel and Kreutzer 1997; Bascom et al. 1997; Pall 2003) and previous empirical studies implicating a low-level inflammation (Dantoft et al. 2014) and deviating CNS responses (Andersson et al. 2014).

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Conflict of interest The authors declare that they have no conflict of interest.

Ethical standard All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards and approved by the Ethics Committee at Umeå University (Dnr 2013-19-31). Informed consent was obtained from all individual participants included in the study. All participants were given written and oral information about the study. All participants were given 500 SEK (~50 EUR) for their participation.

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