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Attention bias and sensitization in chemical sensitivity ☆

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Abstract

Objective: We investigated whether persons with self-reported chemical sensitivity (CS) have an attention bias and enhanced sensitization to chemical exposure. **Methods:** Chemosomatosensory, olfactory, and auditory event-related potentials (ERPs) were recorded from 21 CS subjects and 17 controls in attend and ignore conditions. Reaction times (RTs) and magnitude estimations of perceived intensity were collected in the attend condition. ERPs were averaged over attention conditions and during the first/second part of the testing. **Results:** ERP patterns indicated that CS subjects did not habituate to the same extent as the controls and had difficulties ignoring the chemical exposure. CS subjects had faster overall RT, and the perceived intensities for the chemosomatosensory stimuli did not decrease with time in the CS group, which was the case for the controls. **Conclusions:** These results indicating attention bias and enhanced sensitization in CS suggest alterations in central, cognitive responses to chemical exposure.

Keywords: Attention bias; Chemical sensitivity; Event-related potentials; Psychophysics; Sensitization

Introduction

> "It is impossible for me to study or work when there are odors present."

This statement from one of our participants could probably have come from most of the people who suffer from chemical sensitivity (CS), in clinical terms often labeled multiple chemical sensitivity [1] or idiopathic environmental intolerance (IEI) [2]. CS is an affliction characterized by multi-organ symptoms following chemical exposure to levels considered safe for humans [3]. The symptoms are similar to those found in other medically unexplained illnesses such as sick building syndrome (SBS), fibromyalgia, and Persian Gulf War syndrome [4]. These illnesses are defined by subjective reports rather than measurable organic changes. The same patients often meet the criteria for several diagnoses and the illnesses are often mentioned in combination [5]. The introductory quote provides a hint of the problems faced by CS individuals, but might also touch on some of the underlying mechanisms of the symptoms. First, it suggests a prolonged reaction to the chemical exposure. Sensations caused by everyday chemicals such as perfume or cleaning agents ordinarily diminish over time, until barely perceived at all. Secondly, the inability to work implies that our participant cannot ignore the odors and focus on the task. These two aspects, sensitization and attention bias, have been highlighted as important elements of previous theories of CS.

Sensitization has been described as a nonassociative learning mechanism, implying a progressive response increase to repeated stimulus exposures. It is a broad term used to describe both reactions at a neuronal level and higher psychological functions. Sensitization is the opposite of

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habituation, which means a decrease in response to repeated exposures. A person sensitizes rather than habituates to a stimulus when the exposure is strong or noxious, when it is unpredictable, and when arousal is high [6]. It has been hypothesized that the response amplification in CS is caused by sensitization processes mainly in the limbic circuitry, which is an area especially sensitive to environmental (in this case chemical) stressors [7,8]. A sensitized limbic system might explain the diversity of symptoms, as limbic dysfunction can lead to both neurobehavioral and somatic symptoms [9]. Similarly, sensitization in limbic structures has been suggested as the underlying mechanism of several other medically unexplained afflictions, such as SBS, chronic fatigue syndrome, and sensitivity to electric and magnetic fields [10].

Closely related to sensitization is the concept of attention bias [11]. Attention bias implies facilitated or automatic shifts of attention toward information that is perceived as threatening and has been studied mainly in anxiety disorders. It has been hypothesized that the presence of threatening

