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NEURAL CORRELATES OF EMOTIONAL PROCESSING IN IDIOPATHIC ENVIRONMENTAL INTOLERANCE: AN FMRI STUDY

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Idiopathic environmental intolerance (IEI) is still medically unexplained. Conditioning and sensitization have been proposed to contribute to the symptoms. No study to date has used functional magnetic resonance imaging (fMRI) to study brain activation in IEI. The objective of the present study was to investigate whether individuals with IEI during chemosensory exposure activate brain circuitries associated with negative emotional processing and to examine if they sensitize to chemosensory stimuli. Brain activation was studied with fMRI in 26 female subjects with IEI and 30 age- and gender-matched healthy controls during exposure to olfactory and chemosomatosensory stimuli. Stimuli were presented in a blocked design with intensity ratings during each block. Subjects with IEI showed increased activation in amygdala, insula, dorsal anterior cingulate cortex and dorsal prefrontal cortex during exposure to carbon dioxide. In addition, they showed decreased activation in medial prefrontal cortex. These results imply negative emotional processing in IEI that is similar to what is seen in anxiety disorders. Further, specific phobia is proposed as a model for the understanding of how IEI develops and is maintained. The findings might have implications for the treatment of IEI.

A hint of perfume or smoke from a cigarette are common odors often barely noticed. However, for some people ordinary odorants like these are associated with disabling symptoms affecting their daily life. Idiopathic environmental intolerance (IEI; IPCS/WHO, 1996), also referred to as multiple chemical sensitivity (MCS; Cullen, 1987), is a term describing reoccurring, nonspecific symptoms affecting different organ systems. The symptoms are associated with exposure to chemicals commonly found in the environment at levels assumed to be non-toxic (Das-Munshi, Rubin, & Wessely, 2007; Labarge & McCaffrey, 2000). The presence of IEI cannot be established by any specific test since there is no biological marker or validated quantitative measure. Therefore subjective criteria are used as diagnostic instrument (IPCS/WHO, 1996). Idiopathic environmental intolerance is defined as (1) an acquired disorder with multiple recurrent symptoms (2) associated with diverse environmental factors tolerated by the majority of people, and (3) not explained by any known medical or psychiatric/psychological disorder (IPCS/WHO, 1996).

Individuals suffering from IEI report a wide range of symptoms such as headache, fatigue, muscle pain, swelling of throat or nose, itching and burning of skin or mucous membranes, disturbed sleep and dizziness (Bornschein, Hausteiner, Zilker, & Förstl, 2002). Triggers differ between affected individuals. Perfume, food or solvents are substances often associated with IEI but there are many more (Fiedler & Kipen, 1997; Miller & Mitzel, 1995). The prevalence numbers of self-reported sensitivity to chemicals in the general population differs between studies from 9 to 33 % (Berg, Linneberg, Dirksen, & Elberling, 2008; Hausteiner, Bornschein, Hansen, Zilker, & Forstl, 2005; Johansson, Brämerson, Millqvist, Nordin, & Bende, 2005; Meggs, Dunn, Bloch, Goodman, & Davidoff, 1996). Prevalence of physician diagnosed chemical sensitivity range from 0.5 to 6.3 % (Caress & Steinemann, 2004; Hausteiner et al.; Johansson et al., 2006). The symptoms are often regarded as more common in women than in men (Johansson et al., 2005). IEI is to a large

degree comorbid with many unexplained medical illnesses, e.g. chronic fatigue syndrome and fibromyalgia (Jason, Taylor, & Kennedy, 2000). These illnesses are sometimes categorized as functional somatic syndromes (Kanaan, Lepine, & Wessely, 2007).

There is no widely accepted treatment for sensitivity associated with chemicals. Self-care often consists of avoidance, detoxification and emotional self-care (Lipson, 2001). Some turn to alternative treatments methods like heat depuration and vitamins (Fox, Joffres, Sampalli, & Casey, 2007). IEI is also sometimes regarded as a psychiatric disorder and therefore treated with psychopharmacological drugs like selective serotonin reuptake inhibitors (Black, 2002).

The etiology of IEI remains unclear. Some researcher stress physiological or organic factors while others have emphasized the psychological mechanisms associated with the symptoms (Labarge & McCaffrey, 2000). However, all major models of IEI involve learning mechanisms as a contributing factor (Meulders et al., 2010). Learning and memory also seem to be involved in conditions sharing some similarity to IEI, such as fibromyalgia, where failure to extinguish conditioned responses may be an important component of the condition (Apkarian, Baliki, & Geha, 2009; Hölzl, Kleinböhl, & Huse, 2005).

