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POST-CONDITIONING PHENOMENA IN A
LEARNING MODEL OF MULTIPLE CHEMICAL
SENSITIVITY

Proefschrift aangeboden tot
het behalen van de graad van
Doctor in de psychologie

door

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Voorwoord

Het document dat u opengeslagen hebt, is de neerslag van de voorbije jaren die ik doorgebracht heb in de Onderzoeksgroep voor Stress, Gezondheid en Welzijn (OSGW, voorheen het Centrum voor Ergonomie en Gezondheidspsychologie). Hierin zit meteen vervat dat, alhoewel enkel mijn naam en deze van mijn promotoren op de voorpagina staan, heel wat mensen hebben bijgedragen aan het tot stand komen van dit boekje en via dit voorwoord wil ik hen dan ook bedanken.

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Chapter 1

Conditioning and Multiple Chemical Sensitivity

1.1 Introduction

For science, it takes a long way to come from a patient's complaints to an effective understanding of the why and how of these complaints. Certainly when the symptom pattern reported by the patient does not seem to conform to present disease theories. The advancement of medicine and psychology in the previous century has clarified a large amount of 'unexplained' diseases and conditions and has changed our view of illness in more than one way. I would go even so far as to state that medicine and psychology have again grown towards one another, considering the division between them that existed ever since the dawn of psychology as a science.

Despite our ever growing understanding of illness, science has not been able to provide an answer for some conditions yet. One of these conditions is called Multiple Chemical Sensitivity (MCS) among other names. The typical somatic symptom pattern of these patients is elicited by chemical substances in generally tolerated doses. MCS resembles dysfunctions caused by toxic exposures or an allergy to certain chemical substances, but the mechanisms that normally apply for these dysfunctions, do not seem to apply for MCS patients. There is currently very little evidence for a mere physiological mechanism or, for that matter, for a mere psychological mechanism, as the following section will argue.

A multidisciplinary model seems to be the only way to capture all aspects involved in MCS. From that, it can be suggested that explanations for MCS will contain both physiological and psychological variables. Both can be investigated separately (and due to the complexity of the phenomenon, this seems to be the most practical course of action), but eventually, they will have to be united in one model.

This doctoral thesis uses one of the current psychological models suggested

in the literature, namely a classical conditioning account of MCS. Our research group has developed an operationalization of this theory, which allows scientific scrutinizing of the conditioning model for MCS. The research I will present here, is mainly concerned with mechanisms that come into play once an initial conditioning phase has occurred. It will deal with generalization, US–inflation, and contingency awareness as principle variables of interest (these variables will be explained in detail further on).

In this first chapter, I will present an overview of MCS as it is perceived in the current scientific community. A detailed presentation of the conditioning account for MCS and the operationalization used in my research follows the overview. In the second chapter a first post–conditioning phenomenon, namely generalization will be discussed. A second post–conditioning phenomenon, namely US–inflation will be presented in the third chapter. Contingency awareness is discussed in the fourth chapter followed by the concluding chapter.

1.2 Multiple Chemical Sensitivity (MCS)

In this section, I will discuss the current status of Multiple Chemical Sensitivity (MCS). In the first part, issues concerning definition and diagnosis will be treated. The second part will critically examine the different etiological views currently presented in the literature. The third part will give an overview of the conditioning account of MCS I use in this doctoral thesis.

1.2.1 How to define Multiple Chemical Sensitivity?

A first issue concerning MCS is the label itself. Throughout the history of the illness, many names have been used (Reid, 1999). Two of them have become the standard denotation: Multiple Chemical Sensitivities (MCS) and Idiopathic Environmental Illness. The first, Multiple Chemical Sensitivities, has become disreputed mainly because of its inherent suggestion to sensitization as a causal mechanism, while this link has not yet been established (Sparks, 2000). Although the MCS label has been dismissed by some authors and organizations, it is still the most frequently used designation in the literature. Therefore, the name 'Multiple Chemical Sensitivity' (MCS) will be used throughout this doctoral thesis.

A second issue concerning the delineation of MCS is that there is no widely accepted set of criteria that demarcate MCS (Kreutzer, 2000). Since Cullen proposed a working definition, researchers and medical practitioners have been using these guidelines (with or without alterations) in order to select participants for research or to identify patients for treatment (Cullen, 1987).

