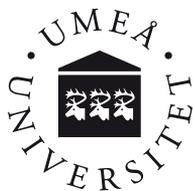


Sick of Smells

Empirical Findings and a Theoretical Framework for Chemical Intolerance

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Linus Andersson
Umeå, 2011-12-02

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Abstract

Chemical intolerance (CI) is a term that refers to the surprisingly common phenomenon of persons getting ill from everyday chemicals. Although seemingly similar to asthma and allergies, CI sufferers do not react to exposures with increased histamine release. CI neither conforms to toxicological dose-response relationships as sufferers react to very low concentrations of chemicals assumed to be harmless. In addition, no particular chemical can be tied to any particular set of symptoms as in the case of other kinds of toxic injuries. The two overarching goals of this thesis were to empirically investigate important hypotheses regarding CI, and to develop a theoretical framework that integrates previous theories of CI into a coherent whole.

There are four empirical studies in this thesis. Utilizing event-related potentials (ERPs), magnitude estimations of perceived intensity, detection tests and functional magnetic resonance imaging (fMRI), the studies provided support for the following hypotheses: (1) persons with self-reported CI sensitize to olfactory and chemosomatosensory stimuli, whereas non-intolerant individuals habituate; (2) sensitization in CI is similar in terms of brain activation patterns to both non-clinical sensitization and other unexplained illnesses such as fibromyalgia; (3) persons with CI have an attention bias to chemical exposures, reflected by problems with withdrawing attention from such stimuli; (4) measures of peripheral hyperreactivity are correlated with chemosensory ERP measures; but failed to corroborate (5) the reactions of women resemble those found in persons with CI to a greater degree than the case in men.

Three major theories of CI are also discussed. The neural sensitization theory describes CI as pathological and non-immunological increases in neural responsiveness. The conditioning theory describes CI as the result of basic associative learning mechanisms. The neurogenic inflammation theory describes CI as proliferation of sensory c-fibers and inflammatory responses carried to several parts of the body through axon reflexes and release of inflammatory mediators. The main point of the theoretical synthesis is that the theories offer different and complementary perspectives on CI, rather than presenting conflicting ontologies. With an integrated perspective, infected debates whether CI is a psychological or organic illness can hopefully be avoided.

Finally, the unexplained characteristics of CI, the empirical findings and the theoretical accounts are described within the theoretical framework of signal detection theory. Several features of CI, e.g. sensitization and peripheral hyperreactivity, are described in terms of applying a low criterion (β).

List of abbreviations

CATS	Cognitive activation theory of stress
CI	Chemical intolerance
CNS	Central nervous system
CR	Conditioned response
CS	Conditioned stimulus
CSS-SHR	Chemical Sensitivity Scale for Sensory Hyperreactivity
EEG	Electroencephalography
ERPS	Event-related potentials
fMRI	Functional magnetic resonance imaging
IEI	Idiopathic environmental intolerance
MCS	Multiple chemical sensitivity
NA	Negative affectivity
NK-1R	Neurokinin-1 receptor
PTSD	Post-traumatic stress disorder
rACC	Rostral anterior cingulate cortex
rCBF	Regional cerebral blood flow
SBS	Sick building syndrome
SHR	Sensory hyperreactivity
SP	Substance P
UR	Unconditioned response
US	Unconditioned stimulus

List of papers

1. Andersson, L., Bende, M., Millqvist, E., & Nordin, S. (2009). Attention bias and sensitization in chemical sensitivity. *Journal of Psychosomatic Research*, *66*, 407-416. doi:10.1016/j.jpsychores.2008.11.005
2. Andersson, L., Nordin, S., Millqvist, E., & Bende, M. (2009). On the relation between capsaicin sensitivity and responsiveness to CO₂: detection sensitivity and event-related brain potentials. *International Archives of Occupational and Environmental Health*, *82*, 285-290. doi:10.1007/s00420-008-0333-1
3. Andersson, L., Lundberg, C., Åström, J., & Nordin, S. (2010). Chemosensory attention, habituation and detection in women and men. *International Journal of Psychophysiology*, *79*, 316-322. doi:10.1016/j.ijpsycho.2010.11.008
4. Andersson, L., Claesson, A-S., Nyberg, L., Nordin, S. (2012). *An fMRI study of sensitization in chemical intolerance*. Manuscript in preparation.

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Sammanfattning

Kemisk intolerans, det vill säga att få symtom av vardagliga lukter, är ett förvånansvärt vanligt problem. Trots att åkomsten i många avseenden liknar astma och allergi, reagerar de drabbade inte med exempelvis ökad histaminfrisättning. Kemisk intolerans överensstämmer inte heller med toxikologiska dos-responsförhållanden, eftersom de drabbade blir sjuka av väldigt låga koncentrationer av luktämnen. Enskilda kemikalier kan inte kopplas till en karaktäristisk symtombild, vilket är vanligt vid andra typer av toxikologiska skador. I denna avhandling har jag två mål. För det första undersöker jag viktiga hypoteser om kemisk intolerans. För det andra erbjuder jag ett teoretiskt ramverk där jag integrerar tidigare teorier om kemisk intolerans till en sammanhängande helhet.

Den empiriska delen av avhandlingen består av fyra forskningsstudier. Baserat på händelserelaterade hjärnpotentialer (ERPs), magnitudestimationer av upplevd styrka, detektionstest samt funktionell magnetresonansavbildning (fMRI) stöder studierna följande hypoteser: (1) personer med självrapporterad kemisk intolerans sensitiserar till olfaktoriska och kemosomatosensoriska stimuli, medan icke-intoleranta individer habituerar; (2) med avseende på hjärnaktiveringsmönster liknar sensitisering hos kemiskt intoleranta det mönster man finner både i icke-klinisk sensitisering och i exempelvis fibromyalgi; (3) personer med kemisk intolerans har en benägenhet att uppmärksamma kemisk exponering, vilket reflekteras i en oförmåga att ignorera sådana stimuli; (4) mått på perifer hyperaktivitet korrelerar med kemosensoriska ERP-mått. Hypotesen att (5) kvinnors reaktioner på kemosensoriska stimuli liknar de man kan finna hos de kemiskt intoleranta i större utsträckning än vad fallet är för män, stöds däremot inte.

Tre teorier om kemisk intolerans diskuteras. Den neurala sensitiseringsteorin beskriver intoleransen som en patologisk ökning av neural aktivitet. Betingningsteorin beskriver kemisk intolerans som ett resultat av grundläggande associativa inlägningsmekanismer. Slutligen beskriver teorin om neurogen inflammation intoleransen som en förhöjd aktivering av c-fiberaktivitet och ökade inflammatoriska processer. Huvudargumentet i den teoretiska sammanfattningen är att dessa teorier erbjuder komplementära perspektiv på kemisk intolerans. Med ett integrerat perspektiv kan förhoppningsvis infekterade debatter om huruvida kemisk intolerans är en psykologisk eller organisk åkomma undvikas.

De oförklarade egenskaperna av kemisk intolerans, de empiriska fynden, samt de teoretiska förklaringarna beskrivs slutligen inom ett teoretiskt ramverk som utgår från signaldetektionsteorin. Flera egenskaper hos kemisk intolerans beskrivs i termer av ett förändrat eller lågt satt kriterium (β).

Introduction

*My dear friend, you know I can't bear any perfume...
the last time you were so good as to come and see me...*

*I was obliged to take the chair you sat in
and keep it out in the courtyard for three days.*

— Marcel Proust (1871 – 1922)

Chemical intolerance (CI) is an illness of unknown cause, characterized by severe reactions to everyday odorous compounds. A person who gets headache and nausea from passing the perfume counter at the local mall may be described as having CI. The label can also be applied to someone who avoids smokers by passing over to the other side of the street, to someone who feels suffocated by the after-shave used by the colleague next door or to the person who is forced to live at the outskirts of society as even the slightest whiff of an airborne chemical triggers a multitude of debilitating symptoms. Estimations suggest that CI is surprisingly prevalent, even when constraining the definitions to only the most severe cases. CI thus seems to constitute a major public health problem.

There are two overarching goals of this thesis. The first is to empirically investigate hypotheses about assumed mechanisms behind CI. The second is to provide a theoretical synthesis that integrates previous theories of CI into a coherent whole. Although theoretical consensus is not a goal in itself, I will argue that CI researchers from different disciplines have complementary perspectives rather than conflicting ontologies.

Three perplexing characteristics of CI

CI constitutes a medical unexplained symptom, a label defined as “physical symptoms that prompt the sufferer to seek health care but remain unexplained after an appropriate medical evaluation” (Richardson & Engel, 2004). The reason for categorizing CI into this domain is its following three characteristic features:

1. No identified dose-response relationship

CI symptoms seem to be triggered by very low concentrations of odorants or chemicals. A fundamental principle of toxicology, i.e. the study of adverse effects of chem-

icals on living organisms, is captured by the phrase “the dose makes the poison”¹ coined by the Swiss Renaissance man Paracelsus. In essence, a high enough dose of any substance will be hazardous to an organism. This also implies that very low doses of any kind of chemicals seldom are toxic. In the case of CI, affected individuals develop severe symptoms from chemical exposure far below toxic levels (Sorg, 1999). The toxicological model of dose-response relationships state that chemicals only affect an organism if above a certain concentration, i.e. its threshold dose. The exposures that lead to symptoms in CI are generally below this threshold dose.

2. No characteristic symptom patterns

A toxic injury ordinarily involves a characteristic pattern of symptoms. In CI, there is no clear relationship between the exposure and the symptoms. Being exposed to *Eau de Cologne* may cause dizziness and nausea in one person but breathing difficulties in another (Sorg, 1999). Hence, it is impossible to tie one particular chemical exposure to a particular set of symptoms. Closely related to the non-specificity of symptoms is the so called “spreading phenomenon”. The label refers to the common feature of CI that the number of chemicals that elicit symptoms increase over time (Winder, 2002). At an initial stage, persons with CI often report a few symptom-eliciting odorants, whereas more severe cases seem to react to a large number of chemicals with diverse molecular structures.

3. No physiological markers

Persons who suffer from CI generally do not show any deviations in standard medical assessment. For instance, persons with CI do not react to the exposures with increased histamine release such as in the case of allergies. No other immunological markers have yet been found to deviate from those of healthy controls (Labarge & McCaffrey, 2000).

Because of these three features, it is debated whether CI constitutes a discrete disorder or an expression of a general dysfunction that also underlies other medically unexplained symptoms (Binder & Campbell, 2004; Richardson & Engel, 2004). Regardless of which, CI is a label that does not (yet) fulfill the criteria for being called a “disease” – a term that necessitates a measurable physical deviation from a healthy state (Jennings, 1986). Obviously, differences in labeling do not make the suffering any less real.

1. Actually a misquote. A more correct translation from German is “*What is there that is not poison? All things are poison and nothing [is] without poison. Solely, the dose determines that a thing is not a poison.*” (Lane & Borzelleca, 2008).

Defining CI according to severity of self-reports

A consequence of the unknown nature of CI is that it is difficult to define. Lacking physiological diagnostic markers, the disorder is almost exclusively defined in accordance to self-reports. In the scientific literature, CI is often separated into two different levels of severity. General or self-reported CI can be understood as negative and unwanted reactions to common odorants that may be annoying but not debilitating. General CI is commonly defined as affirmative answers to variations of the question “are you sensitive to smells?” or through instruments such as the Chemical Sensitivity Scale (CSS; Nordin, Millqvist, Löwhagen, & Bende, 2003). Severe or clinical CI can be understood as debilitating symptoms that hinder sufferers in their work, studies or when participating in society. It is commonly defined in accordance to criteria definitions. Multiple chemical sensitivity (MCS) is the most commonly used label for clinical CI, a term that itself have many definitions. Two are given in Table 1.

The term idiopathic environmental intolerance (IEI) was introduced in 1996 as a replacement of MCS (IPCS, 1996). The main argument for using this label is that definitions of MCS implicate that chemical substances are the cause of symptoms. As no causal relations between exposure and illness have been found, this criterion has been removed in the IEI definition (IPCS, 1996). The suggested name change has not gained undivided support. In the scientific literature, MCS and IEI are therefore often used synonymously when referring to severe or clinical CI.

The MCS criteria contain several uncertainties. How low is “low level exposure”? Do exposures barely detectable by current instruments still count? Must the symptoms occur *only* after exposure, and is it necessary that they disappear altogether when the source of the chemical is no longer present? Does “multiple organ systems” refer to anatomical areas or physiological systems and functions (McKeown-Eyssen, Baines, L. M. Marshall, Jazmaji, & Sokoloff, 2001)? The IEI criteria have similar problems. They are phrased in such a manner that any individual who gets multiple recurrent symptoms that somehow can be associated with exposure to something in the environment may be classified as suffering from IEI. If the individual does not have another illness that may explain the symptoms, all criteria for IEI are met. A person who experiences headache and dizziness when, say, working on a thesis would arguably fulfill the criteria for IEI.

Sensory hyperreactivity (SHR) constitutes a special case of CI definitions, as it contains a provocation test. The number of coughs following inhalation of nebulized capsaicin, the hot substance in chili peppers, is used as a measure of hyperreactivity in airway c-fibers (Johansson, Löwhagen, Millqvist, & Bende, 2002; Johansson, Nordin, Millqvist, & Bende 2007; Millqvist, Bende, & Löwhagen, 1998). Although capsaicin inhalation is a promising method of diagnosis, one drawback is the prob-

Table 1: Some definitions of clinical chemical intolerance.

Source	Term	Definition
Cullen (1987)	MCS	<i>“Multiple chemical sensitivities (MCS) is an acquired disorder characterized by recurrent symptoms, referable to multiple organ systems, occurring in response to demonstrable exposure to many chemically unrelated compounds at doses far below those established in the general population to cause harmful effects. No single widely accepted physiological function can be shown to correlate with symptoms”</i>
Nethercott, Davidoff, Curbow, & Abbey (1993) with additions in Multiple chemical sensitivity: a 1999 consensus (1999)	MCS	<ol style="list-style-type: none">1. The symptoms are reproducible with [repeated chemical] exposure.2. The condition is chronic.3. Low levels of exposure [lower than previously or commonly tolerated] result in manifestations of the syndrome.4. The symptoms improve or resolve when the incitants are removed.5. Responses occur to multiple chemically unrelated substances.6. [Added in 1999]: Symptoms involve multiple organ systems.
International Programme on Chemical Safety (IPCS, 1996)	IEI	<ol style="list-style-type: none">1. An acquired disorder with multiple recurrent symptoms.2. Associated with diverse environmental factors tolerated by the majority of people.3. Not explained by any known medical or psychiatric/psychologic disorder.
Johansson, Millqvist, Nordin, & Bende (2007)	SHR	<ol style="list-style-type: none">1. A score of 43 or higher on the Chemical Sensitivity Scale for Sensory Hyperreactivity (Nordin, Millqvist, Löwhagen, & Bende, 2004)2. Thirty-five or more coughs following inhalation of nebulized capsaicin (2 µmol/L).

lem of making blind provocations. One concern is that patients who know about the test may induce coughs to fulfill the criteria.

These issues raise questions regarding the sensitivity and specificity of CI diagnoses. This is a general problem in all forms of definitions based on subjective symptom reports (Hyams, 1998). It is also a serious issue for researchers investigating CI. As these definitions often are used as grouping variables, the non-specificity makes for heterogeneous groups when conducting research.