In IEI, an often-discussed term is sensitization. It is a form of non-associative learning that occurs when repeated presentations of a stimulus lead to an increased response to that stimulus (Overmier, 2002). Sensitization effects can be measured in different ways. For example, Andersson, Bende, Millqvist, and Nordin (2009) used event related potentials, reaction times and estimations of intensity to study habituation/sensitization effects. They concluded that participants suffering from chemical sensitivity did not habituate to the same extent as the control group to chemosomatosensory, olfactory and auditory stimuli (Andersson et al., 2009). Other authors have proposed theories about the limbic system and its interconnections with the olfactory nerve as being of special interest for sensitization in IEI (Graveling, Pilkington, George, Butler, & Tannahill, 1999; Miller & Mitzel, 1995). These theories remains however unproven.

Conditioning is a form of associative learning and is closely related to sensitization (Hölzl et al., 2005). In recent years, researchers have been able to map important areas in the brain associated with conditioning, especially conditioning of fear and anxiety. Areas commonly found to be of importance in this context are amygdala, insula, anterior cingulate cortex (ACC) and prefrontal cortex (PFC) (Bishop, 2007; Etkin & Wager, 2007; Lang, Davis, & Ohman, 2000; Phelps & LeDoux, 2005). Amygdala is responsive to stimuli predicting threat and has been found to show increased activity during exposure to aversive olfactory stimuli in healthy subjects (Shin & Liberzon, 2010; Zald & Pardo, 1997). Amygdala is linked to medial PFC (mPFC) and these structures are important in fear conditioning (Phelps & LeDoux, 2005). Insula activity often correlates positively with amygdala. Hyperactivity in insula is associated with the experience of disgust and has also been shown during fear conditioning (Britton et al., 2006; Sehlmeyer et al., 2009).

Dorsal PFC (dPFC) and dorsal ACC (dACC) are considered having an evaluative function in emotion processing and they have been shown playing a part in appraisal and expression of emotion (Etkin, Egner, & Kalisch, 2010). Activity is these areas has been found reflecting the amount of emotional conflict (Etkin, Egner, Peraza, Kandel, & Hirsch, 2006). Increased sensitivity to negative emotions and ambiguity is also associated with higher activity in dACC and dPFC (Etkin et al., 2010). Medial and ventromedial PFC (m/vmPFC) and rostral ACC (rACC) are areas closely related. A key function of these areas is emotion regulation (Etkin et al., 2010).

There are two earlier studies of brain activation in individuals with IEI (Hillert, Musabasic, Berglund, Ciumas, & Savic, 2007; Orriols et al., 2009). Hillert and colleagues (2007) used positron emission tomography to compare brain activation in individuals with IEI with controls on several different odorants. Results showed decreased activation in odor-processing areas in the IEI-group, with the largest difference in amygdala, insular cortex and piriform cortex. Another finding was that in individuals with IEI, exposure to odorants was associated with increased activation in anterior cingulate cortex (ACC) and cuneus-precuneus. The authors suggested that the findings could be explained by a top-down modulation of activation in olfactory regions in IEI individuals, which would serve the purpose of harm avoidance (Hillert et al., 2007). Using single-photon emission computed tomography (SPECT), Orriols et al. (2009) found that individuals with IEI showed decreased activation in hippocampus, amygdala and in an area seemingly including vmPFC after exposure to chemicals. Similar brain areas have been studied with fMRI in other functional somatic syndromes. Landgrebe et al. (2008) found that electrosensitive patients showed increased activation compared to controls in ACC, insular cortex and fusiform gyrus exposure to sham mobile phone radiation.

In summary, there is research indicating a sensitization effect in individuals with IEI. Since sensitization is closely related to conditioning, studies of anxiety and fear conditioning are of interest for the study of IEI. In addition, areas of special interest in anxiety and fear overlap to a large extent with those found to be of interest in research of brain activation in IEI during chemosensory exposure. Therefore, the present study investigated if individuals with IEI (1) showed signs of sensitization after repeated exposure to chemosensory stimuli (2) during exposure to chemosensory stimuli showed similar patterns of brain activation as that in anxiety disorder and fear conditioning.

Effects of sensitization were studied through individual ratings of perceived intensity during exposures to olfactory and chemosomatosensory stimuli. The hypothesis was that the IEI-group would sensitize to stimuli to a larger degree than controls. Brain activation was studied through functional magnetic resonance imaging (fMRI) during exposure to chemosensory stimuli. Regions of interest (ROI) were selected based on previous studies on fear/anxiety conditioning and on brain activity in functional somatic syndromes (Bishop, 2007; Etkin & Wager,

2007; Hillert et al., 2007; Landgrebe et al., 2008; Lang, Davis, & Ohman, 2000; Orriols et al., 2009; Phelps & LeDoux, 2005; Shin & Liberzon, 2010). Defined ROI:s were amygdala, insula, dPFC, m/vmPFC, rACC, and dACC. The hypothesis were that individuals with IEI compared to controls would show (1) an increased activation in dACC and dPFC (2) an increased or a decreased activation in insula and amygdala (3) a decreased activation in rACC and m/vmPFC.