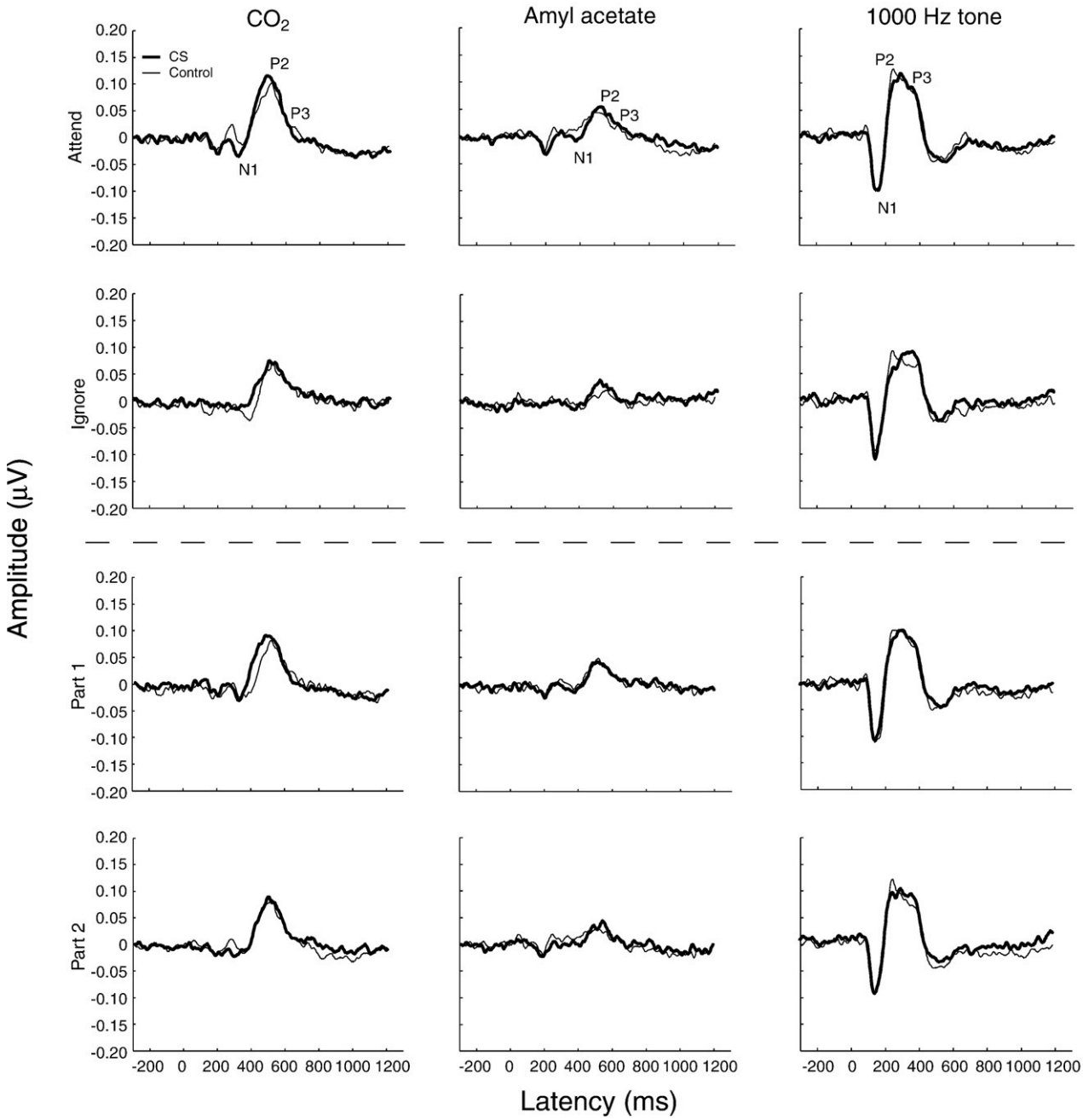

Fig. 1. Grand averaged chemosomatosensory, olfactory, and auditory ERPs for the group with CS and for controls in attend/ignore conditions and in the first part/second part of the recording session. Approximated positions of N1, P2, and P3 components are shown. Electrode position is Cz.

stimuli in anxious subjects affects the ability to reallocate attentional resources. That is, attention bias to a threatening stimulus seems to implicate difficulties in disengaging attention from that stimulus [12]. Several authors have suggested that persons with CS have an attention bias to chemical exposures [13–15]. This would imply that attention systems in CS individuals are biased to identify and avoid chemical exposure, and that such an exposure will have processing priority over other tasks. This might explain why attention difficulties are among the most disabling and most frequently reported symptom of CS [9]. The processing of threat-related information in subjects with an attention bias is assumed to be fast and crude, and involves limbic areas of the brain [11].

Previous studies have investigated whether persons with CS have different brain activation patterns compared with controls. The findings, however, have been inconsistent. There are reports that CS persons have increased electroencephalographic (EEG) theta activity, which in part has been attributed to concentration difficulties [9,16]. Such alterations in cognitive or perceptual processes have not been found using event-related potentials (ERPs) following chemosomatosensory or olfactory exposure [17–20]. The ERP method measures changes in averaged neural responses following time-locked exposures. The shape of the ERP waveform (for a grand average example, see Fig. 1) differs depending on the sensory modality of the stimulus, attention, intensity, and several other factors. Regarding intensity, increasing stimulus concentration causes shortened latencies and increased amplitudes of both early (e.g., the first negative wave, N1) and late (e.g., the second and third positive waves, P2 and P3) olfactory [21] and chemosomatosensory [22] ERP peaks. Allocation of attention has been found to shorten the overall chemosensory ERP latencies, but most prominently for the later peaks [23].

Reaction time (RT) has been used as a cognitive marker for CS. Bell et al. [24] reported that persons with CS compared to those without CS had slower RT on a visual divided attention task. Witthöft et al. [15] reported, contrary to their expectations, that CS (IEI) patients had slower RT than controls and somatoform disorder patients on an emotional Stroop test with neutral and CS-trigger words as stimuli. The authors argued that words might not constitute ecologically valid fear triggers in CS patients. Physiological and psychological data indicate that increased perceived intensity, alertness, and attention are associated with faster RT [25,26].

With the hypothesis that attention bias and sensitization are key components of CS, we investigated (1) whether persons with CS would have difficulties ignoring chemical stimuli when prompted to pay attention to another task; (2) whether CS individuals would show signs of sensitization instead of habituation after repeated chemical exposure.

The assumed attention bias to chemosensory exposure in CS was assessed in the present study by recording ERPs in conditions where subjects either focused their attention on or tried to ignore stimuli. We hypothesized that an attention bias would result in shorter chemosensory P2 and/or P3 latencies in the ignore condition for the CS group compared with controls. This would assumedly be an effect of difficulties in disengaging attention from such stimuli [23]. Sensitization effects were studied by analyzing changes in perceived chemosensory intensities over time, assessed with magnitude estimation. We hypothesized that the CS group would show signs of sensitization to chemicals or at least not habituate to the same extent as the controls. ERP results from the first and second half of the test session were also analyzed, with the hypothesis that possible latency increases and/or amplitude decreases in the second part of the test session would be greater for the control group than for the CS group because of weaker perceived intensities over time [21,22]. Simple RT to stimuli was also registered with the hypothesis that responses to sensory stimuli, contrary to previous study with more semantic stimuli [15], would be faster in the CS group because of higher arousal and/or stronger perceived intensities [25,26].

