Structural brain deviations in chemical intolerance:

A voxel-based morphometry study

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Chemical intolerance (CI) is a term that refers to an affliction where a normally harmless smell could give reactions similar to those of allergy. There is no strong physiological evidence explaining this phenomenon and therefore renders the affliction medically unexplained. Furthermore, there is symptomatic overlap between somatoform disorders, depression and medically unexplained symptoms such as chronic fatigue syndrome, fibromyalgia and various definitions of CI. Functional and structural magnetic imaging has demonstrated metabolic, and gray matter density deviations in individuals experiencing these symptoms. Such differences have been found in several similarly unexplained medical conditions like, for example, fibromyalgia and chronic fatigue syndrome. This is an explorative study applying voxel-based morphometry on MR pictures from a CI (n=26) and a healthy control (n=31) group in order to investigate possible regional brain structure deviations in the CI group. The participants are all women aged 18 to 70 years. The results indicate significant gray-matter reduction in hippocampus, caudate and 13 other areas, which provides physiological evidence for long term stress as a contributor to the etiology of the affliction.

Kemisk intollerans (på engelska: "Chemical intolerance", förkortat "CI") är ett begrepp som refererar till en åkomma där en vanligtvis harmlös lukt kan utlösa reaktioner som liknar de i allergi. Det finns inga starka fysiologiska evidens som förklarar detta fenomen och därför anses det vara ett medicinskt oförklarat tillstånd. Utöver detta finns det ett symptomatiskt överlapp mellan somatoforma sjukdomar, depression, fibromyalgi och ett antal definitioner av kemisk intollerans. Funktionella och strukturella magnetiska resonansavbildningar har påvisat avvikelser i metabolism och densitet av grå substans i individer som lider av dessa symptom. Sådana skillnader har hittats i ett antal medicinskt oförklarade åkommor, som t.ex. fibromyalgi och kronisk trötthetssyndrom. Detta är en explorativ studie som tillämpar voxel-baserad morfometri på MR bilder från en kemiskt intolerant (n=26) och frisk kontroll (n=31) grupp för att upptäcka möjliga morfologiska hjärnavvikelser i den kemiskt intoleranta gruppen. Alla deltagare var kvinnor i åldern 18 till 70 år. Resultaten påvisar en signifikant minskning av grå substans i hippocampus, caudatus och 13 andra områden, vilket ger evidens för långtidsstress som en faktor i åkommans uppkomst.
Chemical intolerance (CI) denotes an affliction where an individual experiences various forms of symptoms upon exposure to a usually typical and common smell. The list of reactions induced by smells is extensive; drying paint, smoke, car exhaust and nail polish are some examples. Different individuals exposed to a particular smell may also display a variety of different, apparently unrelated symptoms, with the exposure of the smell being the only common denominator. Some of the symptoms include dizziness, headache, eye irritation, cough and fatigue. Broadly speaking, there are two types of chemical intolerance; clinical and a milder, “general” CI. While the clinical definition is a more extreme form of intolerance (which impedes everyday life), they both utilize self-reports for diagnostic purposes. However, mechanisms behind these reactions are not well understood, neither whether it is the chemicals that cause the symptoms. Furthermore, toxicological dose-response relationships do not seen to describe and predict the symptoms. A few theories have been proposed, such as neural sensitization, neurogenic inflammation and conditioning (Andersson, 2012). The uncertainty regarding underlying mechanisms has been a contributor to a diversity of CI definitions; multiple chemical sensitivity (MCS), idiopathic environmental intolerance (IEI) and sensory hyperreactivity (SHR, standing for “sensorisk hyperreaktivitet” in Swedish). While IEI and MCS are sometimes used interchangeably, MCS emphasizes that a chemical must be the cause of the reaction (Dantoft, Andersson, Nordin, & Skovbjerg, 2015).

