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Short-term olfactory sensitization involves brain networks relevant for pain, and indicates chemical intolerance

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ABSTRACT

Chemical intolerance is a medically unexplained affliction that implies deleterious reactions to non-toxic everyday chemical exposure. Sensitization (i.e. increased reactivity to repeated, invariant stimulation) to odorous stimulation is an important component in theoretical explanations of chemical intolerance, but empirical evidence is scarce. We hypothesized that (1) individuals who sensitize to repeated olfactory stimulation, compared with those who habituate, would express a lower blood oxygenated level dependent (BOLD) response in key inhibitory areas such as the rACC, and higher signal in pain/saliency detection regions, as well as primary and/or secondary olfactory projection areas; and (2) olfactory sensitization, compared with habituation, would be associated with greater self-reported chemical intolerance. Moreover, we assessed whether olfactory sensitization was paralleled by comparable trigeminal processing – in terms of perceptual ratings and BOLD responses. We grouped women from a previous functional magnetic imaging study based on intensity ratings of repeated amyl acetate exposure over time. Fourteen women sensitized to the exposure, 15 habituated, and 20 were considered "intermediate" (i.e. neither sensitizers nor habituaters). Olfactory sensitizers, compared with habituaters, displayed a BOLD-pattern in line with the hypothesis, and reported greater problems with odours in everyday life. They also expressed greater reactions to CO_2 in terms of both perceived intensity and BOLD signal. The similarities with pain are discussed.

1. Introduction

Chemical intolerance (CI) is a prevalent, medically unexplained affliction characterized by diverse, non-specific symptoms attributed to chemical exposure at doses assumed to be harmless. The general CI label encompasses a wide range of problems of varied severity. Someone who gets nauseous by passing the perfume counter at the mall would fit the description. So would he (or more often she) who gets debilitating symptoms for several days following exposure to the slightest doses of everyday chemical products (Dantoft et al., 2015a). The latter cases often fulfil criteria for multiple chemical sensitivity (MCS; Lacour et al., 2005; "Multiple chemical sensitivity: a 1999 consensus", 1999) and idiopathic environmental intolerance (IEI; IPCS/WHO, 1996).

Although symptoms often mimic those of asthma and allergy, CI sufferers do not express an exposure-specific deviation in immune system responses, or other organ systems for that matter (Dantoft et al., 2015b). Two chemosensory systems of particular relevance have previously been investigated for deviations in CI – olfaction, that mediates sensations commonly referred to as smell, and the trigeminal system, that mediates e.g. pungency and temperature. Psychophysical studies have not generally revealed a more acute sense of smell in terms of olfactory detection thresholds (Caccappolo et al., 2000; Doty et al., 1988; Papo et al., 2006). Andersson et al. (2015) found lower detection thresholds for CO_2 in CI sufferers, whereas such deviations in trigeminal detection thresholds are absent in other studies (Caccappolo et al., 2000; Papo et al., 2006). Perceptual ratings of chemical exposure have been reported to deviate from non-sufferers (Andersson et al., 2015,

Abbreviations: CI, chemical intolerance; MCS, multiple chemical sensitivity; IEI, idiopathic environmental intolerance; rACC, rostral anterior cingulate cortex; OFC, orbitofrontal cortex; BOLD, blood oxygenated level-dependent; CSS, chemical sensitivity scale.

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2009), but not consistently (Hillert et al., 2007; Papo et al., 2006), and arguably not to the degree that is expected by a condition characterized by severe reactions to chemicals.

Psychophysiological studies have revealed differences between sufferers and controls, but the pattern of responses is not easily comparable and synthesized. Andersson et al. (2009) reported differences between CI and controls in both latency and amplitude measures of olfactory and trigeminal event-related potentials. Using positron emission tomography, Hillert et al. (2007) reported greater regional cerebral blood flow in the anterior cingulate cortex when comparing MCS sufferers and controls, but lower signal in olfactory brain regions. Orriols et al. (2009) found that MCS patients had a greater deactivation pattern in several brain regions 30 min after exposure, assessed with single photon emission computed tomography. Azuma et al. (2013), using near-infrared spectroscopy, reported higher prefrontal activity during chemical exposure in MCS patients compared with controls. This is contrasted by Andersson et al. (2014) who reported that IEI sufferers, compared with controls, expressed a greater blood oxygenated level dependent (BOLD) signal in the thalamus and parietal brain regions during trigeminal, and lower in the superior frontal gyrus during olfactory exposure. Group differences to well-controlled exposure are sometimes absent (Papo et al., 2006).

One possible explanation for the relative paucity of empirical evidence has to do with how the criteria definitions are applied. MCS (Lacour et al., 2005), IEI (IPCS/WHO, 1996) or for that matter CI in general (Dantoft et al., 2015a), are labels that are based on self-reports of everyday problems. An issue in research and clinical settings regarding CI is therefore that the classification is restricted to subjective experiences that often are general in nature. McKeown-Eyssen et al. (2001) reported that over one fifth of all patients in general clinics meet the criteria for MCS. Severe CI is either extremely common or, perhaps more plausible, the criteria, at least when solely based on self-reports, are non-specific to the extent that their usefulness should be questioned. When ill or otherwise unbalanced, the chances of fulfilling the MCS criteria seems unacceptably large, which calls for other complementary measures.