Materials and methods

Participants

A total of 129 individuals between 18 and 64 years of age were recruited through flyer and local newspaper advertisement. The adverts asked for people who considered themselves especially sensitive or nonsensitive to odors. Persons interested in participating received information about the study through email and were asked to fill out a web-based questionnaire designed to assess behavioral and affective reactions to odorous/pungent substances (the Chemical Sensitivity Scale for Sensory Hyperreactivity, CSS-SHR). The participants rated the degree to which they agreed to 11 statements (e.g., "At movies, other persons' perfume and aftershave disturb me.") on a scale ranging from, for example, "agree" to "disagree strongly." It has previously been reported that the CSS-SHR has good test–retest reliability, internal consistency, and predictive validity [27].

Individuals with a CSS-SHR score of $\geq$43 were considered sensitive, and those with a score of $\leq$34 nonsensitive, based on optimal cut-off scores from prior comparison of CS and normal groups [27]. Twenty-one sensitive (14 women, 7 men; mean age: 42.3, S.D.±11.6; mean CSS-SHR score: 47.5) and 17 nonsensitive (9 women, 8 men; mean age: 39.2, S.D.±13.4; mean CSS-SHR score: 22.6) persons were chosen from among the sensitive and nonsensitive subgroups and scheduled for a test session in the laboratory. The internal reliability of the CSS-SHR in this study was regarded as high, with a Cronbach α of .947. In the CS group, seven persons reported sleeping problems, six reported migraine, and three reported depression. Four controls reported sleeping problems, two reported migraine, and one reported depression.

The study was conducted in accordance with the Helsinki Declaration and approved by the ethics committee at Umeå University. A signed informed consent was obtained from each participant.

Screening for chemosomatosensory, olfactory, and auditory deficit

Participants were screened for chemosomatosensory (pungency), olfactory, and auditory detection deficits by means of forced choice, two-alternative (stimulus/blank) ascending methods of limits tests [28]. Chemosomatosensory stimuli were presented through a dynamic olfactometer (OM2s, Burghart Instruments, Germany) and consisted of CO_2 ranging from 5% to 35% v/v in concentration steps of 2.5%, paired with clean air blanks. Stimuli were presented in the most patent nostril (flow rate 8.0 l/min; 39°C; 80% relative humidity). Olfactory stimuli consisted of butanol ranging from dilution step 9 (6.8×10^{-5}%) in threefold increases to 0 (4.0%) in opaque glass bottles with nose masks. Distilled water was used as blank [29]. Auditory stimuli consisted of 1000-Hz tones presented binaurally through headphones (Häger Mower SJ 601). Loudness ranged from 20 to 50 dB(A) in steps of 10 dB(A). In all three screening tests, stimulus pairs were presented at approximately 10-s intervals. The threshold was defined as correct detection of five out of five stimuli at a concentration or loudness step. Three control participants were not able to detect the 35% CO_2 stimuli, but had no problems perceiving the experimental CO_2 stimulus. All participants were considered to have a functional sense of smell. All but one participant [detecting 30 dB(A)] detected 20 dB(A).

Stimuli

CO_2 (47.5% v/v) was used as a chemosomatosensory stimulus; amyl acetate (16.5%, 2400 ppm) as an olfactory stimulus; and a 1000-Hz, 70-dB(A) tone, presented binaurally via headphones, as an auditory stimulus. Chemosomatosensory and olfactory stimuli were presented using the olfactometer setup described above. The olfactory stimulus had been chosen in accordance with a pilot test in which 24 other individuals rated the sensory properties of amyl acetate of different concentrations, to find a distinct but nonpungent stimulus (unpublished data). The CO_2 concentration was also selected as a distinct stimulus acceptable to sensitive individuals and intense enough to elicit a clear sensation in nonsensitive individuals. All stimulus presentations had durations of 200 ms. White noise of 50 dB(A) was presented through the headphones during the session to mask auditory artifacts from the olfactometer. The recording session consisted of four 20-min blocks with 5-min pauses in between. Each block contained 18 stimuli of each modality (chemosomatosensory, olfactory, and auditory). Stimuli were presented in a semi-randomized order so that no more than three stimuli of the same modality were presented in consecutive order. To enhance the more cognitive ERP peaks (P2/P3), the inter stimulus interval (ISI) varied between 10 and 20 s, with an average of 15 s between two stimuli, and 45 s between stimuli of the same modality. A total of 72 stimuli of each modality were presented to the participants during approximately 1.5 h.

Attention modulation and study design

Participants alternated between an attend and an ignore task during the session, similar to methods used in previous ERP research [30]. In the attend task, participants were told to respond to a stimulus as fast as possible by pressing a mouse button. In addition, they were instructed to rate the intensity of the chemosomatosensory and olfactory stimuli by means of cross-modal magnitude estimation [31]. The auditory stimulus was used as a modulus with a perceived intensity of 100. The participants assigned numbers representing perceived intensities to each chemosomatosensory and olfactory stimulus in proportion to the modulus. The participants were not aware that the concentration of chemosensory and olfactory stimuli remained constant throughout the testing. To minimize ERP eye-blink artifacts, participants were also instructed to try not to blink as a reaction to a stimulus presentation.

In the ignore tasks, participants were told not to pay attention to the stimuli and to silently count backwards from 1000 in steps of seven (i.e., 1000, 993, 986, etc.). When they reached the number closest to each even hundred (e.g., 902), they told this number to the experimenter. If this number was incorrect, the experimenter corrected the participant.