Relation to other conditions

Clinical CI definitions have much in common with other definitions of environmental intolerances such as noise sensitivity (Baguley, 2003), idiopathic environmental intolerance attributed to electromagnetic fields (Rubin, Nieto-Hernandez, & Wessely, 2010) and sick building syndrome (SBS; Eriksson & Stenberg, 2006). CI also resembles other medically unexplained symptoms such as chronic fatigue syndrome, fibromyalgia and irritable bowel syndrome, both in terms of defining characteristics and symptoms (Barsky & Borus, 1999). CI definitions also have much in common with definitions of a number of psychiatric and psychosomatic disorders (Bornschein, Hausteiner, Zilker, & Förstl, 2002). For instance, shortness of breath, palpitations and dizziness are characteristic symptoms in both CI and anxiety disorders (American Psychiatric Association [DSM-IV-TR], 2000). Based on symptom reports alone, it is difficult to separate the defining characteristics of CI from other medically unexplained conditions, or for that matter clinical diagnoses such as asthma and allergies (McKeown-Eyssen et al., 2001). These issues raise concerns regarding the extent of overlap between CI and other illnesses. Good estimations of overlap can only be made if the definitions themselves are clearly demarcated. If they are not, it is impossible to know whether it is the pathophysiology or the semantic categories that overlap (Preskorn & B. Baker, 2002).

Estimations of prevalence

The vagueness of CI definitions also makes estimations of prevalence difficult. Results from several sizeable studies nevertheless suggest that the problem is surprisingly common in the population. Prevalence numbers are even “provocative” according to Kreutzer and colleagues (1999). Studies using random sampling of the general population in several industrialized countries have yielded prevalence numbers of general or self-reported CI ranging from 9 to 33% (Berg, Linneberg, Dirksen, & Elberling, 2008; Caress & Steinemann, 2004a, 2004b; Carlsson, Karlsson, Ørbaek, Österberg, & Östergren, 2005; Hausteiner, Bornschein, Hansen, Zilker, & Förstl, 2005; Centre for Epidemiology and Research, NSW Department of Health, 2003; Johansson, Brämerson, Millqvist, Nordin, & Bende, 2005; Kreutzer et al., 1999; Meggs, Dunn, Bloch, Goodman, & Davidoff, 1996). Severe or clinical CI is reported by between 0.5 and 6.3% of the population (Caress & Steinemann, 2004a, 2004b; Hausteiner et al., 2005; Centre for Epidemiology and Research, NSW Department of Health, 2003; Johansson et al., 2007; Park & Knudson, 2007).

Risk-factors associated with CI

Sex / gender

Female sex has been reported to be a risk factor for both general and clinical CI (D. W. Black et al., 2000; Johansson et al., 2005; Kreutzer et al., 1999; L. Andersson, Johansson, Millqvist, Nordin, & Bende, 2008), with the exception of Kreutzer et al. (1999) who did not find sex as a risk factor for MCS. Nevertheless, there seems to be a consensus in the scientific community that CI is an affliction mainly affecting women (see e.g. Labarge & McCaffrey, 2000; Miller, 2001; Sorg, 1999; Sullivan, Bell, & Meggs, 2001).

There is no clearly discerned cause for this female bias in CI prevalence, but several hypotheses have been put forward. The issue is related to the question of whether women outperform men in chemosensory perception – in itself is a complicated subject. For instance, it could be the case that women are more willing than men to report health problems, and that CI is in fact equally prevalent in both sexes (Miller, 2001). Girls, compared with boys, may arguably from an early age have a sociocultural pressure to evaluate odors as important environmental cues. This pressure may in turn lead to aversive reactions (Ferdenzi, Coureaud, Camos, & Schaal, 2008) that may act as a predisposing factor for CI. Women may also have keener chemical senses than men that might explain greater irritation from chemical exposures. However, although it is commonly reported that women outperform men in several chemosensory functions, a comparable number of studies fail to find such differences (for a review, see Doty & Cameron, 2009).

Age

Almost all studies of CI have investigated adult populations. Some authors nevertheless hypothesize that the incidence may be highest during adolescence (Caress & Steinemann, 2004b; Kreutzer et al., 1999). In contrast, D. W. Black and colleagues (2000) reported that persons over 25 years are at higher risk of developing MCS. Johansson and colleagues (2005) did not find age to be a risk factor for general CI. Neither did Kreutzer et al. (1999) for MCS. In a study by L. Andersson and co-workers (2008), adolescents were found to report CI problems to a lesser degree than adults. Nearly three times as many persons aged 20 to 29 years reported CI (i.e. answered yes to the question “are you bothered by strong odors?”) compared to an adolescent population. These results indicate that CI is an affliction that in many cases develops during the course of life.

Psychiatric conditions and other medically unexplained symptoms

CI has been assumed to be co-morbid with psychiatric illnesses. Some researchers have even suggested that CI is a misdiagnosis for or a symptom of such conditions (Gots, 1995). Whether or not this is the case, post-traumatic stress disorder (PTSD), generalized anxiety disorder and panic disorder are salient risk factors for clinical CI (D. W. Black et al., 2000). Several studies using smaller samples have reported substantial overlap between CI and psychiatric conditions, including anxiety and affective and somatoform disorders (Bornschein et al., 2002; Hausteiner, Mergeay, Bornschein, Zilker, & Förstl, 2006; Papo et al., 2006; Poonai et al., 2000; Witthöft, Gerlach, & Bailer, 2006).

In addition to psychiatric conditions, CI has been reported to overlap considerably with other medically unexplained symptoms (Aaron & Buchwald, 2001; Binder & Campbell, 2004; Jason, R. R. Taylor, & Kennedy, 2000). However, as mentioned earlier, the definitions of many psychiatric conditions and medically unexplained symptoms overlap the definitions of CI to a degree that makes comparisons of co-prevalence very problematic. Moreover, it is difficult to assess whether psychiatric conditions preceded CI or the other way around. For instance, Caress and Steinemann (2003) argues that psychiatric conditions tend to develop after the onset of CI.

Personality factors

In addition to the overlap with clinical diagnoses, certain personality traits have been associated with CI. These include negative affectivity (NA; Bolt & Kiesswetter, 2002; Dalton, 2003) and trait anxiety (Bolt & Kiesswetter, 2002; Papo et al., 2006; Persson, Björk, Ardö, Albin, & Jakobsson, 2007). NA has also been associated with SBS, but only when mediated through somatization (Berglund & Gidlöf Gunnarsson, 2000). Trait neuroticism has been reported as a predictor for heightened olfactory sensitivity in non-clinical groups (Chen & Dalton, 2005; Pause, Ferstl, & Fehm-Wolfsdorf, 1998). It should, however, be noted that the personality factors have not been studied in larger samples.

Sociocultural factors

The impact of social factors can refer to many phenomena. It can be the discourse or atmosphere within a small workplace or cultural understandings of environmental stimuli within a nation or ethnic group (Hinton, Pich, Chhean, & Pollack, 2004). Österberg and colleagues (2007) reported that employees with CI report lower overall work satisfaction and ability to solve personal issues at the workplace and less satisfaction with assignments compared with non-ill controls. They are

also more fatigued by work and need longer periods to recover from strenuous work situations. Similarly, results from a longitudinal study showed that health complaints, dissatisfaction with work, lack of recovery and low social support were significant risk factors for environmental intolerances (Eek, Karlson, Österberg, & Östergren, 2010). Although a siding from the focus of this thesis, a short note on the sociocultural ideas about odors throughout history is given in Appendix 1.

CI symptoms

From the viewpoint of the CI sufferer, the main characteristics of the illness are not deviations from dose-response relationships or non-specificity of symptom patterns. It is the symptoms themselves and the consequences in daily life (Skovbjerg, Brorson, Rasmussen, Johansen, & Elberling, 2009).

M. J. E. Andersson and colleagues (2009) assessed the most prevalent CI symptoms and found five general symptom categories. Head-related problems such as headache were reported by 49% of the participants, airway, mucosae and skin symptoms such as eye irritation and shortness of breath by 45%, cognitive and affective symptoms such as feeling tired or having concentration difficulties by 30%, gastrointestinal problems such as abdominal swelling by 26%, and cardiac, nausea and dizziness symptoms such as nausea and heart pounding by 24%. Similar symptom patterns have also been found in other studies (Bornschein et al., 2002; Hausteiner et al., 2005). The pattern that can be discerned from such reports is that CI symptoms indeed are general. In addition to cognitive and head-related problems, symptoms also seem to be occurring mainly in barrier tissues such as the skin, the gastrointestinal system and airways (Rosenkranz, 2007).

Relevance of the chemical senses for CI

Odors have an altogether peculiar force, in affecting us through association; a force differing essentially from that of objects addressing the touch, the taste, the sight or the hearing.
— Edgar Allan Poe (1809 – 1849)

What is commonly meant by the term smell is actually not mediated by a single sensory system. The two major systems are the olfactory (what we commonly mean by our sense of smell) and the chemosomatosensory system (mediating burning, cooling, astringent and sensory irritant sensations). Almost all odorants elicit both olfactory and chemosomatosensory sensations. It is often the case that low level of chemicals are mediated mainly through olfaction, whereas pungent sensations are elicited by stronger concentrations (for an overview of the chemical senses,

see Lundström, Boesveldt, & Albrecht, 2011). For instance, amyl acetate is at low levels assumed to affect mainly the olfactory system, whereas CO_2 elicits chemosomatosensory sensations. These two chemicals are incidentally used in all empirical studies in this thesis.

What we assume to be a unitary sense of smell is thus divided between at least two separate systems. Chemosomatosensory sensations are in part mediated by the trigeminal cranial nerve v (Hummel & Livermore, 2002). This cranial nerve is branched into three separate nerves that innervate different areas of the face, but only the face. This complicates the definition of e.g. pungent stimulation, as sensory irritancy from the face is mediated by the trigeminal nerve, whereas such sensations from e.g. the airways are in part mediated by non-trigeminal nerves. Although the term trigeminal is often used to describe pungent (sensory irritant), burning and cooling sensations, a more correct term is chemosomatosensation. Chemosomatosensation is thus the encompassing term for such sensations.

Olfaction is mediated by cranial nerve I. The projections of olfactory nerves are different from other sensory systems. Whereas other sensory nerves are relayed through thalamus, the olfactory system is not, or at least only weakly so (Plailly, Howard, Gitelman, & Gottfried, 2008). As thalamus is assumed to be an important relay in the attentional modulation of sensory stimuli, there has been some discussion whether olfactory stimuli can be attended in the same way as those of other sensory modalities, or whether olfaction has a separate attentional relay system (Smythies, 1997). A flow-chart of the definitions is provided in Figure 1.

Our chemical senses constitute important warning systems. If we eat or inhale a toxic substance, we must quickly learn to avoid it in the future (Stevenson, 2010). The necessity for developing such avoidance responses may however have unfortunate consequences. One example is when patients who are treated for cancer develop aversions to the food they eat while receiving cell toxins (S. Siegel, 1999). Sensations mediated by the chemical senses are thus particularly prone to sensitization and classical conditioning. These aspects of the chemical senses may be of relevance for CI.

Interestingly and somewhat perplexing, persons with CI do not seem to have particularly sensitive chemical senses. Doty and colleagues (1988) reported that MCS patients did not differ from healthy controls in terms of olfactory detection sensitivity. Similar findings were reported by Papo et al. (2006).

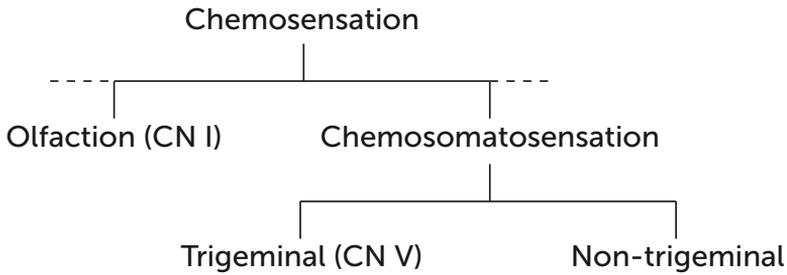


Figure 1: Labels used to separate chemosensory systems. CN = cranial nerve.

Theories of CI

Several largely untested theories of CI have been put forward (Winder, 2002). These constitute a framework for empirical observations of CI, and a basis from which hypotheses may be extracted. In addition to a general description of three major theories of CI, I will provide the initial steps toward a synthesis of the theories. This integration is necessary in order to properly interpret the findings of the empirical studies. My overreaching argument is that the three theories refer to the same underlying construct, albeit from different perspectives. This means that the empirical studies in this thesis do not adhere to or corroborate any theory over any other.

The theory of neural sensitization

According to the neural sensitization theory, CI symptoms can be attributed to pathological and progressive non-immunological increases in neural responsiveness (Bell, Baldwin, Fernandez, & G. E. Schwartz, 1999; Bell, Miller, & G. E. Schwartz, 1992; Sorg, 1999). Neural sensitization is assumed to be a two-step process consisting of an initiation and elicitation phase. Initiation refers to the physiological states and events that are necessary to develop intolerance to an exposure. When in this state, repeated exposures of low to medium strength, or a single strong exposure will result in permanent increases in responsiveness within a system. In the elicitation phase the system has already been affected, and exposures to the sensitized stressor or one that has been cross-sensitized are amplified (Bell et al., 1999; Sorg, 1999). Cross-sensitization is an important feature of the model and refers to the phenomenon that once sensitization has developed to a certain kind of exposure, reactions to other exposures may yield similar responses (Sorg, 1999). This effect is assumed to be similar to the finding that stress and a drug (amphetamine) can be used interchangeably to induce sensitization in rodents (Antelman, Eichler, C. A. Black, & Kocan, 1980). The cross-sensitizing aspect of sensitization may explain the spreading phenomenon.

Bell and colleagues (1992) have suggested that neural sensitization is to be understood as a form of limbic kindling. Kindling is a subtype of time-dependent sensitization, and has mostly been studied in animal models where electrical shocks to the amygdala that initially do not cause severe reactions, can lead to full-blown seizures after repeated stimulations (Sorg & Prasad, 1997). It should thus be understood as a severe hyper-reactivity of limbic neurons. According to the neural sensitization model, the CI symptoms can be understood as non-convulsive type of reactions in olfactory and limbic areas of the brain (Bell et al., 1992). Although limbic areas are assumed to play a major role in the defining characteristics of neural sensitization, the term is encompassing and can refer to persistent changes in all kinds of systems, including behavioral, autonomic, hormonal and the immune system (Bell, Baldwin, & G. E. Schwartz, 2001).

Bell (1996) proposed that other illnesses and characteristics should be present in individuals with CI because of the pathological sensitization. These include trait shyness, other environmental sensitivities such as noise sensitivity, heightened startle reflexes, difficulties with attention, failures to habituate to the environment and sleep disruptions. Furthermore, it has been suggested that increased sensitization should be seen as an inherited trait, especially prevalent in families with a history of substance abuse. According to this hypothesis, addiction, cravings and intolerance are very similar in their etiology (Bell, 1996; Bell, Hardin, Baldwin, & G. E. Schwartz, 1995; Bell et al., 1992). Sorg and Prasad (1997) argued that the neural sensitization model seems to be valid for CI in animal (rodent) models, but that this not necessarily proves that the theory is applicable to humans. The authors further suggest that the assumed limbic sensitization should cause measurable alterations in olfactory detection thresholds, conditioned avoidance responses, memory tasks and attention. The hypotheses remain largely unproven.

The theory of classical conditioning²

The second prominent theory is one that describes CI as the result of classical conditioning (Van den Bergh et al., 2001; Bolla-Wilson, Wilson, & Blecker, 1988; Otto & Giardino, 2001). According to this theory, a neutral exposure (conditioned stimulus; CS) has been associated with a noxious or stressful event (unconditioned stimulus; US) which results in an unconditioned response (UR). The result of this associative learning is that the CS in the future will be regarded as harmful and that the reactions to the formerly neutral stimulus, called the conditioned response (CR) will be as severe as the UR (see Figure 2).