Cullen's first criterion requires MCS patients to have had an initial environmental exposure. A large number of patients indeed report an initial exposure to some toxic chemical(s) (Davidoff, Keyl, & Meggs, 1998; Davidoff & Keyl, 1996) in some sub-toxic environment (Andin, Rnnbck, & Jrvholm, 1997) living in a home under construction (Ross, 1997) or working with air-conditioning systems (Kipen & Fiedler, 1997). But not all patients can pinpoint a specific event (Staudenmayer, 1997). This criterion is one of the most debated in the literature (Graveling, Pilkington, George, Butler, & Tannahill, 1999) and a large number of authors do not subscribe this criterion for the diagnosis of MCS. The second criterion demands that patients report symptoms in more than one organ system. Symptoms can occur in almost any organ system. Miller for example lists symptoms reported by 112 MCS patients of neuromuscular, musculoskeletal, gastrointestinal, head-related, cardiac, affective, airway-related, and cognitive nature (Miller, 2001). The third criterion states that symptoms should demonstrable and repeatable occur in response to one or several chemical substances. The forth criterion builds on the third and demands that the levels of the chemicals to which MCS patients respond, should be below established toxic levels. Finally, no other medical conditions can be present at the same time. This criterion has received a great deal of criticism. Partially because the etiology of MCS is still unclear, the question has been raised whether one should include patients with (mostly psychiatric) comorbidity or not. At present, there is no clear guideline which option to choose.

Despite the criticisms on the Cullen criteria, most authors still use them as it seems to be the only set on which a consensus exists (Graveling et al., 1999).

1.2.2 Etiology of MCS

Part of why no consensus exists on the definition of MCS is the absence of a clear cut explanation of the symptoms MCS patients experience. As mentioned before, a number of explanatory models of either physiological or psychological nature have been proposed and, to a certain amount, been tested. None however is able to provide evidence to account for the complete symptom pattern found in MCS patients. This section intends to provide an overview of the current models and research supporting or rejecting these models. I have not, as in most reviews, subdivided models and theories in either psychological or physiological. It is my personal vision that, although the emphasis of the model can be psychological or physiological, they often consist of both type of processes. Also, the order of discussion is randomly chosen. Due to the vast amount of research generated on this topic, this overview can not be exhaustive.

The clinical ecologists

Among the first to try to develop a model of MCS are the clinical ecologists (Dickey, 1976 in Guglielmi, Cox, & Spyker, 1994). The basic idea is that the immune system can only handle a limited amount of antigenic material. Symptom manifestation occurs on stepping over the limit (immune dysregulation), which can be reached by either a toxic exposure or repeated low-level exposure to some chemical substance (Levin & Byers, 1987). Clinical ecologists state that the continuous exposure to these chemicals leads to hypersensitivity in patients. This hypersensitivity keeps patients vulnerable and may result in symptom reports to almost any chemical substance. Therefore, the proper course of action for patients is to avoid any contact with the offending chemicals. Considerable effort is put in identifying these chemicals, usually through non-blinded procedures.

Clinical ecology has not been without criticism. Mainstream medical science has never acknowledged the immune dysregulation theory as put forward by clinical ecologists. Especially the absence of sound research (no use of control groups or double-blinded procedures) is regarded as crucial in dismissing clinical ecology as a valuable model for MCS (Guglielmi et al., 1994).

The central nervous systems theories

A number of theories consider altered processes or physiology in the central nervous system as the causal mechanism for MCS. One of these models proposes limbic kindling and sensitization as the essential processes that lead to MCS (Bell, Baldwin, & Schwartz, 2001). The basic idea of the model that Bell and coworkers (Bell, Miller, & Schwartz, 1992; Bell et al., 1997; Bell, Schwartz, Bootzin, & Wyatt, 1997) present is that chemical substances access the central nervous system through the olfactory system (which lacks a blood-brain barrier) and the limbic structures, and, as such, can alter neuronal behavior. Kindling is the phenomenon whereby the appliance of a local electrical or chemical stimulation in the brain does not initially provoke a seizure, but after repeated administration of this electrical or chemical stimulation does elicit a seizure at the brain site. The olfactory pathways and the limbic structures appear to be particularly susceptible to kindling. Time-dependent sensitization (TDS) is the more general form of kindling. In TDS, repeated administrations or the mere passage of time since the first presentation, can augment the response to a stimulus (whatever its nature) initially provoking little or no response. The difference with kindling is that TDS can occur in any number of physiological systems and as such can influence several behavioral components. TDS in different physiological systems would then be the mechanism that is responsible for the symptom pattern reported by MCS patients.

The evidence for this model of sensitization is largely based on animal stud-

ies the resulting behavioral changes in the animals. There is currently no direct electrophysiological evidence in humans of kindling or TDS, mainly because of ethical considerations (Bell et al., 1992, 1997). However, there is indirect evidence: individuals with chemical intolerance tend to be more sensitizable in multiple organ systems than controls (Bell et al., 2001). Also, elderly individuals with a high degree of chemical intolerance (as reported on a questionnaire) showed increased sympathetic tone in the cardiovascular system following a dairy containing diet compared to elderly individuals with a low degree of chemical intolerance (Bell, 1997) (Bell et al., 1997). According to the authors, this shows that the repeated administration of an environmental stressor (i.e. laboratory setting and dietary conditions) can sensitize several organ system (i.e. cardiovascular system and diastolic blood pressure).