Participants did each task twice according to an ABBA design that was balanced across groups. This setup enabled investigation of attention effects (attend/ignore) while balancing sensitization or habituation effects, and vice versa. In both tasks, participants were told to breathe through their mouth to avoid exhaling the chemical stimuli, to keep their eyes open, and fixate within a small area on a computer screen.

Event-related potentials and reaction time

EEG was recorded using gold-plated electrodes placed according to the International 10/20 system at midline (Fz, Cz, Pz), with reference electrodes at the mastoid bones (A1+A2). An electrooculogram (EOG) was recorded (Fp2/A1+A2) and a ground was placed at the forehead. Impedance was kept below 10 kΩ. The recordings were amplified (20,000 times), filtered (0.02–30 Hz band-pass filter), and digitized at 250 Hz for 1496 ms with a 300-ms prestimulus baseline. Waveforms were averaged off-line, rejecting trials in which EOG activity exceeded±100 μV. Five sensitive (five women) and two nonsensitive participants (one woman, one man) were excluded from the ERP analysis because of excessive blinking. Simple RT was recorded during the attend condition using a USB-connected mouse (Apple Pro Mouse).

Results

Event-related potentials

Grand averages for attend/ignore and first/second part of the recording sessions are given in Fig. 1. Mean peak latencies for the two groups during the different recording conditions can be found in Table 1, and peak amplitudes in Table 2. Results from a 2×3×3 (attention×modality×electrode site) repeated measures analyses of variance (ANOVAs) with Greenhouse–Geisser correction and group (CS/control) as a between-subjects factor are reported in Table 3. For P2 latencies, there was a significant group×attention interaction [$F(2,28)=5.206$, $P=.03$]. A post hoc ANOVA revealed a group×modality interaction effect in the ignore condition [$F(2,28)=7.100$, $P=.003$]. Further post hoc ANOVAs for the three modalities showed that the CS group, compared with the control group, had significantly shorter chemosomatosensory [$F(1,29)=10.211$, $P=.003$] and olfactory [$F(1,29)=6.374$, $P=.017$], but not auditory [$F(1,29)=1.985$, $P=.169$], P2 latencies in the ignore condition. These effects can be seen in the parameter estimates given in Fig. 2.

There was also a significant group×modality interaction [$F(2,28)=5.970$, $P=.009$] for the P2 latencies. Post hoc ANOVAs showed that the CS group had shorter overall chemosomatosensory [$F(1,29)=4.354$, $P=.046$], but not olfactory [$F(1,29)=3.243$, $P=.082$] or auditory [$F(1,29)=2.839$, $P=.103$], P2 latencies.

Table 4 shows results from a 2×3×3 (part×modality×electrode site) Greenhouse–Geisser corrected ANOVA with group as a between-subjects factor. There was a significant group×part interaction effect for N1 amplitude [$F(2,28)=6.304$, $P=.018$]. Post hoc ANOVAs showed that N1 amplitudes across all modalities decreased in the second part of the test for the controls [$F(1,14)=21.668$, $P=.000$], but not for the CS group [$F(1,15)=0.651$, $P=.433$]. Assumptions of normality and homogeneity of variance were evaluated as satisfactory, both for latency and amplitude data (through visual inspection, Levene's tests, and Kolmogorov–Smirnov tests).

Perceived intensity

Mean estimations of chemosomatosensory and olfactory perceived intensities for both groups can be seen in Fig. 3. A

Table 1
Mean (±S.D.) ERP latencies for the group with CS and controls in different recording conditions

	N1			P2			P3		
	Fz	Cz	Pz	Fz	Cz	Pz	Fz	Cz	Pz
Chemosomatosensory									
CS									
Attend	346 (47)	340 (46)	334 (45)	486 (44)	486 (43)	488 (38)	600 (56)	600 (56)	600 (49)
Ignore	355 (38)	354 (41)	351 (43)	473 (41)	476 (38)	474 (37)	596 (46)	599 (44)	598 (46)
Part 1	342 (33)	340 (33)	341 (39)	475 (38)	477 (38)	476 (38)	599 (47)	593 (44)	594 (43)
Part 2	350 (38)	349 (37)	348 (38)	490 (43)	487 (34)	489 (33)	597 (38)	598 (39)	599 (40)
Control									
Attend	364 (63)	363 (64)	360 (67)	498 (54)	499 (54)	499 (54)	609 (61)	610 (61)	610 (59)
Ignore	380 (59)	381 (60)	386 (61)	521 (45)	521 (45)	523 (45)	623 (53)	623 (51)	623 (52)
Part 1	371 (51)	371 (51)	371 (52)	510 (53)	510 (53)	513 (49)	623 (48)	623 (48)	622 (49)
Part 2	374 (45)	372 (44)	371 (49)	500 (49)	500 (49)	502 (49)	618 (49)	621 (47)	622 (47)
Olfactory									
CS									
Attend	393 (43)	393 (45)	390 (51)	508 (35)	509 (36)	507 (41)	624 (58)	623 (57)	627 (58)
Ignore	396 (35)	395 (34)	396 (35)	511 (27)	511 (27)	513 (28)	624 (46)	623 (48)	626 (45)
Part 1	387 (24)	386 (27)	388 (27)	525 (32)	522 (33)	521 (32)	632 (55)	633 (57)	632 (57)
Part 2	383 (41)	384 (41)	383 (46)	505 (31)	505 (31)	505 (33)	608 (45)	608 (45)	608 (44)
Control									
Attend	394 (64)	391 (63)	388 (64)	525 (64)	524 (66)	526 (64)	645 (73)	644 (74)	643 (68)
Ignore	410 (60)	410 (63)	413 (64)	547 (50)	548 (50)	548 (50)	653 (50)	652 (50)	652 (50)
Part 1	394 (69)	395 (69)	396 (68)	533 (53)	533 (53)	532 (52)	645 (51)	645 (52)	647 (55)
Part 2	406 (62)	407 (61)	406 (60)	531 (66)	530 (62)	530 (61)	643 (63)	640 (67)	643 (65)
Auditory									
CS									
Attend	145 (18)	152 (16)	152 (17)	275 (27)	273 (27)	275 (30)	378 (17)	376 (17)	379 (18)
Ignore	141 (13)	148 (15)	148 (15)	272 (36)	274 (37)	271 (38)	377 (22)	378 (22)	379 (19)
Part 1	142 (16)	150 (17)	150 (17)	277 (30)	276 (26)	279 (28)	375 (19)	373 (18)	377 (18)
Part 2	143 (17)	147 (15)	149 (17)	269 (33)	267 (34)	269 (34)	380 (22)	376 (21)	378 (22)
Control									
Attend	149 (24)	151 (19)	149 (16)	258 (27)	258 (26)	258 (28)	378 (26)	378 (26)	379 (22)
Ignore	146 (19)	147 (18)	145 (18)	258 (27)	257 (27)	253 (25)	372 (30)	371 (27)	369 (24)
Part 1	147 (19)	150 (18)	150 (17)	272 (26)	269 (28)	272 (34)	387 (20)	387 (23)	388 (25)
Part 2	142 (14)	146 (15)	147 (15)	258 (21)	256 (21)	253 (20)	379 (24)	377 (24)	375 (23)