Materials and Method

Participants

Participants were recruited through advertisement in the local newspaper and through the University hospital of Umeå. The advertisement asked for non-pregnant, right-handed women that either experienced or did not experience discomfort associated with chemicals. A total of 91 individuals were interested of participating in the study. Information from a questionnaire was used to select participants. To be included in the IEI-group individuals had to answer "yes" to the question: "Do you experience discomfort from smelling or pungent substances (that are not restricted to "sick buildings"), e.g. perfume or detergents, that you believe most people are not troubled by?" Participants also had to report having at least two symptoms once a week during the last three months to be included in the IEI-group. Those reported experiencing these difficulties for their whole life were excluded as it invalidates the first IEI criterion (IPCS/WHO, 1996). Fifty-six right-handed, non-pregnant women between 18 to 70 years of age participated in the study. Twenty-six individuals met the IPCS/WHO (1996) criterions and thus constitute the IEI-group. The control group was made up of 30 individuals not meeting the criterions of IEI. Table 1 shows some characteristics of the two groups. No differences in age can be seen. In Table 2 the most common symptoms in the IEI-group are listed.

Table 1
Descriptive Data of IEI and Controls

	IEI (*n*=26)	Controls (*n*=30)
Age, mean	47 (S.D. ±15)	45 (S.D. ±12)
Sought medical care, % (*n*)	42 (11)	0
Received treatment, % (*n*)	30 (7)	0
Threshold test:		
Normosmics, % (*n*)	85 (22)	90 (27)
Hyposmics, % (*n*)	15(4)	10 (3)
Anosmics, % (*n*)	0 (0)	0 (0)

Table 2
Most Common Symptoms Reported by Participants with Idiopathic Environmental Intolerance

Symptoms in % (*n*)	IEI (*n*=26)
Symptoms in airways, mucous membranes and skin	*96 (25)*
Sneezing	54 (14)
Irritation in throat/hoarseness	50 (13)
Nasal obstruction/rheum	46 (12)
Irritation of mucous membrane in nose	42 (11)
Cognitive and affective symptoms	*96 (25)*
Fatigue	62 (16)
Absent-mindedness	38 (10)
Irritation/touchiness	38 (10)
Head-related symptoms	*69 (18)*
Headache	46 (12)

All individuals were given written and spoken information about the study. 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. All participants were given a monetary reward of 400 SEK for their participation. Data were collected during the fall of 2010.

Screening for olfactory deficit and camera training
At a first visit prior to the experiment, the participants were screened for olfactory deficits using a short-version of a clinical threshold test (CCRC; Cain, 1989). The test consisted of butanol (99%, Merck) in plastic bottles with dilution step 6 and 2. Distillated water was used as blank stimuli. Participants that were able to detect step 6 were regarded as having a normal sense of smell (i.e. normosmic) and those detecting only step 2 were regarded as having an impaired sense of smell (i.e. hyposmic). Results from the threshold test indicated no significant difference between the IEI-group and controls (see Table 1). None of the participants were anosmic. At the end of the visit the participants lay in a MR-camera mockup to get familiar with the situation.

Stimuli
To include both olfactory and chemosomatosensory activation (i.e. chemosomatosensory information mediated by the trigeminal nerve) two different stimuli were used. The olfactory stimuli consisted of iso amyl acetate (Merck, 99%), 5mg/m^3. The smell of amyl acetate resembles banana. The chemosomatosensory stimuli consisted of carbon dioxide (CO_2) 13.5% v/v. CO_2 is odorless but evokes a pungent sensation in the nose. Amyl acetate and CO_2 were presented in the nasal cavity with a dynamic olfactometer (OM2s, Burghart

Instruments, Germany), which permits good control of stimulus concentration and duration for presentation of odors. Stimuli were presented through a 5m Teflon hose that ended with a nosepiece in the participants' right nostril. Because of technical difficulties it was impossible to heat or humidify the air, which increases the risk of mechanoreceptor activation in the nose. To prevent this, airflow rate was set to 3l/min.

Study design

All participants answered a questionnaire that assessed amount of symptoms from different organ-systems. The procedure was described to the participants before the experiment began. They were informed that they would be in the camera for about an hour and that they would be exposed to odors that *could* vary in intensity. Before entering the camera, the participants got exposed to the two odors later being used in the experiment. They were told that these were the strongest exposures they would experience. Participants with visual defects got lenses attached to their faces with tape. All participants were provided with headphones, alarm button and olfactometer hose. Two keypads with four buttons each were attached to the clothes of the participants. These were used to rate perceived intensity. The first 16 minutes in the camera were used for structural pictures. Meanwhile the participant listened to the radio.