2. The term “conditioning” will in this thesis henceforth refer to classical conditioning.

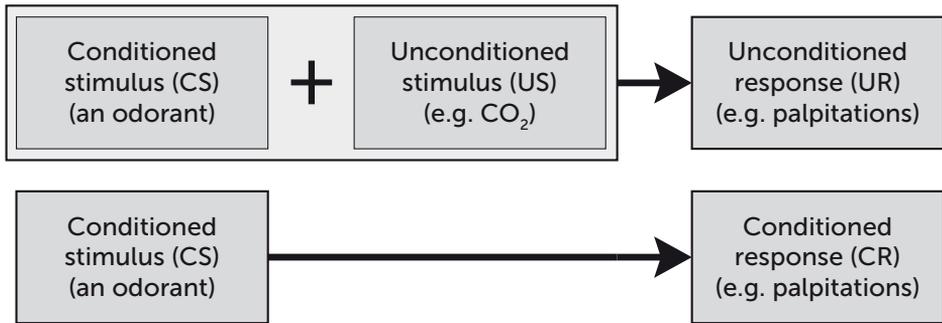


Figure 2: Schematic illustration of classical conditioning.

Van den Bergh and colleagues (2001) have conducted a series of experiments that shows that a CS in the form of an odorant mixed with an US consisting of CO₂ results in CRs that mimics the properties of CI. For instance, exposure to ammonia ordinarily does not result in symptom reports. Breathing air enriched with CO₂ is unpleasant and triggers panic attacks in a majority of persons with panic disorder. When ammonia is mixed with CO₂-enriched air that triggers an UR in the form of symptoms, subsequent exposures to ammonia without CO₂ will result in a signature CR response similar to the UR. This conditioning is fast and occurred even when the participants of the studies were unaware of the contingency between ammonia and CO₂, suggesting that such conditioning can occur unconsciously. The valence of the CS was important. The relatively foul smelling ammonia was conditioned, whereas niaouli that smells like eucalyptus, was not. Once conditioning had occurred, the CR could be elicited by other odorants than the initial conditioned stimulus. This effect could serve as an explanation of the spreading phenomenon within the conditioning theory of CI. Although conditioning to chemical exposures may seem to be of the greatest relevance for CI, the authors reported that visual images or mental cues could act as CS. This suggests that the theory can be applied to all kinds of environmental intolerances.

The conditioning theory also offers an explanation for the co-prevalence of psychiatric diagnoses in CI. Neuroticism, negative affectivity and somatization problems are predictors of conditioned learning. Persons who score high on these measures, compared with those who score low, have also been found to report more symptoms, and adverse reactions generalize to other stimuli to a greater degree (Van den Bergh et al., 2001). Devriese and colleagues (2000) reported that conditioning to odorants is most prominently seen in humans who score high on NA and suggested that persons with high NA have stronger attentional bias to bodily symptoms and are more inclined to report negative health effects after a condition-

ing session. Finally, the conditioned responses to odorants could be greatly reduced by an extinction procedure (Van den Bergh et al., 2001). If the conditioning theory is relevant for CI, this suggests that the symptoms can be treated.

A common argument against the conditioning theory is that CI patients in many cases do not have a previous history of a toxic us (Staudenmayer, 1997). Van den Bergh and colleagues (2001) respond that several factors can initiate a conditioned response. A toxic exposure is one, but stress, anxiety or other problematic conditions may be equally potent events. For instance, it has been shown that stressed animals are much more prone to conditioning than those who are not (Peeke, Dark, Ellman, McCurry, & Salfi, 1987).

S. Siegel and Kreutzer (1997) highlighted the similarities between conditioning and CI, but found it unlikely that a single explanatory model could account for all manifestations of the affliction. They note that much evidence point to large similarities between conditioning and sensitization, and that sensitization in part is attributable to conditioning. Furthermore, the authors argue against seeing conditioning solely as a psychological mechanism. Conditioned responses are mediated by physiological changes, and affects peripheral responses such as protease release. Although it is common that the conditioning theory of CI is seen as psychological rather than physiological, proponents of the theory tend to avoid such divisions (Van den Bergh et al., 2001). The conditioning theory has nevertheless been the topic of heated debates. For a contemporary example, see the furious letter to the editor by Pall (2010) and the response by Van den Bergh et al. (2010).

The neurogenic inflammation theory

Whereas the neural sensitization and conditioning theories of CI have focused more on altered reactions in the central nervous system and behavior, the neurogenic inflammation theory mainly deals with peripheral changes. Meggs (1999) have argued that CI and allergies are similar in expression – both debilitation imply an inflammatory reaction to an environmental exposure. Whereas allergic inflammation is caused by abnormal IgE release following exposure to proteins, CI inflammation is (supposedly) caused by abnormal sensitivity to chemicals of low molecular weight.

Meggs describes the process behind CI as a breakdown of adaptation³, following four steps. In the tolerance stage (stage 0), chemicals are tolerated without illness. In stage 1, the person reports multiple complaints such as nausea and headaches,

3. Adaptation is commonly used as a label for decreased responsiveness in the peripheral nervous system, whereas habituation refers to decreases in the central nervous system (Dalton, 2000).

but with little physiological evidence of what may cause these symptoms. Stage 2 implies that one or more organs have become inflamed. At stage 3, tissue has been damaged beyond recovery and the individual has little or no tolerance to exposures. The breakdown of adaptation is assumed to be mediated through the central nervous system (CNS), but the exact mechanism behind this is not stated (Meggs, 1999, 1994).

Bascom and colleagues (1997) have described the neurogenic inflammation theory in greater detail. According to them, the mechanism behind CI may be a proliferation of sensory c-fibers. As chemicals bind to chemoreceptors, a local inflammatory response is initiated with the release of substance P (SP) and other inflammatory mediators. Afferent c-fibers propagate signals to the CNS and axon reflexes carries inflammation to other sites. Central structures mediate the inflammatory response to other parts of the body through the sympathetic and parasympathetic nervous system, eliciting release of inflammatory mediators at other sites. Neurogenic inflammation does not necessarily occur at the peripheral level but at a central level as well.

Bascom et al. (1997) proposed several testable hypotheses about CI. For instance, persons with CI should have increased density of c-fiber neurons in sensitized tissue, produce greater amounts of neuropeptides and prostaglandins than non-intolerant, and have lower trigeminal detection thresholds and increased and prolonged responses to exogenous c-fiber activators such as capsaicin or CO₂. In addition to deviations hypothesized to be found at biochemical and sensory levels, persons with CI should have alterations in habituation, perception, cognition and hedonic value ascribed to chemical stressors (for the complete list of hypotheses, see Bascom et al., 1997).

Meggs (1999) discusses the comorbidity of psychiatric conditions and CI, and suggests that depression is associated with allergy, and not CI. Moreover, he suggests that conditioning may play a role in CI, but only for the odorous aspects of a chemical exposure. He assumes that it is the irritancy that causes CI – the odorous property of an exposure may become associated with malaise, but this is a mechanism different from the actual neurogenic inflammation. Proponents of the neural sensitization and neurogenic inflammation theories do not seem to have any major problems with merging their theories (Sullivan et al., 2001).

Toward an integration of theories

An important goal of this thesis is to present a theoretical framework for CI. Instead of building a new theory, I will argue that the above mentioned theories can be integrated into a coherent whole that covers the major aspects of CI. At a glance,

it seems as if the neural sensitization (Bell et al., 1999), neurogenic inflammation (Meggs, 1994) and conditioning (Van den Bergh et al., 2001) theories offer different explanations regarding the mechanisms of CI. Although the neural sensitization and neurogenic inflammation theories can be merged (Sullivan et al., 2001), there seems to be an inherent resistance between these two and the conditioning theory. A prevalent theme in the literature is that the neural sensitization and neurogenic inflammation theories are perceived as biological, whereas the conditioning theory is psychological. A reader may therefore get the impression that the conflict is not between the theories themselves, but between assumed ontological differences between different scientific fields.

I will now argue that the separation of the theories is unnecessary, even unfortunate. If we assume that our minds, in any aspect, cannot be separated from our bodily systems – that is, if we adhere to the view that no link in the chain of events leading up to a mental state is non-physical – all three theories are in fact based on physiology⁴. The first step in integrating the theories is therefore to assume that there are no differences between them in terms of basic ontological assumptions. The second step is to scrutinize core concepts of the theories and relate them with each other.

Relationship between neural sensitization and conditioning

Sensitization is defined as a progressive increase of responsiveness after repeated stimulus exposure. Sensitization is the opposite of habituation, which is defined as a progressive decrease in responses after repeated stimulus exposures (Overmier, 2002). Sensitization and habituation is commonly seen as opposite endpoints of a system made up of two independent processes – one excitatory and one inhibitory (for a review, see Thompson, 2009). In situations where the inhibitory process is greater than the excitatory, habituation occurs. Sensitization arises when the excitatory process is greater than the inhibitory. This dual-process model can be applied to a wide range of phenomena, including neural, immunological and behavioral reactions (Rankin et al., 2009).

Sensitization according to Bell et al. (1999) is similar to the accounts above. The authors argue that sensitization is a function or characteristic found in all parts of the body – in the immune system, in the function but not necessarily structure of cells, in behavior and, most prominently, in reactions of the limbic system. Bell and colleagues (1999) emphasize that sensitization is a form of non-associative learning, distinct from the associative learning that underlies conditioning.

4. N.B. that arguing against this would imply a dualistic view of man with the necessary assumption that mental states at least in part have non-physical underpinnings.

The discrepancy between associative and non-associative learning mechanisms is however debated. There is a distinction between the operational definitions of sensitization and conditioning (Thompson, 2009), which means that studies pertaining to either of the two may be separated⁵. When referring to sensitization in the nervous system, i.e. the major focus of the neural sensitization theory (Bell et al., 1999), the mechanisms seem to be similar to conditioning. In a seminal work on learning mechanisms in *Aplysia*, Hawkins and colleagues (1983) showed that classical conditioning is best viewed as an elaboration of the mechanism underlying sensitization. When investigating the neural underpinnings of a conditioned gill withdrawal reflex, the authors found that the presynaptic facilitation of this associative learning response paralleled the mechanism of non-associative reflex sensitization (Hawkins, 1984). Similarities between conditioning and sensitization are also found when investigating the neural underpinnings of these processes in the CNS. For instance, a review of several brain imaging studies highlighted the anterior cingulate cortex, amygdala and insular cortex as key players in human fear conditioning (Sehlmeyer et al., 2009). Although less studied, the same structures have been implicated in central habituation and sensitization (Bingel, Lorenz, Schoell, Weiller, & Büchel, 2006; Phan, Liberzon, Welsh, Britton, & S. F. Taylor, 2003; Wiech & Tracey, 2009).

It seems as if the major differences between neural sensitization and conditioning are neither ontological nor related to the underlying mechanisms. There is however a difference in perspective. The neural sensitization theory has the characteristics of a bottom-up model. The focus is on how external stressors and mechanisms in the periphery of the nervous system act upon central structures such as the limbic system, which in turn causes a wide spectrum of symptoms and distress (Bell et al., 1999, 1992).

The perspective of the conditioning theory is, on the other hand, relatively top-down in nature. It is first and foremost concerned with the basic learning – how a neutral exposure may become associated with a *us*. Less emphasis is placed on the physiological underpinnings of this mechanism (Van den Bergh et al., 2001), which seems to have been interpreted incorrectly as a lack thereof. If the differences between the neural sensitization and conditioning theories are a matter of perspective, it may be possible to merge them with each other. Incidentally, proponents of the different theories use the same argument for distinguishing between the two:

5. Even these differences are debated. It has proven difficult to conduct studies where associative learning is omitted. That is, as it is impossible to separate an organism from an environment, it is difficult to rule out that the learning that has taken place is associative. Even though a researcher does not present a CS, it is plausible that the experimental context itself becomes one (B. Schwartz, 1989, p.128).

“This [conditioning] model would require the involvement of an initiating toxic chemical as the UCS [sic] and thus would potentially apply to the subset of patients who can identify an initiating chemical.” (Bell et al., 1999)

AND

“One important difference at the procedural level, however, is that a sensitization paradigm requires a reactivity to an initial exposure of a stimulus, whereas a conditioning paradigm does not.” (Van den Bergh et al., 2001)

I do not argue that sensitization and conditioning are the same. What I argue for is that these basic forms of learning are not dissimilar to a degree that permits a sharp line to be drawn between the two theories.

Neurogenic inflammation and central mechanisms

The neurogenic inflammation and neural sensitization theories have already been integrated with each other. Sullivan, Bell and Meggs (2001) argue that the two theories offer different viewpoints of CI, one with an emphasis on peripheral functions, and one with a central focus. If we accept the arguments for merging the neural sensitization and conditioning theory, the inclusion of the neurogenic inflammation theory thus seems to follow.

There is however reason for going a bit further with this issue. It is not sufficient to propose that peripheral and central mechanisms can fit within the same theory. The relations between these concepts must be specified. In this endeavour, it is fruitful to explore if and how basic learning mechanisms may affect inflammatory responses in peripheral regions of the nervous system.

The label neurogenic inflammation refers to an inflammatory process triggered by mediators such as SP released from nerve endings (Rosenkranz, 2007). As such, it can be understood as an interface between the nervous and immune systems. By investigating this process in detail, P. H. Black (2002) and Rosenkranz (2007) have provided the means by which the neurogenic inflammation, conditioning and neural sensitization theories can be merged into a single framework.

Inflammation is an intrinsic part of our defences against threatening and noxious stimuli. When we are exposed to a toxic stressor – a wound, an infection or burning our fingers on the stove – a cascade of events takes place both locally and at other places of the body. One reaction in this cascade is the release of SP, predominantly from afferent c-fibers. SP's primary binding site is the Neurokinin-1 receptor (NK-1R) which is distributed widely both in the periphery and centrally in the CNS. The greatest concentration of NK-1R is found in the gut, airways and skin, i.e. in barrier tissues. In addition to promoting local inflammation, SP is involved

in the generation of an integrated cardiovascular, behavioural and endocrine response pattern with the purpose of neutralizing or avoiding the stressor as well as healing possible tissue damage. Inflammation is thus only one of a wide variety of changes taking place in the organism. Other common effects are evacuation of the gastrointestinal tract, increased mucous production, coughing and sneezing to expunge possible airway stressors, and lower breathing depth (Rosenkranz, 2007; Sertl et al., 1988).

SP release also affects the nervous system by lowering neuronal response thresholds. In addition to amplifying local nerve signalling, this response is propagated to other parts of the nervous system where second-order neurons also begin to express SP. Several areas in the CNS, including the periaqueductal grey, amygdala, prefrontal cortex and hippocampus have a large distribution of NK-1R, and are thus hypothesized to be greatly affected by SP. These central areas relay the local inflammatory response through the autonomic nervous system, which results in SP release throughout the body. Through these mechanisms, the reactions to a local injury are propagated to other parts of the organism. This way of illustrating neurogenic inflammation is in close correspondence with the CI theory (Meggs, 1994). As inflammatory responses influence neural response thresholds both peripherally and centrally, this illustration provides a basis for merging the neurogenic inflammation and sensitization theories of CI.

Neurogenic inflammation, stress and conditioning

An aspect of the mechanisms behind neurogenic inflammation that is mentioned but not emphasized by Meggs (1994) is its consequences for stress, behaviour and conditioning. In addition to relaying inflammation to other parts of the body, the involvement of central areas suggests that SP release has implications also for more complex behaviours and functions. Rosenkranz (2007) argues that SP carries negative emotional salience; that inflammation thus causes a more general stress response. As SP sensitizes neural activity both peripherally and centrally, the effect seems to be that the CNS is primed to be more responsive to all kinds of stressors. Rosenkranz (2007) argues that **one consequence of being injured is a general predisposition of perceiving the situation as more threatening**. Emphasizing the role of SP with an increased risk of perceiving situations as threatening implies an increased risk for the development of aversive responses, i.e. conditioning.