Table 2
Mean (±S.D.) ERP amplitudes for the group with CS and controls in different recording conditions

	N1			P2			P3		
	Fz	Cz	Pz	Fz	Cz	Pz	Fz	Cz	Pz
Chemosomatosensory									
CS group									
Attend	−1.4 (4.9)	−5.8 (5.4)	−2.6 (3.6)	10.4 (5.5)	14.1 (6.1)	14.2 (5.9)	4.2 (4.1)	4.7 (5.0)	6.0 (5.0)
Ignore	−1.2 (2.5)	−4.3 (3.9)	−2.7 (3.3)	9.0 (4.0)	10.6 (5.1)	8.6 (3.5)	5.2 (3.3)	5.6 (3.1)	5.3 (2.3)
Part 1	−1.6 (3.2)	−5.2 (6.6)	−1.9 (4.9)	10.2 (5.6)	12.6 (6.9)	11.9 (6.3)	4.9 (2.6)	5.3 (4.0)	5.9 (3.6)
Part 2	−1.3 (4.0)	−4.5 (4.5)	−2.7 (3.3)	9.4 (4.3)	11.9 (4.9)	11.0 (4.2)	4.1 (3.2)	4.9 (2.5)	5.1 (2.2)
Control group									
Attend	−1.5 (3.2)	−3.6 (6.2)	−1.3 (5.8)	9.0 (5.2)	13.1 (6.8)	14.6 (7.3)	3.8 (3.3)	5.4 (4.2)	7.4 (4.7)
Ignore	−2.1 (3.2)	−4.2 (3.8)	−3.9 (3.5)	8.8 (6.7)	10.2 (5.2)	8.1 (4.1)	5.1 (4.8)	6.5 (4.7)	5.6 (3.6)
Part 1	−2.3 (2.6)	−4.9 (6.0)	−2.3 (5.8)	8.1 (4.8)	11.6 (5.3)	11.7 (5.1)	4.5 (3.2)	5.9 (4.1)	7.0 (4.0)
Part 2	−0.7 (2.7)	−2.7 (4.4)	−1.3 (4.3)	8.3 (4.0)	11.3 (4.8)	11.7 (4.9)	3.8 (3.7)	4.7 (3.0)	5.5 (3.2)
Olfactory									
CS group									
Attend	−1.3 (1.6)	−2.0 (2.4)	−0.7 (2.4)	6.0 (2.7)	8.1 (3.2)	8.1 (3.8)	1.7 (2.7)	3.7 (2.2)	4.9 (2.6)
Ignore	−1.9 (2.9)	−2.4 (2.3)	−1.6 (2.2)	4.4 (2.6)	5.4 (3.0)	4.8 (2.6)	3.5 (3.0)	4.2 (3.7)	3.5 (3.0)
Part 1	−1.2 (1.3)	−2.4 (1.8)	−1.2 (2.9)	4.9 (3.3)	6.6 (3.6)	6.5 (3.5)	2.0 (1.9)	3.0 (2.5)	3.6 (2.7)
Part 2	−0.7 (2.5)	−1.8 (1.7)	−1.1 (1.8)	5.3 (3.0)	6.6 (3.1)	6.5 (3.7)	3.7 (3.1)	4.7 (2.2)	4.8 (2.3)
Control group									
Attend	−2.7 (3.1)	−2.5 (3.7)	−1.1 (4.1)	5.5 (5.7)	8.6 (5.9)	9.8 (5.8)	1.9 (2.9)	3.8 (2.9)	4.9 (2.9)
Ignore	−2.5 (3.3)	−3.2 (2.9)	−3.3 (3.1)	3.5 (3.6)	4.4 (2.8)	4.0 (2.1)	3.6 (2.3)	3.0 (2.5)	2.1 (2.8)
Part 1	−2.7 (2.7)	−3.8 (2.8)	−2.9 (3.4)	4.7 (4.2)	6.5 (4.8)	7.0 (4.7)	2.2 (2.8)	2.8 (2.9)	3.5 (3.1)
Part 2	−1.5 (2.8)	−1.3 (3.1)	−0.9 (4.3)	4.5 (4.5)	6.1 (4.4)	6.3 (4.8)	0.6 (2.6)	2.5 (2.5)	2.9 (3.4)
Auditory									
CS group									
Attend	−9.8 (5.0)	−12.2 (6.0)	−8.6 (4.1)	13.7 (4.0)	14.7 (5.1)	10.5 (5.1)	8.7 (4.5)	9.2 (5.3)	11.0 (5.4)
Ignore	−10.0 (4.0)	−11.8 (4.0)	−8.6 (3.4)	10.8 (5.2)	11.4 (5.5)	7.8 (4.7)	10.1 (4.5)	9.4 (4.9)	9.1 (4.4)
Part 1	−10.1 (4.2)	−12.1 (5.6)	−8.6 (4.4)	12.1 (5.6)	12.7 (4.9)	9.5 (4.2)	8.6 (4.8)	9.3 (4.4)	10.0 (4.6)
Part 2	−9.7 (4.5)	−11.4 (3.9)	−8.0 (3.4)	12.0 (3.5)	12.8 (4.8)	8.6 (4.2)	9.6 (4.3)	9.0 (5.5)	9.8 (5.3)
Control group									
Attend	−11.3 (4.5)	−13.5 (5.3)	−9.0 (4.7)	9.9 (4.9)	14.6 (7.5)	12.3 (7.4)	6.9 (5.8)	9.1 (7.5)	11.5 (7.3)
Ignore	−10.1 (4.8)	−11.3 (4.7)	−8.5 (3.9)	10.0 (5.8)	12.0 (6.6)	7.8 (5.5)	8.8 (5.9)	9.0 (5.5)	8.6 (4.9)
Part 1	−11.4 (3.7)	−13.8 (3.9)	−9.8 (3.2)	10.2 (6.4)	13.4 (8.3)	10.8 (8.0)	7.6 (4.3)	7.9 (4.7)	9.1 (4.6)
Part 2	−10.0 (4.5)	−11.1 (4.9)	−7.8 (4.0)	9.8 (5.0)	13.6 (6.5)	10.3 (6.1)	7.0 (5.9)	8.8 (6.9)	10.2 (6.4)