Somatization, somatoform disorder (SFD) and functional somatic symptoms are a few terms that has been used interchangeably to refer to medically unexplained conditions (Wessely, Nimnuan & Sharpe, 1999). Gulf war syndrome (GFS), chronic fatigue syndrome (CFS), fibromyalgia (FM), irritable bowel syndrome (IBS) and MCS could be categorized as SFDs. There exists a substantial overlap between the different functional somatic disorders and other medically unexplained conditions including the various definitions of CI (Bell, Baldwin, & Schwartz, 1998; Aaron & Buchwald, 2001; Wessely et al., 1999). Bell and her colleagues also presented evidence that CI populations had higher family histories of depression diagnoses and displayed a general comorbidity between depression and SFDs. The symptoms of CI and other somatoform disorders are also general in nature, making it difficult to disentangle categorize them accordingly. Nimnuan, Rabe-Hesketh, Wessely and Hotopf (2001) found extensive overlap between the symptoms and suggested clustering them under one label. However, they pointed out that different sources had varying stringency of symptom definitions and some functional somatic symptoms lack any criteria at all. In an extensive review, Aaron and Buchwald (2001) demonstrated that there could be up to 70% of patients with FM who also met the criteria for CFS, and similarly vise versa. Wessely et al. (1999) presented similar evidence, furthermore proposing the idea that “...the existence of specific
somatic syndromes is largely an artifact of medical specialization.” Palmquist, Claeson, Neely, Stenberg and Nordin (2014) showed a significant symptom overlap between different types of environmental intolerance, and further advocating the idea of a connection with somatic stress disorders. Bailer, Witthöft, Paul, Bayerl and Rist (2005) provided evidence that IEI (or MCS, which was used interchangeably in that study) is a subset of a somatoform disorder. Whether CI is a subset of a SFD or a part of a continuum is still, however, not definitive. Given this extensive overlap between somatoform disorders and CI, exploring any potential morphological brain deviations of CI individuals and overlapping conditions could shed more light on the affliction and its etiology.

Various functional magnetic resonance imaging (fMRI) and single photon emission computed tomography studies have shown metabolic differences in FM, CFS and similar somatoform groups (Browning, Fletcher, & Sharpe, 2011). Moreover, a decrease in gray-matter density for the same populations have been demonstrated using structural brain imaging. Browning et al. (2011) presented such findings in a review, while categorizing individuals according to reported primary symptoms, as opposed to diagnosis. The reported results showed consistent increase of activity in anterior cingulate cortex and insula, upon presented painful stimuli to the clinical groups. They continued by presenting evidence that activations in these areas correlate with subjective experience of pain. However, as with the overlap of symptoms in the various somatic disorders, the authors pointed out the weak reliability of the functional and structural imaging studies which had significant methodological differences that should accounted for.

De Lange et al. (2005) used voxel-based morphometry (VBM) on structural images from two cohorts of CFS and control populations showing a significant gray-matter reduction in the CFS cohorts. Moreover, a positive correlation between gray-matter volume and physical activity could be seen. Schmidt-Wilcke et al. (2007) conducted a VBM study on FM patients and found decreased gray-matter density in the right superior temporal gyrus and left posterior thalamus in the clinical group. Furthermore, an increase of gray matter density was found in left orbitofrontal cortex, left cerebellum and both right and left striatum. A similar volumetric MRI study was conducted by Atmaca, Sırlıer, Yıldırım and Kayali (2011) who discovered significant left and right amygdala reductions in somatic disorder patients but no difference in total gray matter volume between the groups. Unlike an automated VBM study, Atmaca and colleagues used a manual tracing method to delineate different structures of the brain. The authors also pointed out a few weaknesses in their study such as a small total sample size (n=40) and possible selection bias. In discussing the plasticity properties of hippocampus and its response chronic stress, McEwen, (2001) mentions the possibility of its
involvement in CI “...particularly those aspects that may result from stress and trauma and result in manifestations of chronic pain.” while reviewing evidence for hippocampal involvement in pain processing. It is widely known that depression and PTSD are linked to hippocampal atrophy (Videbech & Ravnikilde, 2015; Karl et al., 2006) and that this atrophy is caused by high levels of stress hormone, such as cortisol (McEwen, 2001). Furthermore, hippocampus plays an important inhibitory role of the hypothalamic-pituitary-adrenal (HPA) axis (Jacobson & Sapolsky, 1991) and that hyperactivity of HPA axis is one of the most consistent findings associated with major depression (Pariante & Lightman, 2008). However, a lot of research is to be done on structural differences of SFDs and the involvement of HPA axis. Rief and Barsky (2005) present evidence for ambiguous HPA axis function in SFDs, but agree that hippocampus and other areas could be relevant structures. Hakala et al. (2004) found increased caudate nuclei in women with somatization disorder, but no clear or definitive conclusions could be made.

Currently, there exists no study looking for anatomical differences in CI groups compared to controls. Given the empirical evidence for anatomical and metabolic differences and a recurrent discussion of HPA axis in FM, CFS, GWS, depression and other somatoform groups, a case could be made for the expectations of finding similar deviations in CI groups as compared to controls.