The close relationship between behavioural and inflammatory reactions has been found both in animal and human studies. SP activity in the amygdala has been shown to be associated with flavour aversion (Basso, de Sá-Rocha, & Palermo-Neto, 2001), stress (Ebner, Rupniak, Saria, & Singewald, 2004) and social isolation (E. Brodin, Rosén, Schött, & K. Brodin, 1994). Injecting SP in the amygdala results

in defensive rage and aggression in cats (Gregg & A. Siegel, 2001) and anxiety-related behaviour in rodents (Ebner et al., 2004; Gavioli, Canteras, & De Lima, 1999). Injecting SP in the periaqueductal grey of rodents increases conditioned place aversion and fear conditioning. By blocking the NK-1R receptor, fear conditioning and place aversion is reduced (De Araújo, Huston, & Brandão, 2001; Rupniak, Webb, Fisher, Smith, & Boyce, 2003). In humans, injections of SP into the blood stream leads to a rapid decline in mood (Lieb et al., 2002). An increased expression of SP has also been found in patients with depression and anxiety disorders (Geraciotti et al., 2006; Rimón et al., 1984), and people with PTSD show an elevated SP release when exposed to stressful stimuli (Geraciotti et al., 2006). These results suggest that the release of SP centrally is directly related to conditioning and negative mood, which in itself is an argument for merging the conditioning model of CI with the other two. Once again, the physiological underpinnings are not dissimilar enough to merit a clear separation between the neurogenic inflammation (Meggs, 1994), neural sensitization (Bell et al., 1999) and conditioning (Van den Bergh et al., 2001) theories.

The bi-directional connections between the central and periphery also suggest that the CNS may play an active role in the development of peripheral neurogenic inflammation. P. H. Black (2002) argues that stress alone, without an external toxic agent, can cause an inflammatory response. The CNS has the capacity to produce and modulate general inflammatory reactions in the body not only as a response to infection or trauma, but also in response to a perceived threat. For instance, SP in the brain is elevated as a result of space flight, parachute jumping, restraint and anxiety. Another example is that an audio-visual cue that has become associated with an allergen in a classical conditioning experiment subsequently triggers not only a CR in terms of a behavioural change, but also SP-release peripherally and mast-cell degranulation (MacQueen, J. Marshall, Perdue, S. Siegel, & Bienenstock, 1989). Additionally, Lutgendorf and colleagues (2000) showed that the size of the flare (the blotch of red skin) caused by an intradermal injection of capsaicin was significantly larger when participants were stressed than when relaxed.

The inflammatory response is one of our most primitive defence mechanisms, from which the stress response evolved, and these are intrinsically linked. In the view proposed by P.H. Black (2002) and Rosenkranz (2007), stress may produce the same inflammatory responses as an actual physical exposure. In the case of CI, this implies that an expectation of toxicity of a chemical, not necessarily the toxicity per se, may cause widespread inflammation in a sensitive individual, and furthermore offers a connection between the neurogenic inflammation, neural sensitization and conditioning theories.

Stress and stressors

Memories and possibilities are even more hideous than realities.

— H.P. Lovecraft (1890 – 1937)

One additional topic must be addressed in the theoretical argument, and that is to define stress. Whereas the mechanisms behind a local inflammation are relatively well known, the boundaries of the stress construct are vague. As stress nevertheless is the concept that ties the theories together, a detailed definition is necessary. In their cognitive activation theory of stress (CATS), Ursin and Eriksen (2004) argue that stress can be operationalized and defined by its eliciting stimuli (stressors), the subjective reports of the experience and a general non-specific increase in arousal.

The stimulus itself may be part of stress, but only if it is perceived as a stressor. Ursin and Eriksen (2004) emphasize that no stimulus in itself and by its physical properties automatically triggers a stress response. Whether an exposure is perceived as a stressor depends on individual appraisal that relies heavily on previous experience and expectancies. With that said, there are stimuli, such as a major injury, that always or nearly always are perceived as stressors. The experience is also an aspect of stress. Appraising a stimulus as threatening or negative elicits an experience in the exposed person. This sensation is an aspect of stress and can be assessed by asking the person about the experience. The stress response is the aspect of the non-specific alarm response that elicits an increase in wakefulness and arousal, as well as responses to deal with the stressor. This increased arousal is discernible in many parts of the body. Feedback from the stress response is in itself stressful, making the system a feedback loop. For instance, experiencing palpitations, increased sweating and breathing rate may enhance these and other responses such as anxiety. Stress occurs when there is a mismatch between expectation and outcome. This means that e.g. novel stimuli or the absence of stimuli may trigger stress. The stress continues until the mismatch is resolved. This alarm system is assumed to be a safety system that guarantees that important discrepancies in the world are attended⁶.

Expectancies are thus important for stress, and are defined as stored stimulus and response relationships that we may have acquired on our own or from others. Expectancies not only contain assumptions of causality, but also perceived probabilities of how common the event is and its affective value.

6. I would like to emphasize the close association with attention and lack of habituation. According to the CATS model, we have an attention bias to stressors, and we will not get used to them until they are removed or no longer stressors.

The affective value is important from a sensitization and conditioning perspective, and can be directly related to the finding by Van den Bergh et al. (2001) who reported that aversive olfactory conditioning was found only when the cs had a negative valence. Perceiving an exposure as negative, as in the case of ammonia, implies a greater risk of associating it with negative outcomes. This results in a general stress response, sensitization and aversive conditioning. When we perceive an exposure as positive, as in the case of niaouli, no such conditioned aversions seem to be formed, meaning that we habituate and the stress response subsides. The acquired positive expectancy is defined as coping according to CATS (Ursin, 2009).

In a healthy organism, short-lasting stress does not seem to lead to any ill effects. It is important to remember that stress in many situations is a desirable response that resets our priorities and primes us to deal with a potential hazard or unexpected situation. Repeated exposures of stressors do however lead to fatigue, which over time may produce lasting detrimental changes to the systems (e.g. hormonal or neural) affected by the stress (Ganzel, Morris, & Wethington, 2010). It is therefore important to deal or cope with the stressor so that pathological states do not develop. As coping, at least according to the CATS model, means acquiring positive expectancies, we can expect to find greater stress and higher rates of aversive conditioning in persons and groups with negative expectancies.

The characteristic features of CI according to the neurogenic inflammation (Meggs, 1994), neural sensitization (Bell et al., 1999) and conditioning (Van den Bergh et al., 2001) theories may also be described in terms of stress. It is thus possible to describe CI as the result of unresolved long-term stress – a stress that may be discerned in the form of e.g. inflammatory responses, sensitization or conditioning.

Methods and instruments used in the thesis

Event-related potentials (ERPs)

Our nervous system transmits signals by means of electricity. As action potentials are released from the cell body, the membrane of the axon becomes polarized and neurotransmitters are released from the synapse. This creates a small electrical field that can be registered by scalp electrodes. The field fluctuations can be illustrated in the form of an electroencephalogram (EEG).

EEG reflects the rhythmic fluctuations of overall neural activity in the brain, and does not yield much in terms of how a certain stimulus is processed. Nevertheless, when we introduce a stimulus to a person from which we record EEG, there will be a slight fluctuation in the waveform. When several such events are presented, and the activity following the events is averaged, the overall EEG will summate to zero as this background activity is random. The activation pattern that is caused by the

non-random event, i.e. the stimulus, is an ERP. By measuring the latency and amplitude of the peaks of this waveform it is possible to analyse the neural response that is triggered by the event.

The peaks in the waveform are assumed to reflect different underlying mechanisms. Early peaks, such as the first negative deflection N1 (N for negative, 1 for first deflection) has been used as an index of basic sensory processes. Later peaks such as the P2 and P3 reflect more cognitive processes such as attention and working memory (Figure 3). The nomenclature for ERP deflections is much more diverse than this, and different peak structures are revealed by different study designs. In the thesis studies, the ordinal labelling system is used (i.e. N1, P2 etc.; Woodman, 2010).

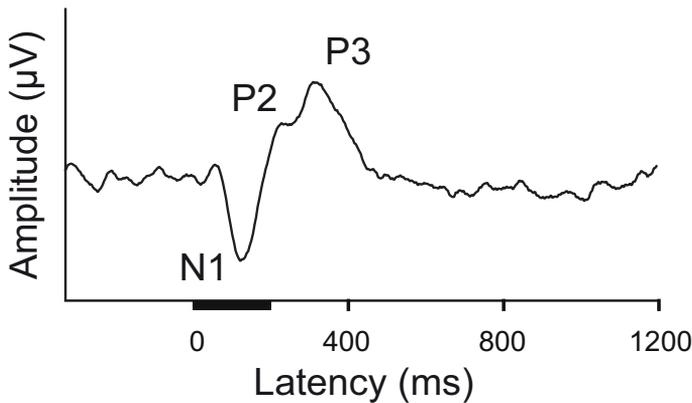


Figure 3: A grand averaged auditory ERP waveform with three major peaks.

The test-retest reliability of ERP amplitudes in different sensory modalities, including olfaction, is generally good (Nordin, L. Andersson, Olofsson, McCormack, & Polich, 2011). The latency measure is not as good in this regard, but still fair (Nordin et al., 2011; Walhovd & Fjell, 2002). Regarding the validity of ERP, it is well recognized that the scalp recordings reflect neural activity in the brain, corroborated by intracranial recordings (Neelon, J. Williams, & Garell, 2006). A more difficult question regards what the different peaks actually tell us. For instance, although the P3 peak is widely used to operationalize attention shifts or working memory functions, it covaries with a wide variety of other tasks and states (Polich & Criado, 2006). A question is therefore whether much can be said about validity if the criterion is vaguely defined. Finding that e.g. P3 covaries with attention, working memory, arousal and several clinical disorders may be the result of validity problems of these constructs rather than the method itself. The ERP technique provides excellent temporal resolution, but lacks in spatial resolution. For an introduction to the ERP technique, see Luck (2005).

Functional magnetic resonance imaging (fMRI)

The brain at work requires energy that is provided by oxygenated blood. A particularly active area of the brain requires more than one that is less active. A measurement of regional blood flow is thus assumed to be an indirect measure of neural activity. The foundation of fMRI lies in the characteristics of atomic nuclei, and how magnetic forces affect them. The protons of atomic nuclei are slightly magnetic, and will line up when within a magnetic field such as one created in a scanner. When an additional magnetic field is introduced, protons of the atomic nuclei found in certain materials will align with this new field. When the field is turned off, these protons will return to their original states, emitting energy that can be detected and registered. Thus, by introducing a magnetic field that excites the protons of oxygen, we may measure the flow of oxygenated blood within the brain. The fMRI method does not match ERPs in terms of temporal resolution, but provides excellent spatial resolution.

The fMRI technique has proven to have good test-retest reliability, both in short and long terms (Aron, Gluck, & Poldrack, 2006; Kiehl & Liddle, 2003). Although the intra-subject variability of fMRI recordings is relatively low, the inter-subject variability is high. Thirion et al. (2007) therefore suggested that fMRI studies should include at least 20 participants to provide reliable results. For a review of the fMRI technique, see Huettel, Song, and McCarthy (2009).

Magnitude estimation and category ratio scaling

Magnitude estimation is a method in which an observer assigns a numerical value to the sensation that a certain stimulus elicits. The rationale behind this method is that observers are able to use the numerical system as an abstract measuring scale to communicate the internal sensation to others. For instance, the length of a line, the pain produced by an electric shock, or the perceived intensity of an odorant can be estimated by assigning to it a positive number or fraction that represents the sensation (Stevens, 1975). Stevens (1975) found that it is possible to express the relationship between the physical properties of a stimulus and the sensation it elicits in the form of a power law stated as $\psi = k\phi^a$, where ψ is sensation magnitude, k is a constant determining the scale unit, ϕ is physical stimulus intensity and a is the exponent that is determined depending on sensory modality and the characteristics of the stimulus. Magnitude estimation constitutes a reliable, simple, yet powerful method of measuring the sensation a certain stimulus elicits (Gescheider, 1997). Category ratio scaling is a scaling procedure in which observers measure a sensation both in terms of the category to which it belongs (e.g. "strong"), as well as its numerical value in the form of a ratio. Different versions of the Borg scale are constructed to make observers utilize this procedure (E. Borg & G. Borg, 2002). Both methods have proven to be reliable (Gescheider, 1997), and both are utilized in the thesis studies.

The empirical studies

There are five hypotheses in this thesis. Four are based on the CI theories described above and pertain to assumptions of sensitization, attention bias and peripheral / central connections in CI. One is extracted from prevalence studies and deals with the assumed over-representation of women in CI.

The two sensitization hypotheses

Sensitization is a key characteristic of CI according to the neural sensitization (Bell et al., 1999), conditioning (Van den Bergh et al., 2001) and neurogenic inflammation (Meggs, 1994) theories. In its simplest but nevertheless defining form, sensitization refers to an increase in response (e.g. neural firing rate or estimated perceived intensity) over time to a stimulus with fixed physical intensity. Habituation is the opposite reaction, i.e. a decrease in response over time to a stimulus with fixed physical intensity (Overmier, 2002; Thompson, 2009). Sensitization and habituation are assumed to be the result of two independent or dual processes, one excitatory and one inhibitory. These two processes can be defined at several levels, from synaptic transmission and neurotransmitter release, to general states of the brain, behaviour and higher functions such as attention (Groves & Thompson, 1970; Thompson, 2009). Accordingly, sensitization and habituation do not necessarily refer to reactions in a specific set of organ systems or brain areas, but can be applied to several bodily systems including hormonal, immunological and neural (Rankin et al., 2009). Within this thesis, sensitization and habituation are assumed to be the effects of a dual process. However, these two processes are also assumed to be instantiated at several levels of the organism, thus being observable from several perspectives and with different methods. Sensitization can be studied using a wide range of methods and instruments, and the basic requisites of study designs are simple – know the properties of the stimuli and measure reactions over time.

Two measures of sensitization are used in the thesis studies. The first pertains to the perceived intensity changes over time, and is assessed by magnitude estimations (Stevens, 1975). The second measure refers to changes in neuronal activity in the CNS over time, and is measured by recording ERPs and regional cerebral blood flow (rCBF) patterns using fMRI. The behavioural and neural aspects of sensitization are important in the above mentioned theories of CI. A lack of sensitization in these aspects would therefore arguably falsify all three theories.

Hypothesis 1: Persons with self-reported CI sensitize to olfactory and chemosomatosensory stimuli, whereas non-CI individuals habituate. *This effect*

should be discernible as higher ERP amplitudes and faster latencies as well as greater perceived intensities over time in the CI group compared with non-CI group. This is investigated in Study 1: Attention bias and sensitization in chemical sensitivity⁷.

Hypothesis 2: Sensitization in CI is similar in terms of brain activation patterns to sensitization found in healthy groups and to that found in other unexplained illnesses such as fibromyalgia. *Sensitization is assumed to be discernible as higher rCBF in sensory areas, amygdala and anterior insula and lower rCBF in rostral anterior cingulate cortex (rACC).* This is investigated in Study 4: An fMRI study of chemical intolerance.

The attention bias hypothesis

Attention bias, i. e. a predisposition to more or less automatically attend certain features of the environment, is closely related to neural sensitization (Brosschot, 2002). A sensitized stimulus is also one that is deemed as salient. The stimulus is thus prioritized over other features in our surrounding. This can be understood as an attention bias (Ursin & Eriksen, 2004). **An attention bias may constitute an explanation for cognitive symptoms such as concentration difficulties in persons with CI (M. J. E. Andersson et al., 2009).** An attention bias is also assumed in the neural sensitization (Bell, 1996; Sorg, 1999), conditioning (Van den Bergh et al., 2001) and neurogenic inflammation (Bascom et al., 1997) theories of CI.

Hypothesis 3: Persons with CI have an attention bias to chemical exposures, reflected in problems with withdrawing attention from such stimuli. *This should be discerned as group differences in ERP amplitudes and latencies when prompting persons with and without CI to ignore chemosensory stimuli.* This is investigated in Study 1: Attention bias and sensitization in chemical sensitivity.