Table 3
F values from ANOVAs of ERP amplitudes and latencies including attention as a factor

	Peak latency			Base-to-peak amplitude		
	N1	P2	P3	N1	P2	P3
Group (G)	1.16 ns	1.83 ns	1.18 ns	0.19 ns	0.09 ns	0.04 ns
Attention (A)	2.9 ns	1.86 ns	0.12 ns	0.15 ns	27.28 ***	0 ns
Modality (M)	548.63 ***	718.32 ***	648.63 ***	113.59 ***	37.80 ***	37.63 ***
Site (S)	0.72 ns	0.16 ns	0.4 ns	15.82 ***	11.30 ***	10.96 ***
G×A	0.63 ns	5.21 *	0.27 ns	0.13 ns	0.02 ns	0.19 ns
G×M	1.36 ns	5.97 **	1.6 ns	0.43 ns	0.035 ns	0.31 ns
G×S	0.28 ns	0.09 ns	1.45 ns	0.45 ns	1.76 ns	0.65 ns
A×M	2.57 ns	1.41 ns	0.52 ns	1.56 ns	0.31 ns	0.21 ns
A×S	3.82 *	0.55 ns	0.73 ns	5.43 *	21.49 ***	25.56 ***
M×S	3.30 *	0.64 ns	0.53 ns	13.85 ***	17.60 ***	0.64 ns
G×A×M	0.37 ns	1.85 ns	0.73 ns	1.64 ns	0.62 ns	0.07 ns
G×A×S	0.38 ns	0.43 ns	0.87 ns	2.05 ns	4.09 *	0.95 ns
G×M×S	2.95 ns	0.26 ns	0.6 ns	0.79 ns	1.78 ns	2.03 ns
A×M×S	1.17 ns	0.68 ns	0.27 ns	1.39 ns	5.49 ***	2.48 ns
G×A×M×S	0.25 ns	0.84 ns	0.73 ns	0.52 ns	1.34 ns	0.24 ns

ns Not significant.
* $P<.05$.
** $P<.01$.
*** $P<.001$.

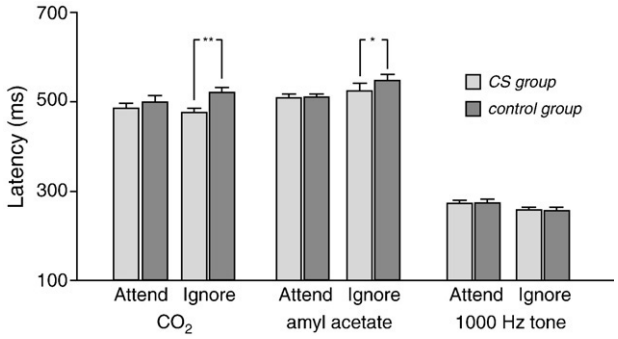

Fig. 2. P2 latencies (mean±S.E.) in the attend-and-ignore conditions for the group with CS and for controls. Asterisks indicate *P* values from parameter estimates (**P*<.05; ***P*<.01).