Stimuli were presented in 20 blocks with stimulus duration of 30s for each block. The order of the stimuli presentation was balanced so that half of the participants started with exposure to amyl acetate and the other half with CO_2. A picture was shown in the beginning and the end of each block, asking the participant to rate the perceived intensity. The scale being used was a level anchored ratio scale ranging from zero to seven (G. Borg & E. Borg, 2001). The stimuli concentration level was kept constant during the whole experiment. Between each block there was a 30s odorless interval during which a visual stimulus (blue circle) where presented. Brain activation during these intervals was regarded as baseline.

fMRI

The fMRI data in this study were collected using a General Electric 3T scanner, with a 32 channel head coil. Functional T2*-weighted images were acquired with an echo planar gradient refocused sequence. The following parameters were used to acquire the functional images: Repetition time, 3000 ms; echo time, 30 ms; flip angle, 80 degrees; voxel size, 2x2x3mm. 56 slices with a thickness of 3 mm were collected. Matrices (128 x 128). Images were exported to an off-line linux workstation and translated to NIfTI format. A preprocessing of the functional images was carried out using SPM8 software (Wellcome Trust Centre for Neuroimaging, London, UK). The preprocessing contained: Slice-timing to correct for time differences between slices, realigning and unwarping to correct for linear and nonlinear movement artifacts, normalizing to the Montreal Neurological Institute (MNI) template, and smoothing using a Gaussian xyz kernel of 4x4x6mm.

Statistical analysis

The fMRI data were analyzed in a two level procedure using SPM8. In the first level analysis boxcar functions were made for olfactory, chemosomatosensory and baseline conditions. The boxcar functions were convolved with the canonical hemodynamic response function (HRF) to form two regressors with natural hemodynamics. In addition, six regressors (for x, y, z, pitch, roll, and yaw) from the movement correction were applied, to capture variance due to movement. After the regression, *t*-contrasts were made for "olfactory-base" and "chemosomatosensory-base" for each subject.

In the second level analysis, the *t*-contrast images of each subject were entered into a 2 X 2 full factorial ANOVA, with the factors group (controls-IEI), which was set to independent and unequal variance, and modality (olfactory-chemosomatosensory), which was set to dependent and equal variance. The contrasts IEI-controls and controls-IEI were performed for both olfactory and chemosomatosensory activation, in total four *t*-contrasts. The analysis was focused on the following ROI; amygdala, insula, dACC, rACC, dPFC and m/vmPFC. ROI definitions were made using Talairach daemon (http://www.talairach.org/daemon.html). Clusters within the ROIs with at least four continuously activated voxels and peak *t*-values of $p<0.005$ uncorrected were considered statistically significant (Straube, Mentzel, & Miltner, 2007). This level was set to minimize the risk of both type I and type II errors. The peak coordinates were translated from MNI to Talairach coordinates using GingerALE (http://brainmap.org/icbm2tal/). Talairach client (http://www.talairach.org/client.html) was used to select peak values located within the ROIs.

Data from intensity ratings were analyzed through mixed model analyses of variance (ANOVA) with the factor (Time) part1, part2, part3 and part4 and (Group) IEI, control as a between-subjects factor. Greenhouse–Geisser correction was applied when $df>1$. In these cases, the uncorrected *df* is reported.

Results

Ratings of perceived intensity

Mean magnitude estimations of amyl acetate and CO_2 for both groups can be seen in Figure 1. Greenhouse-Geisser repeated measure analysis of variance (ANOVA) for perceived intensity with the factor Time (part1, part2, part3 and the last part) was performed. Significant results were found for CO_2 and the factor Time [$F(3.150)=7.398$, p=.001, $\varepsilon=.741$] as a within subjects effect, which indicates habituation to CO_2 in both groups. Group as a between subjects effect were non-significant [amyl acetate $F(1)=1.369$, p=n.s; CO_2 $F(1)=.388$, p=n.s .].

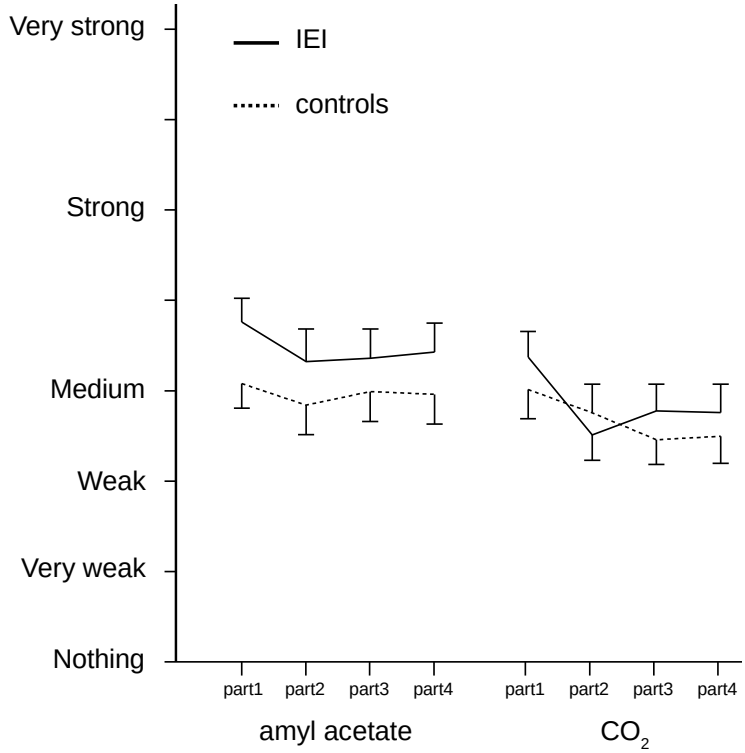

Figure 1. Mean and standard error of perceived intensity during exposure to amyl acetate and CO_2 for the group with idiopathic environmental intolerance (IEI) and for controls.

fMRI

The fMRI results are presented in Table 3. For amyl acetate, decreased activation was seen in the IEI-group in right insula and in left mPFC and vmPFC (see Figure 2). There were no differences in ACC or amygdala. During exposure to CO_2 the IEI-group showed increased activation in left amygdala, right and left insula, right dACC, right rACC, and in dPFC (see Figure 3). Decreased activation was found in mPFC.