The central / peripheral connection hypothesis

An important assumption of the neural sensitization (Bell et al., 1999), conditioning (S. Siegel & Kreutzer, 1997) and neurogenic inflammation (Bascom et al., 1997) theories is the connection between peripheral and central mechanisms. **Accordingly, hyper-responsiveness in peripheral neurons should be paralleled by increased reactivity in the CNS as well.**

7. I have since the publishing of this study adopted the term CI instead of chemical sensitivity as the term “sensitivity” suggests a chemical etiology (IPCS, 1996; Labarge & McCaffrey, 2000) that may be true but not necessarily so.

Hypothesis 4: Measures of peripheral hyperreactivity are correlated with chemosensory ERP measures and CO₂ detection sensitivity. This is investigated in Study 2: **On the relation between capsaicin sensitivity and responsiveness to CO₂: detection sensitivity and event-related brain potentials.**

The sex / gender hypothesis

CI has been described as a disorder mainly affecting women (Labarge & McCaffrey, 2000; Miller, 2001; Sorg, 1999; Sullivan et al., 2001). A relevant question is therefore why this is so.

Hypothesis 5: The reactions of women, following chemical exposure, should resemble those found in persons with CI to a greater degree than the case in men. *This should be discerned as sex differences in ERP latencies when prompting participants to ignore chemosensory stimuli. Men are also assumed to habituate to a greater degree, as seen by magnitude estimations over time. Finally, women are hypothesized to have lower chemosensory detection thresholds than men.* This is investigated in Study 3: **Chemosensory attention, habituation and detection in women and men.**

Study 1

Attention bias and sensitization in chemical sensitivity

Aims and methods

The aim of the first study was to investigate whether persons with self-reported CI show signs of sensitization and attention bias toward odorants. Magnitude estimations, ERPs and reaction time measures were registered from 21 intolerant and 17 non-intolerant persons, grouped according to results from a web version of the CSS-SHR questionnaire (Nordin et al., 2004). The participants were scheduled for two occasions. During the first session, the participants made a capsaicin inhalation test. The results of this provocation challenge were analysed in study 2. During the following session, olfactory and trigeminal thresholds were assessed, followed by an exposure procedure in which ERPs, magnitude estimations and reaction times for olfactory (amyl acetate), chemosomatosensory (CO₂) and auditory (70dB(A), 1000 Hz tone) stimuli were collected.

Participants alternated between an attend and an ignore task during the session. During the attend task, participants were prompted to respond to a stimulus as fast as possible by pressing a mouse button. In addition, they were instructed to estimate the intensity of the olfactory and chemosomatosensory stimuli by means of cross-modal magnitude estimation (Nordin, 1994). The reference stimulus was auditory and represented the perceived intensity of the modulus (an anchoring point), and was set to 100. The participants assigned numbers representing perceived intensities to each olfactory and chemosomatosensory stimulus in relation to the perceived intensity of the modulus. The participants were not aware that the concentration of the stimuli remained constant throughout the testing. Hence, any change in magnitude estimation was assumed to be the result of sensitization / habituation processes. 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.

Results and discussion

At the beginning of the testing, the magnitude estimations of perceived intensity from the sensitive and non-sensitive groups did not differ. However, after about an hour of testing, the sensitive individuals began to sensitize to the CO₂ exposures, whereas the non-sensitive individuals seemed to continue to habituate (Figure 4).

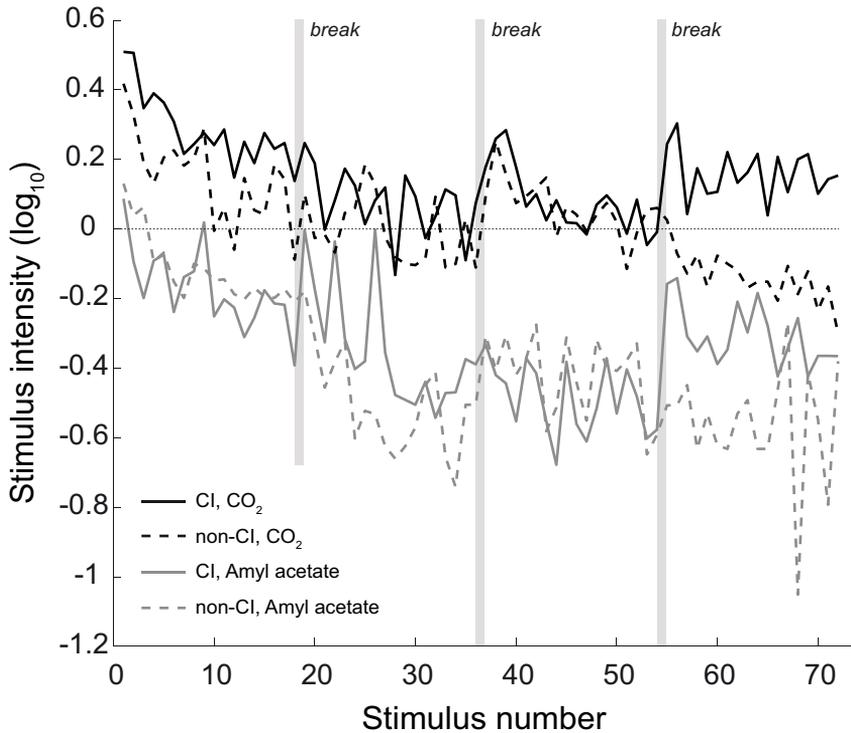


Figure 4: Mean magnitude estimations for the CI and non-CI groups. A 1000Hz, 70 dB(A) tone is used as a modulus with a pre-set perceived intensity value of 100.

A sensitization/habituation effect could also be discerned in the ERP waves. The amplitude of the first negative deflection was decreased during the second part of the test in the non-CI group. No such decrease was found in the CI group. This peak, labelled the N1, has by others been associated with early sensory filtering and allocation of perceptual resources (Kok, 1997). Moreover, it has been shown that olfactory (Tateyama, Hummel, Roscher, Post, & Kobal, 1998) and chemosomatosensory (Frasnelli, Lötsch, & Hummel, 2003) N1 amplitudes increase with greater stimulus intensities.

The ERP analyses can also be interpreted as the effect of an attention bias in the CI group. Whereas the non-intolerant group had significantly delayed chemosomatosensory and olfactory P2 peaks when prompted to ignore the exposures, no effect of attention was seen in the CI group (Figure 5). The chemosensory P2 and P3 peaks have previously been associated with allocation of attention (Krauel, Pause, Sojka, Schott, & Ferstl, 1998), which lends merit to the idea of an attention bias in CI.

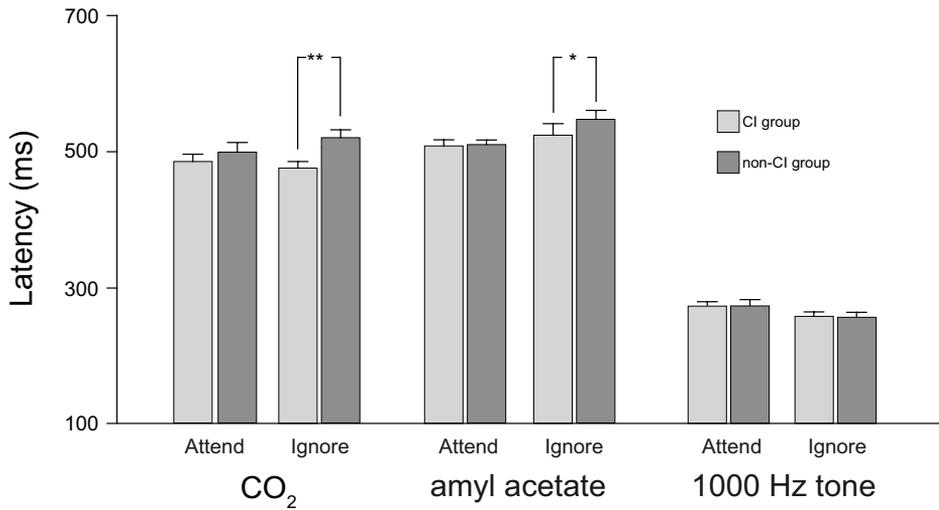


Figure 5: P2 latencies (mean \pm SEM) in the attend and the ignore conditions for the CI and non-CI groups. Asterisks indicate p -values from parameter estimates. (* $p < .05$; ** $p < .01$).

Finally, persons in the CI group had faster reaction times than the non-CI to the exposures of all sensory modalities. This may be an effect of higher overall arousal in the CI group during testing and might be related to the effects found in the NI amplitudes.

Although the results raise some important questions – for instance, why the sensitive participants did not sensitize to amyl acetate, and why there were no sensitization effects in later ERP peaks – the overall picture seems to indicate both sensitization and attention bias in CI.

Study 2

On the relation between capsaicin sensitivity and responsiveness to CO₂: detection sensitivity and event-related brain potentials

Aims and methods

This study addressed the connection between peripheral and central mechanisms in CI. This was done by correlating the number of coughs following capsaicin provocation, chemosomatosensory and olfactory detection thresholds and ERP measures. In addition to these analyses, capsaicin cough sensitivity and detection thresholds were analyzed in two groups based on the CSS-SHR. The data on which this study is based partly overlaps that of Study 1, although different analyzing methods were used.

The ERP recording session was the same as in Study 1, but the ERPs were averaged without regarding different attention tasks and parts of the study. Nebulized capsaicin at concentrations of 0.4 and 2.0 $\mu\text{mol/L}$ was used for the inhalation test. Participants inhaled the solutions and the number of coughs following each concentration was registered. Chemosomatosensory and olfactory detection sensitivity was assessed using two-alternative (stimulus/blank) ascending methods of limits utilizing a forced-choice procedure (Gescheider, 1997). This meant that participants were presented with two consecutive stimuli – one blank and one containing the chemical. If they failed to correctly identify the chemical in five consecutive trials, the chemical stimulus intensity was increased. This went on until the participant had identified all stimuli at a certain concentration step. This step was regarded as the detection threshold.

Results and discussion

Persons with a high CSS-SHR score (≥ 43) coughed significantly more than those with a low score (< 42). The persons with a high score also had significantly lower CO₂ detection thresholds than those with a low score. This can be seen as an indication that persons who report CI also have greater capsaicin and CO₂ sensitivity. Investigating the relationship between the ERPs and number of capsaicin induced coughs revealed a tendency of correlation between coughs and chemosomatosensory N1 and P2 latencies. A tendency of correlations was also seen for auditory N1 amplitudes and latencies. Arguing that the result of this study reveals a clear relationship between peripheral and central measures of sensitivity would be an exaggeration. The results should however neither be dismissed as they support the central/peripheral relation hypothesis. The finding suggests that there is an association between peripheral and central mechanisms in CI.

Study 3

Chemosensory attention, habituation and detection in women and men

Aims and methods

The setup of this study was almost identical to the first, with the exception that the grouping variable was sex and not self-reported CI, and that detection thresholds were determined. In addition, no capsaicin provocation test was performed. The rationale for studying women and men within this paradigm was that possible differences in the responses of women and men may yield some insight into why CI mainly is reported by women. Eighteen women and the same number of men, selected to be comparable in terms of age and self-reported CI, participated in the study. The stimuli, methods and attend/ignore tasks were the same as in Study 1.

Results and discussion

First of all, women and men did not differ in terms of sensitization measures. Both groups showed the same amount of habituation when assessed with magnitude estimations over time (Figure 6) and no time-dependent group differences were found in ERP measures.

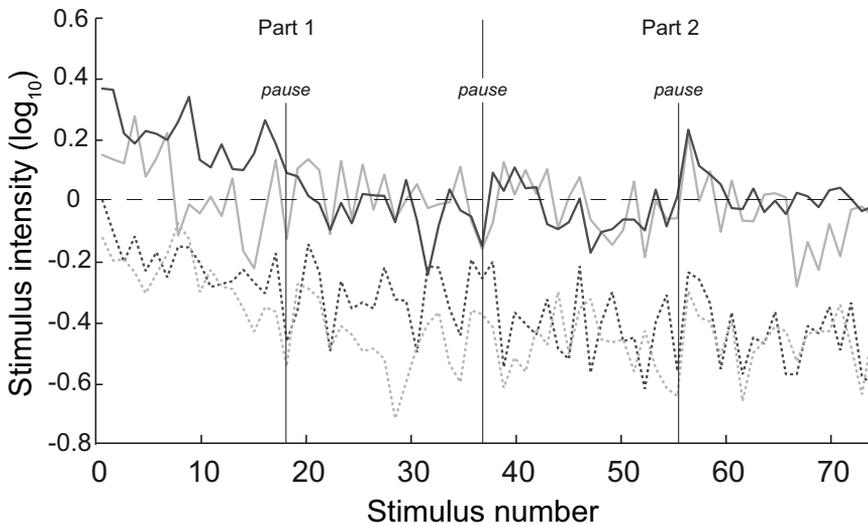


Figure 6: Intensity ratings of CO₂ (solid line) and amyl acetate (dotted line) stimuli. Black lines indicate ratings given by women, whereas grey lines indicate ratings by men. The dashed line refers to an auditory modulus with a pre-set intensity of 100.

Women and men did not differ in ERP measures when prompted to ignore the stimuli. However, women had significantly higher olfactory and chemosomatosensory P₃ amplitudes than men when attending the stimuli (Figure 7). Such an effect was not found for the auditory stimuli. This is interesting. If women would have had larger amplitudes than men regardless of task, it would be reasonable to argue that the chemosensory systems generally are keener in women. The effect is however only found when introducing an attention shift. Does this mean that women are better at modulating attention toward such exposures and in that case, why? One hypothesis that does not require an assumption that women and men differ in fundamental cognitive processes such as attention, deals with culture and learning. Ferdenzi et al. (2008) have suggested that girls from an early age are more attentive to everyday odors than boys, possibly because of a greater social expectancy to evaluate odors as significant cues. Girls have more aversive reactions to smells, e.g. to cigarette smoke and car exhausts, and are more concerned with the control of odors already from a pre-school age (Ferdenzi et al., 2008).

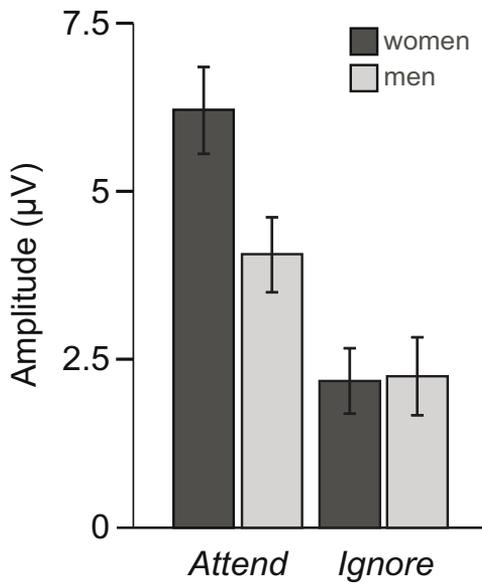


Figure 7: Averaged chemosensory and olfactory P₃ amplitudes (\pm SEM) in the attend and ignore condition.

Women and men differed in one more aspect, and that is CO₂ detection thresholds, where women had the lower thresholds. Why women outperform men in this regard remains to be elucidated. Other researchers with similar results are also at a loss (Shusterman, 2007).

In this study, the only aspect of chemosensation in which there are similarities between women and a CI group is chemosomatosensory detection thresholds. Results from Study 1 suggest that CI individuals have an attention bias to chemosensory exposures, i.e. have difficulties ignoring them. The current results rather indicate that women are remarkably good at modulating their responses based on the task-related relevance of the stimuli. Neither were any differences in sensitization found between women and men similar in age and level of CI.

Study 4

An fMRI study of sensitization in chemical intolerance

Aims and methods

The neural sensitization (Bell et al., 1999), neurogenic inflammation (Meggs, 1994) and conditioning (Van den Bergh et al., 2001) theories of CI assume some kind of sensitization processes in the CNS. This increased reactivity is hypothesized to be present mainly in the limbic system. An important issue is therefore to investigate whether this really is the case. In Study 4, the focus is moved to the brain structures assumed to mediate a sensitized response to chemosensory stimuli.