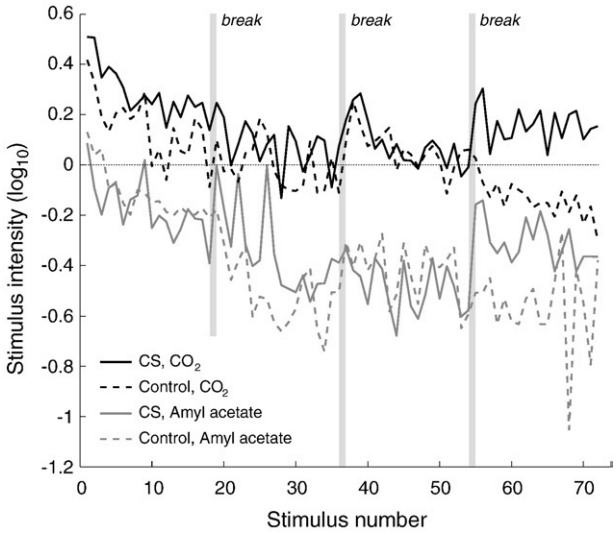

Fig. 3. Mean magnitude estimations for the group with CS and for controls. A 1000-Hz, 70-dB(A) tone is used as a modulus with intensity of 100 (dotted line).

Greenhouse–Geisser corrected repeated measures ANOVA for perceived chemosomatosensory intensities with the factor time (four parts) and group (CS/control) as a between-subjects factor yielded significant main effects of time [$F(1,16)=3.788$, $P=.029$] and group [$F(1,16)=5.639$, $P=.031$]. Post hoc ANOVAs showed that perceived intensities decreased with time (i.e., habituated) in the control group [$F(1,7)=3.553$, $P=.045$], but not in the CS group [$F(1,8)=1.219$, $P=.322$]. Corresponding analyses for perceived odor intensity showed an effect of decreased perceived intensity over time [$F(1,16)=5.284$, $P=.009$], but no differences between groups [$F(1,16)=1.530$, $P=.235$].

Reaction time

Visual inspection and Kolmogorov–Smirnov tests indicated that the RT data were positively skewed rather than normally distributed. Therefore, analyses were performed on log-transformed RT data. Mean log RT to the chemosomatosensory stimulus was 6.72 (S.D.±.51) for the CS group and 6.78 (S.D.±.40) for the nonsensitive group. To the olfactory stimulus, mean log RT was 6.85 (S.D.±.51) for the CS group and 6.98 (S.D.±.41) for the nonsensitive group. Mean log auditory RT was 6.54 (S.D.±.28) for the CS group and 6.58 (S.D.±.28) for the nonsensitive group. A multivariate analysis of variance was performed with RT from the three sensory modalities (chemosomatosensory, olfactory, and auditory) and group (CS and control) as a between-subjects factor. There was a significant main effect of group [$F(3,35)=152.595$, $P=.000$], indicating that the CS group had faster overall

Table 4
F values from ANOVAs of ERP amplitudes and latencies including part as a factor

	Peak latency			Base-to-peak amplitude		
	N1	P2	P3	N1	P2	P3
Group (G)	2.26 ns	1.17 ns	2.89 ns	0.16 ns	0.053 ns	0.79 ns
Part (P)	0.26 ns	5.00 *	2.21 ns	13.71 ***	0.36 ns	0.03 ns
Modality (M)	647.19 ***	668.19 ***	707.83 ***	92.16 ***	31.29 ***	35.81 ***
Site (S)	2.22 ns	0.84 ns	0.72 ns	17.80 ***	14.5 ***	13.70 ***
G×P	0.05 ns	0.57 ns	0.01 ns	6.30 **	0.01 ns	0.69 ns
G×M	1.65 ns	2.7 ns	1.08 ns	0.52 ns	0.15 ns	0.58 ns
G×S	0.11 ns	0.02 ns	0.27 ns	0.31 ns	2.99 ns	1.82 ns
P×M	0.51 ns	1.71 ns	1.32 ns	0.25 ns	0.05 ns	1.67 ns
P×S	0.13 ns	0.35 ns	0.08 ns	3.78 *	0.91 ns	0.5 ns
M×S	3.35 *	0.75 ns	0.32 ns	9.66 ***	20.77 ***	0.51 ns
G×P×M	1.1 ns	3.06 ns	1.97 ns	0 ns	0.3 ns	1.7 ns
G×P×S	0.01 ns	0.44 ns	0.443 ns	1.12 ns	0.03 nsns	1.82 ns
G×M×S	0.33 ns	0.71 ns	1.14 ns	0.2 ns	2.55 ns	0.45 ns
P×M×S	0.35 ns	1.01 ns	2.67 ns	0.96 ns	0.55 ns	0.64 ns
G×P×M×S	0.36 ns	0.48 ns	0.1 ns	0.21 ns	0.24 ns	2.5 ns

ns Not significant.
* *P*<05.
** *P*<01.
*** *P*<001.

RT. Parameter estimates yielded effects for chemosomatosensory [$t(37)=2.420$, $P=.016$], olfactory [$t(37)=4.620$, $P=.000$], and auditory [$t(37)=4.307$, $P=.000$] RT.