Table 3

Significant Differences in Brain Activation Between IEI and Controls

ROI		Amyl acetate						Carbone dioxide					
		x	y	z	*t*-value	k		x	y	z	*t*-value	k	
Amydala	L							-30	-1	-23	2.89	6	↑
Insula	R	30	-2	19	3.08	7	↓	36	9	8	3.06	14	↑
	L							-40	6	4	3.06	16	↑
ACC													
Dorsal	R							2	25	34	3.06	17	↑
PFC													
mPFC	L	-18	40	37	3.30	100	↓	-16	38	37	2.82	5	↓
mPFC	L							-18	35	34	2.78	4	↓
vmPFC	L	-16	51	3	2.93	5	↓						
dPFC	L							-38	21	25	3.04	6	↑

Note. ROI, regions of interest; ACC, anterior cingulate cortex; PFC, prefrontal cortex; mPFC, medial prefrontal cortex; vmPFC, ventromedial prefrontal cortex; dPFC, dorsal prefrontal cortex; L, left; R, right; (x, y, z), Talairach coordinates of maximally activated voxels (activation threshold: p>0.005, minimum of 4 continuously activated voxels); k = numbers of voxels activated in cluster. Down-arrow indicates decreased activation in IEI compared to controls; up-arrow indicates increased activation in IEI compared to controls.

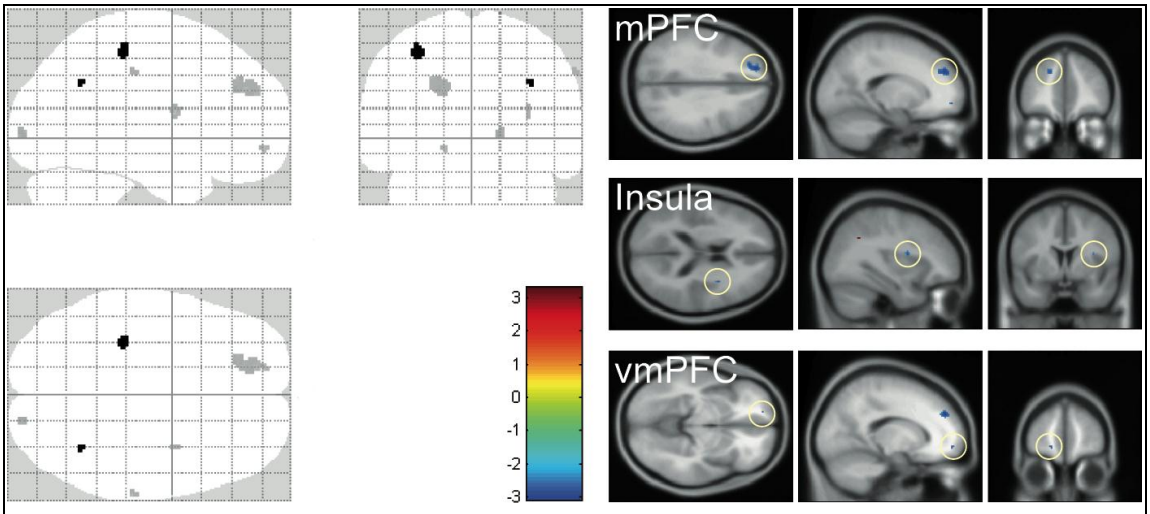

Figure 2. Group comparison between individuals with IEI and controls during exposure to amyl acetate. The color scale indicates z-values. Pictures to the left show all increased (black) and decreased (grey) activations in the IEI group compared to controls. To the right, differences in activation in ROI are marked with a circle. The IEI-group showed less activation in left superior frontal gyrus, insula and ventro-medial prefrontal cortex.