Method

Participants
The brain MR images were adopted from a study by Andersson, Claeson, Nyberg, Stenberg and Nordin (2014) conducted in 2011. All participants were recruited from advertisement in a local newspaper, which yielded 91 participants before screening. Participants were assigned to the IEI group if they fulfilled the following criteria: (1) an affirmative answer to the question “do you experience discomfort from odorous or pungent substances (that are not restricted to “sick buildings”), e.g. perfume or detergents, that you believe most people are not troubled by?"; (2) reporting having at least two symptoms once a week during the last three months that were attributed to chemical exposure; and (3) reporting not having had these problems their whole life (i.e. having acquired the problems). The participants’ sensitivity was assessed with the Chemical Sensitivity Scale (CSS) (Nordin et al., 2004). Participants who did not fulfill the IEI criteria were assigned to the control group. Two participants had to be excluded from this study because of missing or corrupted data, and one participant withdrew during testing. As presented in Table 1, there was no significant age difference between the groups, but a significant difference in CSS scores. The analysis in this study were thus based on a
IEI group of 26 participants and a control group of 31 participants. All participants were female. The participants were given written and spoken information about the study. The study was conducted in accordance with the Helsinki Declaration and approved by the Umeå Regional Ethics Board (09–172 M). A signed informed consent was obtained from each participant. All participants were given 400 SEK (~ 40 EUR) for their participation.

Table 1. Demographic overview of the control group and the IEI group, and results from test of group differences based on t-tests.

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>IEI group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants</td>
<td>31</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Age, range</td>
<td>18 - 65</td>
<td>19 - 70</td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>45 (12)</td>
<td>47 (15)</td>
<td>Ns</td>
</tr>
<tr>
<td>CSS score, mean (SD)</td>
<td>53 (16)</td>
<td>75 (13)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Scanner equipment
Image data were collected using a General Electric 3T scanner with a 32 channel head coil. High-resolution T1-weighted structural images were collected with a 3D fast spoiled gradient echo sequence (180 slices with a 1 mm thickness, TR 8.2 ms, TE 3.2 ms, flip angle 12°, field of view 25 × 25 cm). Images were exported to an off-line UNIX workstation and translated to NIfTI format.

Protocol & analysis
Voxel-based morphometry (VBM) is an operator independent method that allows investigation of volumetric or concentrational differences in gray or white matter between two groups, while accounting for different brain sizes. The method was implemented in MATLAB SPM12 module. Pre-processing of the images consisted of spatial normalization, segmentation and spatial smoothing (8mm FWHM) using a Gaussian kernel. General linear model was used for statistical analysis. The subsequent significance test was performed with t-tests (α =0.001), resulting in a statistical parametric map (SPM). A threshold of 0.1 was used to avoid edge effects, which means that all voxels below this value were excluded. Threshold masking was set to 15 with a voxel size of 1.5 x 1.5 x 1.5 mm. The difference of age between the groups was not significant which led us not to expect total brain size/volume to differ between the groups. Hence, we did not perform modulation during the pre-processing step and looked for relative voxel concentration as opposed to absolute brain volume differences.
Results

Significant reductions in gray matter density was detected in 15 areas in the IEI group as compared to the control group. These areas include the paracentral lobule, inferior parietal lobe, postcentral gyrus, hippocampus, middle temporal gyrus, middle occipital lobe, cerebellum, middle cingulate gyrus, caudate, fusiform gyrus, and supramarginal gyrus. No increased gray matter density was detected in the IEI group. Figure 1 displays the affected areas along with contrast estimates between the groups. Table 2 shows the MNI coordinates of the peak contrast for each area along with corresponding T-values.

### Table 2. Areas with significant \((p<0.001)\) reductions in grey matter density (control - IEI), MNI coordinates of peak contrast and \(T\)-values.

<table>
<thead>
<tr>
<th>Area no.</th>
<th>Brain area*</th>
<th>MNI peak coordinates</th>
<th>(T)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Paracentral Lobule R</td>
<td>13.5 -31.5 54</td>
<td>4.50</td>
</tr>
<tr>
<td>2</td>
<td>Inferior Parietal Lobe R / Postcentral Gyrus R</td>
<td>36 -37.5 49.5</td>
<td>4.43</td>
</tr>
<tr>
<td>3</td>
<td>Hippocampus R</td>
<td>30 -40.5 1.5</td>
<td>3.88</td>
</tr>
<tr>
<td>4</td>
<td>Postcentral Gyrus R</td>
<td>67.5 -6 28.5</td>
<td>3.82</td>
</tr>
<tr>
<td>5</td>
<td>Middle Temporal Gyrus L</td>
<td>-45 -43.5 9</td>
<td>3.80</td>
</tr>
<tr>
<td>6</td>
<td>Middle Occipital Lobe L</td>
<td>-49.5 -76.5 13.5</td>
<td>3.57</td>
</tr>
<tr>
<td>7</td>
<td>Cerebellum Lobule 8 L</td>
<td>19.5 -64.5 -60</td>
<td>3.57</td>
</tr>
<tr>
<td>8</td>
<td>Postcentral Gyrus L</td>
<td>-21 -30 76.5</td>
<td>3.48</td>
</tr>
<tr>
<td>9</td>
<td>Middle Cingulate Gyrus R</td>
<td>19.5 -34.5 39</td>
<td>3.47</td>
</tr>
<tr>
<td>10</td>
<td>Caudate L</td>
<td>-15 16.5 18</td>
<td>3.46</td>
</tr>
<tr>
<td>11</td>
<td>Caudate R</td>
<td>15 22.5 13.5</td>
<td>3.45</td>
</tr>
<tr>
<td>12</td>
<td>Fusiform Gyrus R</td>
<td>33 -58.5 -10.5</td>
<td>3.43</td>
</tr>
<tr>
<td>13</td>
<td>SupraMarginal Gyrus L</td>
<td>-66 -31.5 37.5</td>
<td>3.39</td>
</tr>
<tr>
<td>14</td>
<td>Middle Cingulate Gyrus L</td>
<td>-13.5 16.5 34.5</td>
<td>3.38</td>
</tr>
<tr>
<td>15</td>
<td>Paracentral Lobule L</td>
<td>-9 -39 73.5</td>
<td>3.31</td>
</tr>
</tbody>
</table>