A total of 59 women, including persons with both MCS and SBS, participated in the study and were scheduled to two occasions. During the first session, the study setup was explained and each participant had the opportunity to lie down in a mock scanner to become acquainted with the experience of lying in an fMRI scanner. Individual odor detection thresholds were determined to confirm that all participants had a functional sense of smell.

During the second occasion, participants were placed in a 3-tesla scanner and rCBF was registered while the participants were exposed to low concentrations of amyl acetate and CO₂. Instead of assigning participants into sensitive and non-sensitive groups based on questionnaire data, groups were defined based on perceived intensity assessed with magnitude estimations. Participants who perceived the odor intensity of the invariant stimulus concentration as increasing over time constituted the sensitizer group. Those reporting decreased odor intensity over time were grouped as habituaters (Figure 8). This reflects a change in perspective and a greater emphasis on measures of sensitization rather than results of self-report questionnaires. Based on magnitude estimation results, the fMRI results of 14 sensitizers and 15 habituaters were compared.

Results and discussion

The sensitizers had higher regional rCBF in the amygdala, anterior insula and olfactory regions of the orbitofrontal cortex, but lower rCBF in the rACC compared with habituaters (Figure 9). These results suggest a sensory amplification mediated by CNS areas previously implicated in habituation to pain and placebo analgesia (Bingel et al., 2006; Zubieta & Stohler, 2009), but also clinical conditions such as fibromyalgia (Jensen et al., 2009; Napadow et al., 2010), generalized anxiety disorder (Shin & Liberzon, 2010) and PTSD (Etkin & Wager, 2007). Overall, these results are in line with the hypothesis that sensitization in the central nervous sys-

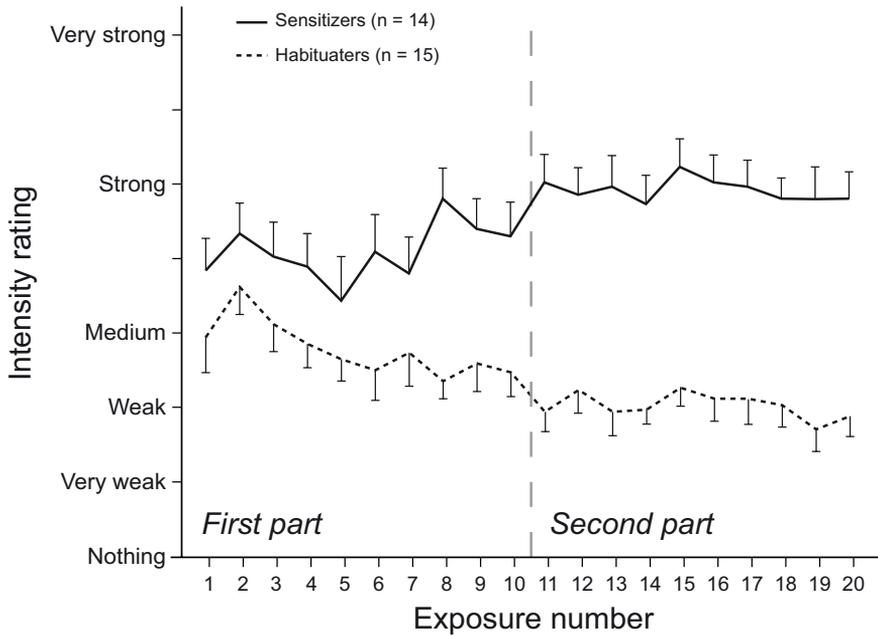


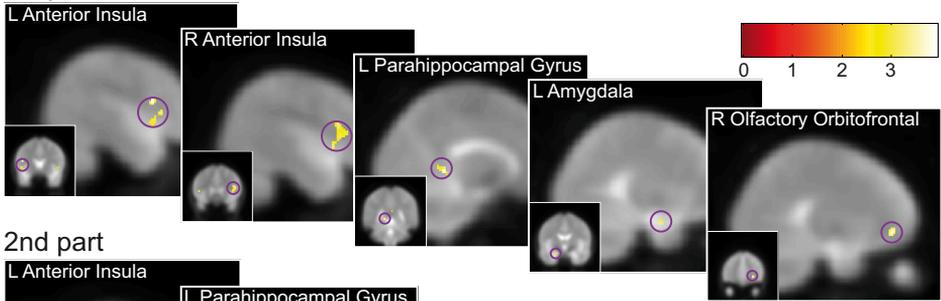
Figure 8: Magnitude estimations of 20 consecutive amyl acetate presentations. The group assignment (sensitizers / habitaters) was based on these results.

tem as a hallmark for CI, postulated by the neural sensitization, conditioning and neurogenic inflammation theories (Bell et al., 1999; Van den Bergh et al., 2001; Meggs, 1994).

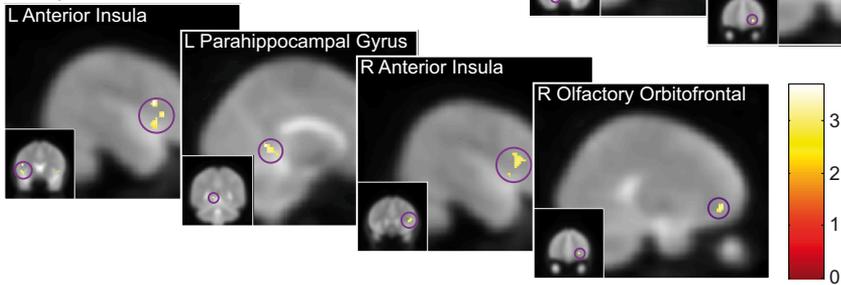
In addition to the fMRI results, the olfactory sensitizers also reported everyday problems with everyday chemical exposures to a greater degree than both olfactory habitaters and the general population (Nordin et al., 2003). Although the emphasis in an expensive fMRI study should be the brain imaging results, this way of grouping participants merits some attention. If a sensitized response in the laboratory implies greater problems with odors in everyday life, sensitization measures may in the future prove to be a reasonable method of diagnosing CI.

Sensitizers – Habituated

1st part

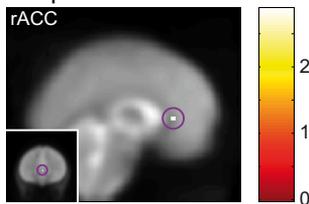


2nd part



Habituated – Sensitizers

1st part



2nd part

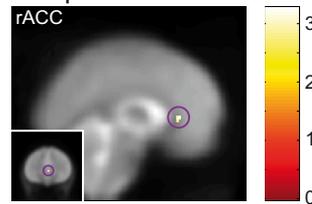


Figure 9: Significant rCBF differences between persons who sensitize to amyl acetate compared with those who habituate. The background image is the template used for normalizing the individual brain images.

Examining the five hypotheses

Hypothesis 1: Persons with self-reported CI sensitize to olfactory and chemosomatosensory stimuli, whereas non-intolerant individuals habituate.

Hypothesis 2: Sensitization in CI is similar in terms of brain activation patterns to sensitization found in healthy groups and to that found in other unexplained illnesses such as fibromyalgia.

Study I revealed that the N1 ERP peak amplitude in the CI group, across all sensory modalities, did not differ between the first and second part of the study. In the non-CI group, the amplitude was attenuated in the second part. This can be interpreted as a habituating process that is present in the non-CI, but not the CI group. Moreover, the magnitude estimations revealed significant differences in perceived intensities of CO₂ exposures between groups. These results corroborate the first sensitization hypothesis, at least to a certain degree. Sensitization effects were neither found in the olfactory magnitude estimations, nor the P2 and P3 ERP peaks. One interpretation of this lack of results is that sensitization, while present in some occasions, does not constitute a permeating factor in CI.

There are however reasons for delving a bit deeper with this issue by investigating the premises of sensitization. The amyl acetate and CO₂ used in Study I were selected to be distinct, with the rationale that relatively strong exposures generates a more distinct ERP wave. However, such strong concentrations of odorants are never found in everyday life. One could argue that a chemical exposure of such strength would constitute stimuli to which everybody would sensitize, not only persons with CI.

Another possible explanation for the lack of olfactory sensitization could be that the CO₂ exposures, being perceived as stronger than the amyl acetate, overshadowed the intensities of the odor stimuli presented in the same stimulus sequence. As sensitization implies an attention bias, it is possible that participants who sensitized to CO₂ focused their attention and became sensitized to the most salient stimulus. It is also possible that sensitization is a major characteristic of some, but not all cases of CI, or that sensitization is specific to certain chemicals. Despite the fact that the questions regarding sensitization in CI has not been adequately answered by Study I, it supports the first hypothesis to a degree that merits further inquiry. If the sensitized response indeed is a major characteristic of CI, it may provide the basis for a new way of assigning participants into different groups, one that does not rely on questionnaire data.

In Study 4, participants were assigned to groups in accordance with their sensitized or habituated perceived intensity. Analyses revealed that the rCBF of sensitizers and habituaters differed in a way that is similar to fibromyalgia patients compared with controls (Jensen et al., 2009). The rCBF of habituaters were also similar to that found in persons who habituated to pain, where the RACC seems to act as an inhibitor of limbic areas and anterior insula (Bingel, Schoell, Herken, Büchel, & May, 2007; Wiech, Ploner, & Tracey, 2008). Study 4 thus corroborates the second sensitization hypothesis.

Hypothesis 3: Persons with CI have an attention bias to chemical exposures, reflected by problems with withdrawing attention from such stimuli.

According to theory, being sensitized to an exposure also implies an attention bias to that stressor (Brosschot, 2002; Ursin & Eriksen, 2004). Study 1 provides partial support for this hypothesis as the results indicated that the ERP responses in the CI group were not affected by task demand. It could however be argued that latency changes of ERP peaks do not really cover the concept of an attention bias. These results thus need to be corroborated at least by some behavioral measures. For instance, one hypothesis could be that an attention bias in CI should be expressed as decreased performance of executive tasks when exposed to smells. Pilot data from our laboratory suggests that this may be the case.

Hypothesis 4: Measures of peripheral hyperreactivity are correlated with chemosensory ERP measures and CO₂ detection sensitivity.

This hypothesis is partly corroborated by Study 2. Persons who rated relatively high annoyance to chemicals coughed more as a response to capsaicin inhalation and had lower CO₂ detection thresholds than those with lower CI ratings. Number of coughs was also weakly related to ERP measures. Although the results are slightly weak, they are in line with the hypothesis that peripheral and central reactions interact in CI. Peripheral and central connections are an aspect of all three CI theories, and may also have implications for future interventions. For instance, focusing on central aspects of sensitization may prove unfruitful if a local inflammatory response remains untreated, thus reproducing the sensitized response. Another possibility is that the symptoms subside if one link in the inflammatory and stress response chain is broken. It is therefore of importance to investigate these matters further in future studies.

Hypothesis 5: The reactions of women, following chemical exposure, should resemble those found in persons with CI to a greater degree than the case in men.

The women in Study 3 do not show the same pattern of reaction as the CI group in Study 1, with the exception of CO₂ thresholds. The women and men in Study 3 habituate to the same degree, and neither of the groups showed signs of sensitization that characterized the CI individuals in Study 1. Women in general had higher ERP amplitudes when attending chemosensory stimuli, but this does not match the lack of latency differences found in the sensitive group when attending and ignoring stimuli.

Overall, this pattern of results does not yield any clear insights into why women are overrepresented in CI, but suggests that the sensitization response is mediated by degree of self-reported CI. It may still be the case that the higher amplitudes found in women, while not a measure of CI, is a predisposing factor for the development of symptoms.

The theoretical synthesis

*And now have I not told you that what you mistake for madness
is but over-acuteness of the senses?*
— Edgar Allan Poe (1809 – 1849)

The empirical studies of this thesis work can be related to previous studies relevant to CI. For instance, the failure to directly tie female sex to sensitization and the similarities in terms of rCBF between fibromyalgia and CI may yield insights into the mechanisms underlying the affliction. The studies also lend support to some of the hypotheses postulated within the theoretical frameworks of CI reviewed above.

It is possible to stop here, to conclude that the thesis work provides support for several theoretical accounts and leave it at that. CI is however a controversial subject. It is not uncommon for researchers interested in this topic to be placed in a ring-corner in a polarized and heated debate. The topic of this debate is whether CI is an affliction of the body or of the mind. The reason why the issue is so infected is that it directly relates to the life conditions of the sufferers. A proven organic aetiology would arguably imply that persons with CI would be embraced by the medical paradigm – that it constitutes a “real” disease (Murphy, 2000). Placing it in a psychological category burdens the affliction with illegitimacy. One of the study participants summarized the issue by saying *“it is so very important that someone studies this disease. Too bad it’s the psychologists who are doing it.”*

Working in the field of psychology, I feel obliged to put the thesis work in proper context by offering a way of viewing CI in which confrontations between scientific fields are avoided. This is a twofold process.

The first step will be to scrutinize the core controversy of CI and then present a way of integrating the neural sensitization (Bell et al., 1999), neurogenic inflammation (Meggs, 1994) and conditioning (Van den Bergh et al., 2001) theories of CI. This synthesis will result in a suggestion of how the construct that is CI should be viewed. I will argue that CI should be defined at several levels, including aspects both of the body and of the mind. The second step will be to offer a theoretical framework, a common language that can be used to interpret the different aspects of CI. This framework should not be seen as a new theory of CI, but rather an integration of previous theories.

Setting the scene of the CI controversy

CI exists at the fringes of, or possibly even outside, our current medical understanding of disease and health (Murphy, 2000). As a consequence, medical practitioners have been reluctant to call CI a disease. This makes CI a non-disease; a form of suffering without any known external cause. Rejecting the notion of external chemical triggers for CI symptoms paves the way for investigating internal, psychosomatic causes of the suffering. This change of perspective burdens CI with illegitimacy, as in the case of most psychiatric conditions. The ramifications go beyond the inability of clinical practitioners to diagnose and treat the CI patient, as our sociocultural and political understanding of health is intertwined with the medical paradigm. Sufferers are often met with skepticism or even hostility both from the medical community and society at large, as CI does not conform to ideas of what constitutes a “real” disease (Skovbjerg et al., 2009). A serious and negative consequence of this skepticism is that CI sufferers become medical, political, social and economic outsiders.

At the heart of the problem lies the division between body and mind. Ailments stemming from measurable bodily injuries are deemed as legit, whereas conditions characterized by psychological suffering are less so. CI has been regarded as belonging to the latter category, and the labels used to describe the affliction often have negative connotations (e.g. “fashionable illness”; Binder & Campbell, 2004). Patients run the risk of being regarded as malingerers, i.e. deliberately lying about their symptoms to gain secondary benefits such as disability pension. Although most clinicians would avoid this label and instead use the term somatization disorder, the problem remains. Somatization, at least from a medical perspective, tend to imply that the symptoms that the sufferer are experiencing in fact has no real cause; that it can be seen as a form of self-deception (Butler, Evans, Greaves, & Simpson, 2004). Consequently, some patient organizations and clinicians have struggled vehemently to include CI in the current biomedical paradigm, rejecting the idea that symptoms can be associated with psychological or psychiatric states (Murphy, 2000). For instance, a visitor at the MCS America website will find that their first mission statement is “to gain medical, legal, and social recognition for multiple chemical sensitivity (MCS) as a disorder of organic biological origin induced by toxic environmental insults” (<http://www.mcs-america.org/>). Claiming an organic origin of symptoms generally seems to rule out psychological factors, and vice versa.

A surprisingly prevalent notion seems to be that the body and mind are discrete and inherently separate entities. This line of reasoning exists despite the underlying assumption of most contemporary neuroscientists that all psychological states

originate from the body or more precisely the brain. An example can be made from the CI literature. Orriols and colleagues (2009) argued that the rCBF of patients with MCS was different than that found in healthy controls. The authors concluded that the results suggest a neurogenic pathogenesis for MCS. They do however use the very same argument against a psychological mechanism. A consequence of this kind of reasoning is that psychological states are seen as separate from the body and nervous system. This in turn implies that such states cannot be studied empirically.