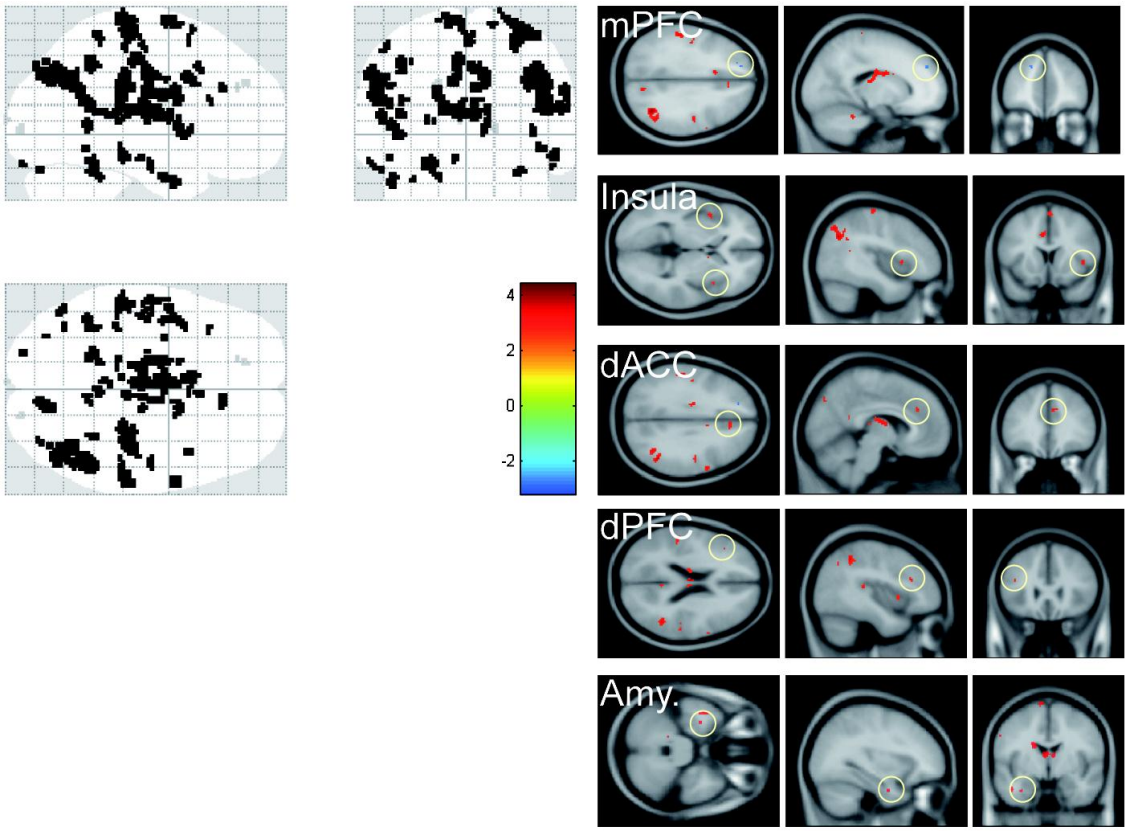

Figure 3. Group comparison between individuals with IEI and controls during exposure to CO_2. The color scale indicates z-values. Pictures to the left show all increased (black) and decreased (grey) activations in the IEI group compared to controls. To the right, differences in activation in ROI are marked with a circle. The IEI-group showed decreased in left superior frontal gyrus. Increased activation in IEI was shown in right and left insula, right dorsal anterior cingulate cortex, left middle frontal gyrus and left amygdala.

Discussion

The purpose of this study was to investigate whether individuals with IEI showed signs of sensitization after repeated exposure to chemosensory stimuli and if they during exposure to chemosensory stimuli showed similar patterns of brain activation as that in anxiety disorder and fear conditioning. The hypothesis was that the IEI-group would sensitize to stimuli to a larger degree than controls and that individuals with IEI compared to controls would show (1) increased activation in dACC and dPFC (2) increased or decreased activation in insula and amygdala (3) decreased activation in m/vmPFC.

The IEI-group did indeed show decreased activation in PFC compared to controls in both conditions. During amyl acetate exposure a decreased activation was also found in insula in the IEI participants. CO_2 exposure was in the IEI-group associated with an increased activation in insula, amygdala, dACC and in dPFC. No difference were seen between IEI and controls in rACC. The pattern of hyper/hypoactivation in the IEI-group during exposure to CO_2 corresponded thus

well with the hypothesis, with rACC as an exception. The results from amyl acetate exposure did only partly correspond with the hypothesis since no differences were seen in amygdala, dACC or rACC.

The increased activation of ACC during CO_2 exposure is in line with prior findings in IEI and other functional somatic syndromes (Hillert et al., 2007; Landgrebe et al., 2008; Orriols et al., 2009). Regarding insula are results from previous studies inconclusive. Earlier brain activation studies of IEI-individuals have found decreased activation in amygdala and insula (Hillert et al., 2007; Orriols et al., 2009). However, Landgrebe and colleagues (2008) found hyperactivation in insula during exposure to sham radiation in electrosensitive subjects. One, possible important, difference between the present study and those made by Hillert et al. (2007) and Orrials et al. (2009) is that they did not include an estimation task during the brain imaging acquisition. Since amygdala and insula have a function both in encoding value and in decision-making, this difference could, at least partly, account for the differences in the results (Pessoa, 2011; Rolls, Grabenhorst, & Parris, 2010).