Theoretical explanations of CI stem from different scientific fields, but share the assumption of an acquired hyperreactivity that is at least partly mediated by the central nervous system (Bascom et al., 1997; Bell et al., 1999; Otto and Giardino, 2001; Pall, 2003). It may be fruitful, or even necessary to address the core question of sensitized responses to low doses of chemicals to gain a better understanding of CI. Studies of sensitization and habituation (i.e. increased and decreased reactivity to repeated, invariant stimulation, respectively) in CI are scarce, but constitutes an active topic in pain research. CI and pain disorders such as fibromyalgia are similar in the sense that both imply adverse reactions to previously non-problematic exposures. They are also comorbid to a large degree (Jason et al., 2000; Slotkoff et al., 1997), and hypothetical explanations are similar (Tran et al., 2013).

Imaging studies have highlighted several areas that are important for the modulation of pain. Habituation to painful stimuli is paralleled by attenuated responses in the mid and anterior insula, secondary somatosensory cortex, putamen, posterior parietal cortex, amygdala, and other subcortical structures (Bingel et al., 2006; Ellerbrock et al., 2015; Mobascher et al., 2010; Peyron et al., 2000; Wiech and Tracey, 2009). These regions are, however, not exclusively implicated in pain, but can be conceptualized as a more general saliency network that dictates how sensory stimulation of different modalities are attended and perceived (Legrain et al., 2011), which makes them relevant also for the CI case.

In contrast to the signal decreases in areas mentioned above, habituation to pain also implies signal increases in prefrontal areas of the brain. The rostral anterior cingulate cortex (rACC) has in this context been highlighted as an important inhibitory node. Individuals who over time perceive decreased pain intensity, express signal increases in the rACC (Bingel et al., 2007; Ellerbrock et al., 2015). Patients with fibromyalgia show opposite patterns when exposed to painful stimuli, with lower activity in the rACC compared with healthy controls (Jensen et al., 2009). The neural underpinnings of habituation (and thus possibly sensitization) to noxious stimuli therefore seem to comprise an inhibitory system in which rACC is an important component, modulating responses in pain or saliency regions.

CI differs from pain as the assumed symptom-eliciting stimulus modalities are olfactory and trigeminal in nature. Olfaction is mediated by the first cranial nerve and projects to the piriform and entorhinal cortices, and the amygdala. The olfactory area of the orbitofrontal cortex (OFC) is an important secondary projection area. The fifth, trigeminal, cranial nerve enter the brainstem at the pons, and extends into the thalamus. Trigeminal perception involves the pain processing network of the brain, as well as regions implicated in olfaction (Kollndorfer et al., 2015; Lundström et al., 2011).

The aim of this study was to investigate whether sensitization and habituation to odours involve the same brain regions as those that have been implicated in pain modulation, and whether such responses would be associated with self-reported CI. We hypothesized that individuals who sensitize to repeated olfactory stimulation, compared with those who habituate, would express a lower BOLD response in key inhibitory areas such as the rACC, and higher signal in pain/saliency detection regions, as well as primary and/or secondary olfactory projection areas. Moreover, we hypothesized that olfactory sensitization, compared with habituation, would be associated with greater self-reported CI. Finally, we assessed whether olfactory sensitization is paralleled by comparable responses in trigeminal processing – in terms of perceptual ratings and BOLD-responses. The analysis was based on data that has been published previously (Andersson et al., 2014).

2. Material and methods

A detailed overview of the method is given in Andersson et al. (2014). In short, 58 non-pregnant, right-handed women with and without self-reported CI, and without anosmia were exposed to 20 consecutive amyl acetate (5 mg/m^3; smells like banana) well below irritation threshold (Claeson and Nordin, 2011), and 20 consecutive CO_2 (13.5% v/v; elicits pungent sensations) stimulations through a dynamic olfactometer (OM2s, Burghart Instruments, Germany) while inside a General Electric 3T scanner with a 32 channel head coil. The exposures had a duration of 30 s, with a 30 s odourless baseline. The order of the presentation sequence (amyl acetate/CO_2) was balanced across participants. The intensity of the exposures was rated repeatedly on a short version of the Borg CR-10 scale (Borg and Borg, 2002) presented on a scanner-compatible screen, which corresponded to buttons on two numerical keypads, one in each hand. One participant withdrew during initial testing, and another during the scanner session, and seven had to be excluded due to technical problems, either with the scanner or the stimulus presentation equipment. During the recruitment phase several weeks before the scanner session, all participants filled out the Chemical Sensitivity Scale (Nordin et al., 2003), which is a validated instrument that assesses behavioural and affective responses to odours in everyday life.

2.1. Olfactory sensitizers, habituaters, and those in between

We composed three groups based on the intensity ratings of the olfactory exposures. Participants who rated the invariant exposures as (1) increasing in magnitude over the course of the session, and