This way of analyzing neurophysiological data may have more to do with legitimizing CI, and less with the body and mind dualism. This pertains to the moral dilemma described by Butler and colleagues (2004) – a clinician meeting a patient with an unexplained condition can either interpret it as a somatization disorder with all its negative undertones, or acknowledge the patient’s view that the symptoms are caused by bodily injury. To sustain the physician – patient relationship, the clinician often accedes to the patient’s view.

This discrepancy is however unnecessary from a theoretical point of view if we adhere to the assumption that all psychological states and symptoms are paralleled by neural activity. Such a view prompts us to view the labels psychological, physiological and immunological as referring to aspects of a unitary system. To make the point even clearer, this perspective suggests that these concepts cannot exist without each other – all behaviors and states of an organism can be expressed in terms of these labels, but not solely by either one of them. This gives us a template as to how we ought to think about results or lack thereof. If a person complains of symptoms without deviations in physiological or immunological measures, the reasonable conclusion would be that this is due to limitations in our instruments, not that there are no physiological or immunological reactions. As Ursin (2009) summarized the issue: Dualism is dead.

Integrating the theories

I have previously argued that the neural sensitization (Bell et al., 1999), the conditioning (Van den Bergh et al., 2001) and the neurogenic inflammation (Meggs, 1999) theories of CI share the same ontological assumptions in that they are all based in physiological processes. I have also argued that sensitization, conditioning and neurogenic inflammation are different expressions of the same underlying system. The final step in this integration is to present the merged model in a way that preserves the individual theories without insinuating that they refer to separate systems.

The paned window parable

Imagine that you are watching an event through a paned window. As you see it, the scene seems to be divided into different sections, and each pane shows something different than the others. It would not be surprising if an unbiased observer without any previous knowledge about the world and the objects in it would come to the conclusion that there are different worlds behind each pane. From a single vantage point, there is no overlap between the scenes seen through the panes.

Because of our experience and knowledge of the world, we assume that there is only one world behind the panes. We assume that the separation suggested by the paned window is caused by imperfections in the medium through which we observe the world. This assumption is corroborated by changing the vantage point slightly or watching a moving event unfold outside. There is now considerable overlap between the panes, to the point where we can reject the notion that the mullions demarcate different worlds.

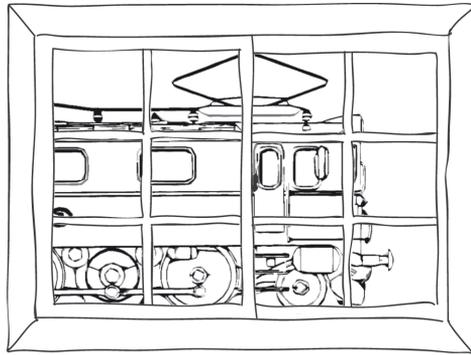


Figure 10: When watching a train passing by through a paned window, do the twelve panes reveal twelve different incomplete trains, or should we see this as an illusion resulting from imperfections of our medium?

Imagine watching a train pass by outside the paned window (Figure 10). As time passes, one can see more of the train and it is now visible through other panes as well. An experienced observer would not assume that the front of the train first seen through the leftmost panes, e.g. its front window, causes the movement of other parts of the train. It would therefore be incorrect to draw causal arrows from one pane to the next. This is not the same thing as to say that there are no causality, just that the panes do not necessarily yield the causal connections.

If we would like to study one part of the train more closely, we can approach one of the window panes. In doing so, we get a more detailed view of that aspect, but we also lose sight of other parts of the train. An incorrect conclusion would

be to assume that the other parts therefore cease to exist. Parallel to this, it is easier to watch some aspects of the train from certain panes. It is easier to view the spokes through the lower panes, while the roof is most visible from the topmost panes.

CI through the paned window

If we apply the paned window parable to CI, different aspects of the disorder would be discernible through different panes. One pane could for instance show reactions in peripheral receptors, whereas another could yield cultural perspectives. Watching the CI process should be seen as parallel to the train example. We may observe that peripheral inflammation seems to come first in one person, which is equivalent to initially seeing only the front of the train through the leftmost window pane. In another person, pressure at work seems to be the initiating factor, which neither implies that it is the cause of the problems, nor that it is the defining characteristic of the phenomenon. We should not assume that we have a clear view of the causal chain of events. Neither should we assume that CI in which peripheral inflammation is seen first is inherently different than the case where stress at work seems to have triggered symptoms. This would be parallel to assuming that different panes show different worlds. The examples can be illustrated accordingly:

CI in which inflammation is seen first (Figure 11)

Observation 1: Iris is exposed to a toxic chemical at work. This triggers a local inflammation, SP release and lower thresholds in the receptors.

Observation 2: The inflammation spreads to nearby tissues via inflammatory mediators and axon reflexes, causing SP release at these sites (Meggs, 1994). The reaction is reflected in increased stress seen by e.g. increased anxiety and a predisposition of perceiving other exposures as toxic. Increased autonomic nervous system reactivity and sensitization to the stressor in the limbic system may also be found (Bell et al., 1999, 1992).

Observation 3: Through the CNS, the inflammatory response is propagated to other organ systems in the body, triggering the release of mediators such as SP (Meggs, 1994). Iris' colleagues, watching her becoming ill from the exposure, are primed for danger and avoid the exposure.

Observation 4: In her current state, Iris is more prone to develop aversions to other stimuli perceived as dangerous, thus associating her state with more stressors (Van den Bergh et al., 2001). This incident leaves a lasting impression in others around her. The way people henceforth talk about chemicals found at the workplace is now changed. This reluctance predisposes others toward seeing chemicals as stressors. This in turn increases the risk of developing aversions, sensitization and neurogenic inflammation in others (Rosenkranz, 2007).

Viewpoints	Sociocultural	According to discourse, the odour or one that is similar is associated with danger.	Watching the reactions to the odour, colleagues are primed for danger.		
	Central	Increased stress responses through feedback loops, higher risk of aversive conditioning.		Increased stress response reflected by e.g. anxiety, sensitization and ANS activity.	
	Peripheral		Increases levels of SP in distant tissues, relayed through central structures.	Release of SP and other mediators in nearby tissues, propagated by axon reflexes.	An event with SP release, inflammation and lowered thresholds.
		Observation 4	Observation 3	Observation 2	Observation 1

Figure 11: Observing CI in which inflammation is seen first. Depending on perspective (broadly defined as peripheral, central and sociocultural), we see different aspects of an event unfolding. The different viewpoints do not allow us to conclude that we are watching different CIs, or in the case of the illustration, different trains.

CI in which individual stress is seen first (Figure 12)

Observation 1: William is stressed at work, which means that he is more prone to perceive environmental stimuli as stressors (Ursin & Eriksen, 2004). This implies a greater risk for developing aversive conditioning (Van den Bergh et al., 2001), sensitized responses to such exposures, and is also paralleled by increased SP in the CNS (Rosenkranz, 2007).

Observation 2: After learning from colleagues that Iris got ill from an environmental chemical, he is especially reluctant toward such stimuli.

Observation 3: Avoiding chemicals is however impossible, and William begins to associate a certain perfume, the smell of the copier and the cleaning products used at work with his stress responses.

Observation 4: This leads to a positive feedback loop that elicits even more stress, higher SP release and even greater reluctance toward chemicals among colleagues.

Viewpoints

Sociocultural	Watching the reactions to the event, colleagues are primed for danger.		According to discourse, an odor present in the workplace is associated with danger.	
Central	Increased stress responses through feedback loops, higher risk of aversive conditioning.	After exposures to an odor seen as dangerous, subsequent presentations elicit a CR.		The individual feels stressed and is thus prone to sensitization and aversive conditioning.
Peripheral	Increased levels of SP in distant tissues, relayed through central structures.			Elevated levels of SP found in central structures such as the amygdala.
	Observation 4	Observation 3	Observation 2	Observation 1

Figure 12: Observing a case of CI in which individual stress is seen first. Can we from our different viewpoints conclude that the underlying event is different than the one in Figure 11?

Interpreting the CI in “Iris” and “William”

One way of interpreting the CI in Iris and William is to assume separate underlying processes – one in which a chemical agent triggers a biological response and the other in which stress seems to be the cause (Sullivan et al., 2001). However, according to the theoretical framework offered above, the underlying mechanisms are the same. Separate observers focusing on different aspects of a train passing by make a mistake by assuming that they observe different trains. If this parable is correct, the three theories offer different vantage points for studying the same process.

Signal detection theory (SDT) and CI

I have argued that the three theories of CI offer different perspectives on the same construct. Turning to the CI construct itself, an important question is whether there is a common term or denominator that can be applied to observations through all panes or perspectives. If it is possible to speak about peripheral, central and socio-cultural expressions of CI using the same term, conflicts between different scientific fields can possibly be avoided.

The requirements of such a framework are that it must be able to explain the perplexing characteristics of CI while adhering to the assumptions of the theoretical models. It should therefore offer an explanation to the deviation from the toxicological dose-response model (Sorg, 1999), the general nature of the symptoms (Sorg, 1999) and the lack of immunological markers (Labarge & McCaffrey, 2000). It should also incorporate neural sensitization (Bell et al., 1999), neurogenic inflammation (Meggs, 1994) and conditioning (Van den Bergh et al., 2001). These aspects can be fitted into the framework provided by SDT.

SDT (for an overview, see Gescheider, 1997) assumes that judgments about sensory stimuli as well as complex decision making are always done under a degree of uncertainty. The judgment procedure can be defined in terms of the ability of the system to separate signal from noise (sensitivity, or d'), but also in terms of a decision rule or criterion (β ; see Figure 13). The criterion is set in accordance with expected gains or losses from making correct and incorrect judgments. In some cases, it may be preferable to be very alert to possible signals resulting in few misses at the cost of making several false alarms, and vice versa.

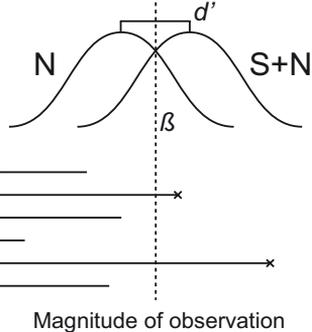


Figure 13: Hypothetical distribution of noise (N) and signal + noise (S+N). The sensitivity of the system is labelled d' and the criterion as β . Observations with magnitudes over the criterion level will be judged, correctly or incorrectly, as signals (marked with an x).

Our defense mechanisms for dealing with potential dangers are arguably also constrained by uncertainty (Ursin & Eriksen, 2004). Whether an exposure triggers e.g. avoidance behaviour or release of inflammatory mediators depends both on its strength and our criterion for threat. This means that the same level of exposure in some cases may lead to symptoms, while eliciting no reactions at another time. In the case of CI, the criterion can be assumed to become lower over time, to the point where even very low exposures are evaluated as threats, i.e. stressors.

CI can be defined within the SDT both in terms of increased sensitivity and a lower criterion. An intolerant individual may, for instance, be better at separating low level exposure from background noise, as in the case of the lower CO₂ thresholds found in Study 2. Within this framework the focus will, nevertheless, be on criterion shifts. The reason for this is that the criterion can be seen as a parallel to the threshold dose. The major difference between the toxicological threshold and the criterion is that the latter changes depending on current situation, whereas the former is relatively fixed.

It is important to appreciate that the criterion is a theoretical construct referring to characteristics of an arbitrary system. It should not be seen as a module or feature within an organism, but as a semantic category which we use to simplify and interpret certain phenomena. The criterion can thus be seen as increased reactivity of sensory neurons following local inflammatory processes. It can however also be described as conscious or non-conscious expectancies we have regarding a certain exposure, or the level of wariness that can be found in the discourse among co-workers. A few examples are given below.

Peripheral reactions as a low criterion

A low criterion peripherally may refer to the release of inflammatory mediators or hyperreactivity of sensory neurons. This could be operationalized as SP release (Meggs, 1994), primary and secondary hyperalgesia, temporal summation (Holst, Arendt-Nielsen, Mosbech, & Elberling, 2011), **dorsal horn windup**, **peripheral sensitization** (Ji, 2003) or repeated coughing (Study 2). Importantly, these reactions should not primarily be seen as an increased ability to separate painful stimulation from noise (i.e. higher sensitivity or d'), but as a greater chance of perceiving any stimulation as threatening or painful. Secondary hyperalgesia, in which even the slightest touch causes pain in the affected area, is thus an example of a lowered criterion (Holst et al., 2011).

Central reactions as a low criterion

Criterion changes pertaining to central aspects of CI, i.e. those that may be referred to as psychological, behavioural or related to CNS activity can also be identified. For instance, an attention bias may be understood as applying a low criterion toward a certain kind of exposures (Study 1). Regardless of whether these stimuli are important features of the environment (i.e. hits) or not (i.e. false alarms), they will constitute stressors. A low criterion can also be described in terms of limbic hyperreactivity such as the one found in Study 4, and assumed by the neural sensitization theory (Bell et al., 1999). Applying a low criterion within this domain may possibly also explain the non-specificity of CI symptoms and the spreading

phenomenon. A person exposed to a stimulus believed to be toxic will be alert to the assumed detrimental effects of the exposure. Internal states previously ignored, such as a slight headache or irritated airways will now be amplified as they pass the criterion. In anticipation of additional threats, the organism becomes vigilant to exposures different than the one initially assumed to be toxic (Ganzel et al., 2010). The criterion can within this domain be seen as the expectancy of a stimulus, as described by Ursin and Eriksen (2004).

Sociocultural reactions as a low criterion

When making judgments of an odorant, people are heavily influenced by social factors. For instance, seeing or getting reports of other persons becoming ill after an exposure increases the risk of experiencing annoyance and symptoms ourselves (Jones et al., 2000). Persons who are being told that an exposure is harmful (Dalton, 1996, 1999), or watch others react negatively to odorants (Dalton, 2003) report symptoms to a greater degree than those who have been neutrally or positively biased to the same exposure. The discourse within a group can be thought of as a lowered criterion. Once again, these reactions should not be seen as better ability to identify threats, but as a predisposition toward perceiving weak stimuli as stressors. It is thus possible to argue that at least one aspect of c_1 should be seen not only as a phenomenon pertaining to the individual, but to a social setting as well.

Short- and long-term criterion shifts

Sensitization and habituation, such as the reactions found in Study 1 and 4, can be understood as a short-time criterion shift. A progressively lower criterion over time would arguably result in increasing responses and vice versa. Applying a low criterion for a short period of time could be expressed as a general stress response to a threatening situation, or for that matter as sensitization. Brief episodes of stress happen to most of us every day, and do not lead to any known ill-effects. However, repeated or extended periods of stress can by itself be damaging to the organism, and may for instance be discernible as endocrine effects, lasting changes in brain functioning, or as conditioned avoidance responses (Ganzel et al., 2010). These changes can be labelled as long-term criterion shifts.

Short- and long-term criterion shifts have counterparts in the theoretical models of c_1 . The elicitation stage of the neural sensitization theory (Bell et al., 1999) and the first and second stage of the breakdown of adaptation described in the neurogenic inflammation theory (Meggs, 1994) can be seen as parallel to a short-term criterion shift. This could arguably also be similar to the memory process leading up to a conditioned rule-learning. The elicitation phase of the neural sensitization theory (Bell et al., 1999), the permanent damages of the third stage of the neuro-

genic inflammation theory (Meggs, 1994) and the formation of an associative rule in the conditioning theory (Van den Bergh et al., 2001) can all be described in terms of a long-term criterion shift applied to different aspects of c_i .

Illustrating a short- and a long-term criterion change

An exposure that passes the threat criterion (β) will trigger a host of defensive reactions. These reactions will by themselves lower the criterion similar to a feedback loop. This constitutes a sensitized state in which the organism is primed to deal with further potential threats. Exposures that previously did not pass the criterion will now be perceived as stressors, and will trigger further defensive reactions. If these reactions stop before permanent changes take place, the criterion will revert to its initial state (Figure 14).