*R = right hemisphere. L = left hemisphere.

### Discussion

The reason behind the initiation of this study was to explore potential structural brain differences in individuals with and without CI, given the existing evidence for an overlap between CI and other somatoform disorders. This overlap is also followed by existing evidence that these disorders are accompanied by structural and metabolic brain deviances. Results from this study indicated that the CI group had, interestingly, significant gray-matter reduction in right hippocampal and bilateral caudate areas. It could be speculated that atrophy of the IEI group is
caused by high levels of cortisol. The findings in this study support the notion that CI is related to stress or that symptoms caused in CI, MCI and IEI could be reactions to low levels of chemicals induced and/or amplified by stress. The comorbidity between depression, stress and CI also receives empirical support because of previously mentioned hippocampal inhibitory function on cortisol production, or more specifically its inhibitory function on the HPA axis (Jacobson & Sapolsky, 1991). Pall, (2001) suggests models of high nitric oxide/peroxynitrite (such as oxidative stress) induced externally and internally to be the common etiology of PTSD, CFS, FM and MCS. However, other theories such as CI being a misdiagnose, a purely social or cultural phenomena are not mutually excluded as they certainly work as contributing factors. However, this serves as a “narrowing down” of the physiological mechanisms of the affliction. To what extension cultural conditioning affects the perception of the affliction is yet to be explored.

As mentioned previously, Bailer and colleagues (2005) found that a group fulfilling both IEI and SFD criteria had a higher prevalence of depression than the other groups individually while Bell et al. (1998) showed that CI populations had more prevalent family histories of depression diagnoses and displayed a general comorbidity between depression and SFDs. This study further support the notion that SFDs, including depression might share similar, if not the same (and/or coinciding) etiological mechanism. Schweinhardt et al. (2008) discusses the comorbidity between FM and depression, presents empirical evidence for alterations in CNS and suggests that FM and other similar stress-related disorders are connected to a dysfunctional HPA axis. Furthermore, they emphasize that it “…substantiates the notion that stress is related to the development of fibromyalgia”. The question can be evoked as to whether hippocampal atrophy precedes or is a consequence of various disorders. In a VBM study performed on CFS groups, De Lange et al. (2005) concluded that “These findings suggest that the central nervous system plays a crucial role in the etiology of CFS”. The same conclusions regarding CI could be drawn here.

Limitations

Some limitations of this study ought to be discussed: the groups were assigned purely on participant’s subjective criteria (i.e. symptoms, no physical or any other objective examination was performed as a basis of group assignment). After all, CI is as if yet an unexplained medical condition and better criteria of what constitutes forms of CI is yet to be developed.

Voxel based morphometry measures voxel-vise intensity of different areas between groups by accounting for volumetric differences. In order to make this comparison possible, all images have to be aligned to the same stereotactic space.
This procedure distorts the original images by “inflating” or “deflating” different areas of the brain and in doing so non-existent brain-matter is introduced and/or existing matter is removed. Controlling for total intracranial volume (TIV) results in absolute volumetric differences between the groups at the end of the analysis. However, if TIV is not expected to differ between the groups, gray-matter density is measured instead. Gray-matter density is not to be confused with the actual cellular density or cell architecture. “Gray-matter” is the received signal, measured by the scanner, represented and mapped in voxels after pre-processing. Generally, each tissue type has different physiological properties and will produce different MR signals. Whether these areas show higher intensity because of actual higher neuron density or different tissue attributes (or any combination thereof) is not known.

Conclusions
This was the first study to explore structural brain differences in CI individuals. Results found in this study further corroborate the possibility of prolonged stress (i.e. increased glucocorticoids damaging the hippocampus) and CNS is related to the etiology of CI, but further research needs to be done in order to pin-point the underlying mechanisms.

References