Discussion

The aim of this study was to investigate whether persons with CS (1) have difficulties ignoring chemical stimuli when prompted to pay attention to another task and (2) show signs of sensitization instead of habituation after repeated chemical exposure. We hypothesized that an attention bias would make it difficult for CS individuals to ignore chemical exposures and that this would result in a group difference for chemosensory ERP latencies (P2/P3) in the ignore condition. ERP results showed that the CS group indeed had shorter chemosensory and olfactory P2 latencies than the control group in the ignore condition (cf. Fig. 2). These group differences can be regarded as an inability of the CS subjects to ignore chemical exposure. This interpretation is in line with previous research by Krauel et al. [23], who have shown that olfactory P2 latencies decrease as a result of attention allocation. No group differences were found for any of the modalities in the attend condition. This might indicate that the attention resources per se are unaffected by CS, but that the sensitive persons have difficulties disengaging attention from chemical exposures. There were no indications of group differences regarding auditory ERP components in the present study. This suggests that the attention bias in CS individuals is sensory specific to chemosomatosensation and olfaction.

Sensitization effects were investigated by psychophysical magnitude estimations and comparisons of ERPs from the first and second part of the testing. Magnitude estimations (cf. Fig. 3) showed that the CS participants did not habituate to the CO_2 exposure, whereas the controls did. The intensity estimation results are remarkably similar to data from a study by Dalton [32]. She found that participants rated intensities of several odorants differently depending on how these were described (healthful, neutral, or harmful). Kobayashi et al. [33] arrived at the same conclusions in a study using a four-block experimental setup that was very similar to the design used in this study. In their study, the odorant anethole was perceived as significantly more intense during the last two blocks. This effect was proposed to be the result of slower central habituation. These studies show that nonsensory, top–down processes can reverse the adaptation (habituation) and induce sensitization. Furthermore, the subjects in Dalton's [32] study with a harmful bias reported symptoms to a larger extent than subjects receiving healthful or neutral bias. Persons with CS obviously have a negative bias to chemosensory exposure. It might well be the case that the negative bias contributes to sensitization, which in turn elicits symptoms.

Sensitization effects were also assessed in the present study by comparing ERPs from the first and second part of the test. Results showed that N1 amplitudes decreased in the control group during the second part, for all sensory modalities. N1 has been described as a component reflecting early sensory filtering and allocation of perceptual resources [34]. It has been shown to habituate after repeated exposure, both for visual [35] and auditory [36] stimuli. Moreover, it has been shown that chemosomatosensory [22] and olfactory [21] N1 amplitudes increase with greater stimulus intensities. We suggest that the decrease in N1 amplitudes for the control group is related to a general habituation process implying decreases in perceived intensities. However, a caveat is needed regarding the ERP habituation results. The method used to assess habituation in this fashion is crude, as we compare the first and second part of the recordings. It was not possible to extract useful ERPs from only one of the four blocks because of low signal-to-noise ratio. Assessing how electrophysiological data are associated with magnitude estimations would be an interesting inquiry for future studies.

Simple RT to stimuli were recorded in the attend condition and showed that the CS group reacted significantly faster to stimuli of all three sensory modalities. Earlier studies have shown that CS subjects have slower RT on divided visual attention tasks [24] and emotional Stroop tasks with word stimuli [15]. These findings may, however, not be in conflict with our results. Simple RT decreased with increased arousal and stimulus intensity [25,26]. If CS individuals have an attention bias to chemical stimuli and do not habituate to the same extent as controls, this might result in faster responses to environmental exposures, but slower processing of other, more semantic (e.g., word) stimuli. The CS group had faster RT to auditory stimuli as well. This may be an effect of higher overall arousal and reduced habituation in the CS group during testing and can be related to the effects found in the N1 amplitudes. The CS subjects probably perceived the chemical stimuli as more stressful than the control group did and might thus have been more alert throughout testing.

Studying a subjectively defined phenomenon such as CS is a difficult endeavor, and it is appropriate to point out some of the limitations of the current study. The CSS-SHR questionnaire assesses behavioral reactions to chemical exposure and is used in the definition of sensory hyperreactivity [27]. It could be assumed that the scale correlates reasonably well with other definitions of CS, e.g., the Cullen criterion [1], but the actual relation is not known. This somewhat impairs the ability to generalize the current results to other definitions of CS. A more thorough assessment of participants, using different definitions of CS, is a topic for future studies. A larger sample size would also be preferred to better be able to generalize the results. The electrophysiological and behavioral data paint a fairly coherent picture of how CS and control subjects differ, but not entirely so. Varying levels of attention seem to affect only chemosensory responses, while results from RT measurements and ERP from the first and second part of the testing indicate that auditory processing is affected in CS as well. We argued that this effect was the result of greater overall

arousal, but it can for example also be an effect of heightened reactions to environmental stressors other than chemicals. Previous research has suggested a relation between chemical and noise sensitivity [37–39]. It should, however, be noted that RT and sensitization analyses of ERP should be interpreted with caution.

Investigating alterations in the brain and cognitive processes seems to be vital to understanding CS symptoms. Attention bias and sensitization are related processes which guide the organism away from exposures perceived as hazardous. Sensitization is a fundamental learning process that, while influenced by cognitive factors such as stress, is largely beyond conscious control. This also seems to be the case for attention bias [11]. Attention modulation and extensive stimulus repetition seem to be important to identify differences in processing between persons with CS and controls and might, at least in part, explain why previous ERP studies [17–20] did not find such effects. Despite limitations, this study has shown that higher functions in CS individuals indeed are different from controls. The results lend support to predictions from theoretical models of CS [8,40,41] and may be applicable to other unexplained medical symptoms as well.

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