The hyperactivation of insula and amygdala during exposure to CO_2 is in accordance with research on anxiety and fear. Heightened activation of insula and amygdala is common during negative emotional processing of disorder relevant exposure in most anxiety disorders. These structures are therefore suggested being part of an exaggerated fear circuitry resulting in shared symptoms in anxiety disorders (Etkin & Wager, 2007; Shin & Liberzon, 2010).

Dorsal PFC and dACC are often seen correlating positively with activity in amygdala during exposure to stimuli with high emotional valence (Kim et al., 2004). Dorsal ACC, mPFC and bilaterally anterior/mid insula also activate when individuals are experiencing pain (Critchley, 2005; Etkin, 2010). It is, however, not likely that the differences seen in these areas are attributed to different perception of pain in IEI compared with controls since the CO_2 concentration level was not high enough to evoke pain.

The hypoactivation in mPFC can be understood from the role rACC and mPFC are thought to have in down-regulating limbic hyperactivity (Etkin, 2010). Increased activation of rACC and mPFC is associated with a simultaneous decreased activation in amygdala. Rostral ACC and m/vmPFC is thus regarded as exhibiting a top-down regulation of negative emotional processing and can be thought of as mediators of emotional control (Etkin, Egner, & Kalisch, 2010; Etkin et al., 2006).

In summary, the hyperactivation in amygdala, insula, dACC and dPFC seen in participant with IEI during exposure to CO_2 can be reflecting a hyperresponsive emotional network. The deactivation of mPFC is in line with the notion of this area as having an emotional regulative function. This suggests that participants with IEI failed to down-regulate the emotional network to the same extent as the control group. These results show that chemosensory exposure of individuals with IEI is associated with an activation pattern commonly seen in anxiety and fear.

The pattern of activation in the IEI-group during exposure to CO_2 more specifically resembles that in specific phobia. Several studies have shown increased activation of amygdala, insula, dACC and dPFC during exposure to phobic relevant stimuli (Etkin & Wager, 2007; Shin & Liberzon, 2010). There are also some findings pointing towards deactivation of rACC and mPFC in specific phobia during exposure (e.g. Hermann et al., 2007; Schienle, Schäfer, Hermann, Rohrmann, & Vaitl, 2007) but results are still inconclusive (Shin & Liberzon, 2010). Specific phobia has earlier been proposed as a model of explanation of IEI/MCS (Gugliemli, Cox & Spyker, 1994). The theoretical basis comes from conditioning theory. In a conditioning paradigm, aversion is created when an unconditioned stimulus is associated with discomfort and the person start avoiding the stimulus, which reinforces the connection between the stimulus and the discomfort (Gugliemli, et al., 1994; Overmier, 2002). A difference between fear conditioning and specific phobia is that far from all phobias can be explained by a traumatic event leading to fear and avoidance of stimuli associated with the event (Mineka & Oehlberg, 2008). In that aspect, IEI resembles specific phobia since a specific event or exposure often cannot be recalled (Fiedler & Kipen, 1997).

Both specific phobia and IEI are associated with a distinct trigger (i.e. phobic stimulus/odor) that people normally do not react to in the same way as those with phobia or IEI (American Psychiatric Association (APA), 2000). The responses to the stimulus associated with discomfort are on the other hand quite different in these two groups. Individuals with phobia react with anxiety and fear whereas individuals with IEI describe a range of symptoms of which some are associated with cognitive or affective reactions and other with airways, skin, mucous membranes etc. (Bornschein et al., 2002; APA, 2000). Since the main complaints of IEI-individuals are not anxiety or fear it seems far-fetched to describe IEI as a specific phobia. A phobic model can however be of use to understand some of the characteristics of IEI. In IEI, a progressively smaller amounts of chemosensory stimuli tends to elicit symptoms and the number of substances associated with symptoms often increase over time. Symptoms also show great variety with no consistent pattern and substances associated with symptoms are often chemically unrelated (Fiedler & Kipen, 1997; Nethercott, Davidoff, Curbow, & Abbey, 1993).

A phobic model might also be proven useful to the understanding of other so-called functional somatic syndromes. The treatment approach of several of these syndromes is already encompassing a psychological view. In chronic pain have biopsychosocial models and psychological research rendered an insight into the role of behavioral, emotional and cognitive factors that perpetuate the condition (Kerns, Sellinger, & Goodin, 2011). For example, cognitive and behavioral therapy has been proven an effective treatment of lower back pain (van Tulder et al., 2001). A similar model underlies treatment with CBT in fibromyalgia (Glombiewski et al., 2010). Increased knowledge of brain activation patterns and understanding of the relationship between negative emotional processing, avoidant behavior and symptoms could contribute to the understanding of these syndromes.

Increased understanding of brain activity associated with IEI can give rise to new treatment initiatives. The findings in the present study implicates that avoidance could be contra-productive since avoidance strengthens the connection between stimuli and the symptoms. Avoidance of chemicals also tends to circumscribe the affected individuals' life. Using specific phobia as a model, an alternative approach would be careful exposure-treatment. It is important that the treatment is based on respect for the experiences of the affected individual. The usage of exposure treatment and other cognitive-behavioral therapy methods does not implicate that IEI has a "psychological" origin. Instead, IEI should be regarded as a consequence of a complicated interplay between the peripheral and the central nervous system.