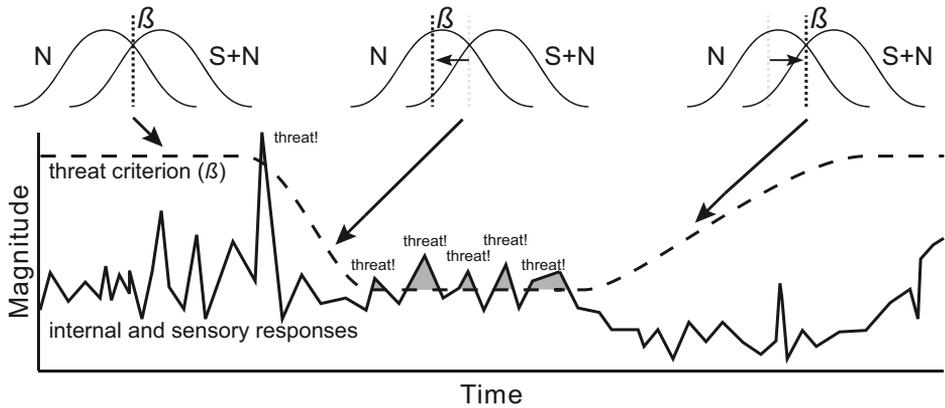


Figure 14: A situation in which short-term sensitization is resolved.

If the stressful situation is unresolved, or if applying a low criterion is deemed to be an optimal response, the criterion will not revert to its original state (Figure 15). Within this tentative theoretical framework, c_i is defined as an enduring predisposition of applying a low criterion to chemical exposures.

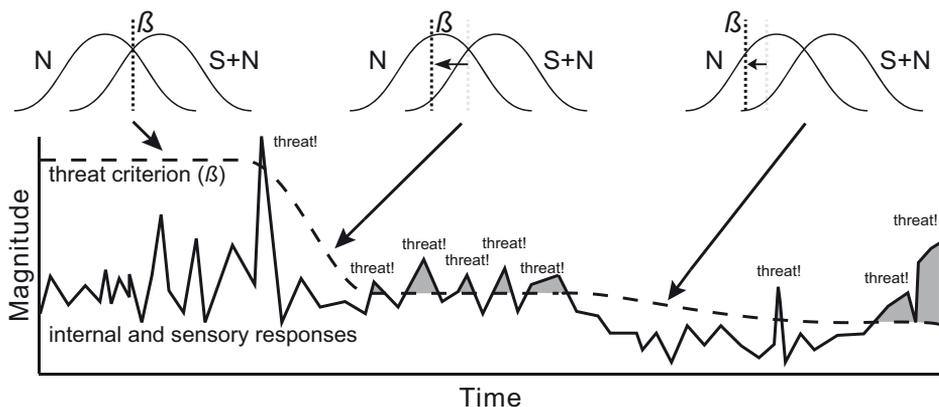


Figure 15: A situation in which short-term sensitization is unresolved. The effect is a long-term criterion shift.

What is gained by applying SDT to CI?

Introducing a new set of concepts to describe a phenomenon such as CI may in some cases add to the confusion rather than providing new insights. However, viewing increased reactions and symptoms as the effect of a lower criterion may provide an explanation for the lack of dose-response relationships in CI (Sorg, 1999). Assuming a moving criterion means that symptoms may be elicited by very low levels of chemical exposures or even expectations of exposure (i.e. reacting to false alarms). An additional advantage of SDT is the separation of sensitivity and criterion. A lower criterion does not necessarily mean a greater ability of separating signal from noise. Within this framework, it is thus possible to offer an explanation to the finding that persons with CI does not have better ability to detect low concentrations of odorants than healthy controls (Doty et al., 1988; Papo et al., 2006): The CI sufferers do not have more sensitive chemical senses, but applies a lower criterion. Although not directly related to CI, an interesting note is that women, compared with men, seem to apply a lower criterion when deciding whether an odorant is present or not (Claeson & Nordin, 2011). A similar method could be used to corroborate the assumption of a lower criterion in individuals with CI.

Applying a low criterion to endogenous signals may also explain the multitude of non-general symptoms in CI, as well as the spreading phenomenon. It is not necessarily the case that chemical exposures initially results in tissue damage in CI individuals. However, the expectancy of toxicity may prime the sufferer to perceive relatively normal fluctuations of internal states as signs of injury (Ursin & Eriksen, 2004). From another perspective, it may be the case that peripheral signalling is increased because of e.g. a local inflammation that also can be explained in terms of a lower criterion.

An important question is whether applying a low criterion is an incorrect reaction or not. Are the chemicals hazardous? It is impossible to be absolutely sure about this from the perspective of *sdt*, as all judgments are uncertain. It may however be the case that the cost of applying a low criterion is greater than the benefits in the long term. The repeated stress response following exposure to relatively non-toxic chemicals may be more deleterious than the effects of the chemicals themselves. If this is the case, *ci* treatments should aim at setting a higher criterion.

The unexplained aspects of *ci*, core features of the neural sensitization (Bell et al., 1999), neurogenic inflammation (Meggs, 1994) and conditioning (Van den Bergh et al., 2001) theories, as well as the empirical findings in this thesis can thus be framed within *sdt*. *sdt* does not necessarily imply new insights into the mechanisms of *ci*. It may however constitute a platform from which new hypotheses can be postulated. The *sdt* account of *ci* should therefore not be seen as a complete model.

What the future may bring

This thesis is both a theoretical and empirical work. By synthesizing the ideas and findings, it is possible to extract some general themes that seem to be important to bring into the future.

Using relevant chemicals

The rationale behind using amyl acetate and CO_2 has been that the characteristics of the stimuli are not of primary relevance as persons with CI react to such a wide variety of exposures. Nevertheless, the sensitive individuals whom I have tested have sometimes been quite specific regarding the kind of chemicals that elicit symptoms. There are therefore good reasons to expand the stimuli to those that are actually reported as problematic. If the instruments permit it and if it is possible to control the chemical composition and concentration, future studies would benefit from using e.g. perfume or household cleaning products.

If the instruments do not allow using such chemicals, I nevertheless suggest using odorants with a neutral or negative hedonic value. As Van den Bergh and colleagues (2001) pointed out, aversive learning took place only when the CS has a negative valence. Amyl acetate is generally perceived as relatively pleasant, which suggests that another odorant may be better suited for CI research.

Designing studies to not simply maximize signal-to-noise ratio

Studying the chemical senses pose a number of unique difficulties that are not present in visual and auditory research. For one, it is often easier to control the stimulus in other modalities. Another aspect is that chemosensory data tend to be noisier than that of other sensory modalities. One way of counteracting noisy data is to increase stimulus concentration (Kobal, 2003), and it is not uncommon to find very strong concentrations of e.g. CO_2 in the literature (Albrecht et al., 2010; Rombaux, Mouraux, Bertrand, Guerit, & Hummel, 2006). The defining characteristic of CI is however that the affected individuals react to low levels of chemicals. In fact, it is reasonable to assume that high concentrations of odorants elicit annoyance, maybe even symptoms in all persons regardless of CI (Smeets & Dalton, 2005). This is reason enough to use lower levels of chemicals to investigate differences between CI and non-CI groups.

In addition to stimulus concentration, researchers tend to avoid study designs that include the possibility of habituation or adaptation. In the case of CI, this may be exactly what we are aiming at. In addition to using lower concentrations of stimuli, it may also be relevant to decrease the inter-stimulus intervals to increase the possibility of adaptation and habituation.

New exposure methods

The ideal way of exposing a person with *CI* would be to do it in her own surroundings. The methods used in this thesis have the drawback of restraining the participants in one way or the other. In the case of *ERP* recordings, this amounts to sitting still in an armchair whereas the *fMRI* study implied even more restraints. It is difficult to say if, and in that case to what degree, this affects the results. It is nevertheless a factor to consider. In addition to the relative un-naturalness of these methods, the olfactometer used in the studies only allows for intranasal exposures of odorants. In ordinary situations, odorants cover the whole body of a person. It may be the case that sensory pathways other than those situated in the nasal mucosa are relevant for *CI*.

These limitations may be overcome by using an exposure chamber that has been developed in our laboratory, in which participants can be seated relatively unrestricted (Figure 16). The chamber allows for exposure of a wide variety of chemicals, and is not restricted in the same way as the olfactometer. In the exposure chamber, we may present continuous, relatively long-term exposures. Once built, the chamber is relatively inexpensive to operate but nevertheless offers the possibility to conduct studies with high ecological validity and relevance to *CI*.

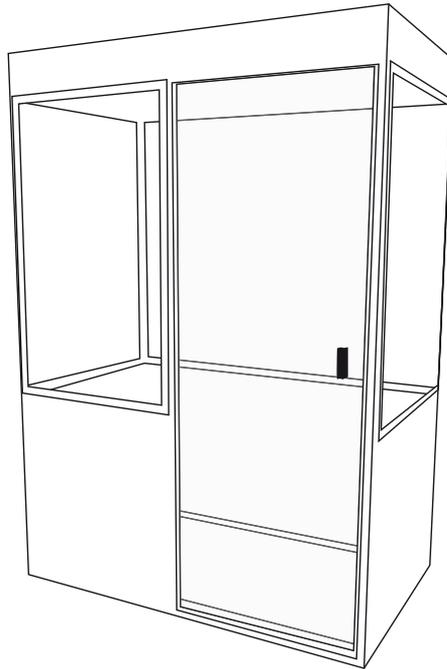


Figure 16: Illustration of the exposure chamber.

Using sensitization as a grouping variable

One reason for the illegitimacy of CI is that the definition is based on questionnaires (Sorg, 1999). Such reports are regarded as relatively uninformative, not in the terms that people cannot express their illness, but in terms of associating exposure with symptoms. The most common way of assigning participants into intolerant and non-intolerant groups is nevertheless by means of questionnaires, with the exception of SHR (Millqvist et al., 1998).

Taking inspiration from SHR and the assumption of CI theories, it should be possible to define groups in accordance with the sensitized response or applying a low criterion toward chemical exposures. As persons with CI are assumed to sensitize to a greater degree than non-intolerant, sensitization may prove to be the defining response in the affliction. This method was utilized in Study 4. The results suggested that sensitization measured by the simple method of magnitude estimations was associated both with a hypothesized brain response pattern, as well as higher self-reported CI.

In order to use sensitization as a basis for diagnosis, some control mechanisms must be introduced into the procedure. It should for instance not be possible to fulfil the criteria by simply reporting greater intensities over time. Whether such a control mechanism implies catch-trials, other measures of sensitization or something else is for the future to tell.

Exposing persons to treat CI

This thesis does not answer the question whether the chemicals themselves are toxic, in the classical sense, to a person with CI. Even if this should be the case, the symptoms experienced by the sufferer may still be disproportional to the actual tissue damage. Targeting and resolving the sensitization may therefore be a way of treating CI, at least in the cases where sensitization is discernible. How such an unwanted reaction should be treated is not within my expertise to discuss, which leads us to the last theme for the future.

Exposing ourselves

It seems fairly probable that an affliction such as CI cannot be understood in its entirety by only looking at it from a single vantage point. In the case of CI and other unexplained illnesses, it seems necessary to include a host of factors that ordinarily exist outside of the medical paradigm. As such, it seems as if the definitions of CI are not bounded by the individual body – it seems to exist at several levels at once, including endocrine as well as cultural. If this indeed is the case, then the task before us seems daunting. Nevertheless, it offers the possibility of constructing a

true interdisciplinary research paradigm. As suggested by this thesis, philosophical, cultural, psychological, chemical, neurophysiological and many other perspectives are needed to investigate this issue in the future. I, for one, cannot wait.

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Appendix

A short note on the cultural history of odor and health

The best recipe for health is to apply sweet scents unto the brain

– Athenaeus of Naucratis, *The Deipnosophists* vol III, book XV, p. 1098

VERSUS

All smell is disease

– Edwin Chadwick, Metropolitan Sewage Committee proceedings.
Parliamentary Papers 1846. p. 10:651.

Sociocultural aspects of odor and health deserve some additional comment. Culture, as it seems, dictates what kind of suffering that is legitimate. It offers us a template for how certain exposures cause illness, and constrains us in terms of how these should be expressed. Importantly, these cultural templates also affects our notions and expressions of health, expectations of what causes illness and even to which sub-group within our society particular symptoms belong (Shorter, 1997). Hence, culture is relevant to CI not only as a discrete factor, but as something that permeates other factors such as sex or age, or for that matter the underlying physiology of CI.

Our western society is remarkably deodorized compared with historic times. In ancient cultures, for instance the Hellenistic and Roman empires, odors permeated every aspect of life. With the abundant odor of excrement and trash, reeking tanneries, fullers and fishmongers, cities and the countryside could be navigated using olfactory landmarks. Odorants were imbued in the architecture in forms of saffron in plaster and floors, beds and clothes washed with perfume. Even the livestock was anointed with perfume.

Odorants in general were assumed to have a beneficial impact on health, which can be discerned from recipes of remedies for common ailments. The scent of apples was assumed to relieve the effect of poison, and the odor of boiling cabbage relieved headaches. Perfume was seen as beneficial, and was imbibed, offered to guests and even applied to wounds (Classen, Howes, & Synnot, 1994).

During the time of the plague, odorants were used to neutralize the effects of bad air which was assumed to carry the disease. The beneficial odorants were not necessarily pleasant, and could for instance constitute a pungent mixture of aromatic wood, herbs, gunpowder and vinegar. During the industrial revolution, a common notion was that too pure air was harmful. Consequently, health officials and scientists argued against using chimneys as household and industrial smoke warded off disease, and that tobacco smoke was beneficial (Classen et al., 1994).

This view of odors changed during the 18th and 19th centuries. Waste and pollution had become such a monumental problem in large cities that governments had to act (Classen et al., 1994). A striking epitome of this is the Great Stink during an unusually hot summer in London in 1858. The massive amount of waste produced by the city caused the sewage system to overflow. The resulting stench was so great that it drove the members of the parliament out of the House of Commons, each man with a handkerchief over his nose (Halliday, 2001). Such extreme conditions in the end necessitated governmental interventions to clean up the industrial cities. In the wake of such projects, the cultural notions of odors also changed.

With this governmental focus on waste control and cleanliness, society grew intolerant to industrial odors. This olfactory revolution was however not restricted to industrial pollution, but became applied to scents in general. As the upper and middle class began purging their bodies and homes, odors became associated with those who could not, i.e. the working class; the deprived. Odors became synonymous with illness and moral promiscuity. It became associated with base emotions, intuition, savagery and, importantly, with women. Up until the end of the eighteenth century, perfume had been used by women and men alike. This changed during the nineteenth century, and both artificial odorants and the sense of smell itself became feminized. At the same time, odors were no longer assumed to have therapeutic powers. Perfume, or for that matter all artificial odorants that earlier were regarded as beneficial for health, were now regarded as unhealthy, as clogging the pores and enfeebling people with its vapours (Classen et al., 1994).

Some points can be made from this short cultural history. First, our olfactory surroundings have changed markedly compared with the situation only a few generations back. While it is true that a large number of new chemical compounds are introduced to our modern society every year, historical sources suggest that our total exposure to chemicals has decreased. Unvented homes and public buildings such as schools and theatres were extremely polluted because of burning of biomass (Sundell, 2004). For instance, Hyman (1881) estimated indoor CO₂ concentrations of homes to be up to three times higher than the threshold values used today. In 19th century schools, these concentrations were even higher. This does not imply that our chemical surroundings are safe, just that the good old times may have been much more abundant with odorous chemicals. As theoretical models of CI suggest that expectancies of toxicity of certain odorants is an important factor in CI (Van den Bergh, Winters, Devriese, & Van Diest, 2002; Sorg, 1999; Ursin, 2009), studying our cultural understanding of odor and disease may prove fruitful.