During exposure to amyl acetate the IEI group showed decreased activation in insula, vmPFC and mPFC. The reason for the difference in pattern of brain activation between the two conditions is unclear. It could be that the concentration level of amyl acetate was too low to evoke a similar reaction as to CO_2. Also, amyl acetate is not a stimulus commonly associated with symptoms in IEI so perhaps results would be different with an olfactory stimulus more closely connected with IEI. On the other hand, it is also possible that individuals with IEI have different patterns of brain activation during olfactory and chemosomatosensory stimuli compared with controls, but this is a question for future research to answer.

The ratings of perceived intensity done by the participants during exposure indicated that no sensitization took place. The IEI-group and the controls habituated to the same extent to CO_2 whilst no habituation effect was seen after exposure to amyl acetate. These results are not in line with previously research using magnitude estimations of perceived intensity (Andersson et al., 2009; Dalton, 1999; Kobayashi et al., 2008). Dalton (1999) and Kobayashi et al. (2008) discovered that participants rated odors as more intense if they were given a negative description of the odor (as harmful or hazardous) instead of a neutral or positive description (neutral or healthy). Andersson and colleagues (2009) found sensitization effects in participants with chemical sensitivity compared to healthy controls.

The absence of sensitization effects in the present study might be explained by the study design and/or the choice of stimuli. In previous studies, the duration of the experiment has been longer (Andersson et al., 2009; Dalton, 1999; Kobayashi et al., 2008) For example, Anderson et al (2009) presented three different stimuli in four blocks, each of 20 minutes. The duration of a single stimuli exposure was 200ms and each stimuli was presented 18x4 times. That is, shorter exposures several times during a longer period compared to present study. This notion is in line with a conclusion drawn by Kobyashi et al (2008). They found that several short-duration exposures to odors over a longer period of time lead to a difference in intensity ratings of odors labeled hazardous or healthy whereas one long exposure did not (Kobayashi et al., 2008). An experiment with longer duration was not possible in this study because of the inconvenience of being in an MR-camera for longer periods of time.

Another possible explanation of the results is that the stimuli being used were not perceived as disturbing by the participants. Those suffering from IEI report a range of chemicals associated with symptoms and it is possible that amyl acetate and CO_2 are not one of those. Amyl acetate is a rather agreeable odor and although CO_2 is pungent it was here presented in a low level of concentration. Hillert et al. (2007) used six different odorants in their study of brain activation in individuals with chemical sensitivity. Others have used individual triggers (e.g. Orriols, 2009). Anderson et al (2009), who used CO_2 and amyl acetate to study sensitization effect, used a higher concentration level of the stimuli compared to the present study.

That exposure to CO_2 in the IEI-group was associated with brain activity in a neural circuitry associated with negative emotional processing implies that IEI subjects experience the stimulus different compared with controls. Therefore, it would have been expected that the ratings of intensity were higher in IEI than in the control group for CO_2. There are several explanations for the lack of differences in ratings. The magnitude estimation scale being used, a level anchored ratio scale (G. Borg & E. Borg, 2001), has eight steps, which could be too few to capture a difference in perceived intensity. Anderson et al (2009) used a more flexible measure for perceived intensities when they found sensitization effects. Their participants compared the chemosensory stimulus with an auditory tone with a perceived intensity of 100. This was not feasible in the present study because of the sound from the fMRI apparatus. It could also be that perceived intensity and activation of these brain regions do not correlated during chemosensory exposure. That the result from the brain imaging data and the behavioral data did not correlate is a weakness in the results of the study and something that needs further elaboration in future research.

A limitation of the present study is that the stimuli being used were not selected to represent chemicals known to be associated with symptoms in the participants.. This should not matter for the selection of chemosomatosensory stimulus since it is odorless. Regarding the olfactory condition, a better match between choice of stimulus and odors perceived as troubling could be of importance. For example, Hillert and colleagues (2007) used odors like cedar oil and butanol that are reported frequently trigger distress in IEI/MCS individuals. Another limitation is that little information was collected about the behavioral consequences of IEI. This would have been interesting in the context of specific phobia. This information should be included in future research. A related question for future research is how avoidance contributes to the development and maintenance of IEI. Also, research on treatment of IEI is much needed.

Conclusions

The present study revealed neural correlates of emotional processing in IEI. During exposure to CO_2 increased activation was found in amygdala, insula, dACC and dPFC of the IEI-group compared with healthy controls. In mPFC decreased activation was found. The observed pattern of activation was suggested to reflect negative emotional processing in individuals with IEI. A connection was made

between the pattern of brain activation in IEI and that of specific phobia. Furthermore, specific phobia was proposed as a model for understanding the development and maintenance of IEI. The findings might have impact on treatment of affected individuals.

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