Two problems have arisen for the kindling / TDS model. Firstly, the model has problems with explaining one trial exposures (patients often report MCS after one mass exposure). Secondly, no evidence for kindling using perfumes as stimuli has been found until now (Ross et al., 1999).

The toxicologists

One of the first theories in toxicology stated that MCS patients have a lowered threshold for chemical substances. In general, it is known that the smell of a chemical substance is perceived by odor binding to receptor cells in the nasal mucosa (Ross et al., 1999). These receptor cells transmit their signals to the brain via the olfactory nerve (cranial nerve I). Pungency on the other hand is probably perceived by common chemical sense (CCS) receptors in the nose. CCS receptors transmit their signals to the brain via the trigeminal nerve (cranial nerve V). Smell thresholds are usually some orders of magnitude lower than pungency thresholds. It is hypothesized that, because of the connections from olfactory neurons and CCS receptors to several different brain regions (like the amygdala and the brain stem), stimulation of these receptors could result in symptoms resembling those reported by MCS patients. A lowered threshold of these receptors could be responsible for this phenomenon.

There is currently no evidence for this explanation. Odor recognition is not impaired or enhanced in MCS patients (Ross et al., 1999). Also a double-blind odor detection experiment (Doty, 1994) revealed no better perception of odors in MCS patients compared to control subjects. The results unfortunately only apply to smell thresholds and not to pungency thresholds because odor presentation never reached this latter threshold.

Another theory currently enunciated in toxicology is the Toxicant Induced Loss of Tolerance (Miller, 1997). Miller argues that current disease theories are insuffi-

cient to explain MCS, which she considers not as a single syndrome but as a new category of diseases. The basic idea is that an initial exposure (whether chronic or acute) causes a loss of tolerance in future patients. The author is not clear about what mechanism causes this initial loss of tolerance (possibly sensitization). In a second phase, low levels of previous tolerated chemical substances elicit symptoms in sensitized subjects. The fact that not everyone exposed develops MCS-like symptoms is overcome by the concept of individual susceptibility (either psychological or physiological).

Currently, little evidence has been generated to test this theory (Graveling et al., 1999), although the author has provided clear guidelines of how the theory might be scrutinized (Miller, 1997). Concerning the first step of initial loss of tolerance, ethical considerations preclude human studies. The second step, triggering symptoms by chemical substances, is much less of a problem to investigate. According to the authors, the appropriate research tool is human challenge studies in an environmental medical unit (EMU). This EMU is constructed in such a way that the presence of chemical emanations is minimized. Patients could be hospitalized in an EMU at first to counteract masking and the problem of stimulus–withdrawal symptom differentiation. Patients are often continuously exposed to chemicals they react to in their environment. A specific challenge sometimes does not augment symptom reporting because of these already existing complaints, a phenomenon called masking. The problem of stimulus–withdrawal symptom differentiation is somewhat dissimilar. MCS patients do not only show a heightened response to chemical substances but they also show symptoms when these chemicals are removed (withdrawal symptoms, like fatigue, loss of concentration). So what is measured after a specific challenge? The EMU thus could render patients in a state of true “non–exposure” and would purify challenge studies.

The biggest problems currently faced by this theory are the lack of experimental evidence (which is in part due to the practical and financial difficulties associated with EMU’s (Miller, 2001)) and the inability to explain spreading of symptoms to other chemical substances (Graveling et al., 1999). The latter phenomenon will be discussed in more detail in the second chapter of this doctoral thesis.

The immunologists

Since the emerging of MCS, immunologists have hypothesized an allergy-like mechanism in MCS (Levin & Byers, 1987). It was believed that the chemical substances to which patients react, provoked immunoglobulin E (IgE) and immunoglobulin G (IgG) mediated immune responses, much like the typical food or glycyphagus (or mite) allergy, resulting in the symptom pattern reported by MCS patients (Cohen et al., 1997). currently no consistent evidence supporting this hy-

pothesis (Mitchell, Donnay, Hoover, & Margolick, 2000). Besides this “overreaction” of the immune system as a possible mechanism, dysregulation has been proposed. In this case, several actors of the immune system (like lymphocytes) are affected and as such cause a disturbance of the functioning of the immune system.

Some evidence for this dysregulation hypothesis has been reported by, for example, Kipen and coworkers (Kipen et al., 1992). They compared 11 MCS patients with healthy controls and patients with chronic fatigue, and performed a number of immunological tests on all groups. They found elevated CD4/CD8 ratios due to lower percentages of CD8+ T-cells¹. In a study of 68 MCS patients, a large amount of immunological tests were done and sent to several laboratories (Ziem & McTamney, 1997). The authors report some abnormal values compared to laboratory normal values (no controls subjects were used). A critical review of these two (and other studies) expressed several concerns about the validity of their results (Mitchell et al., 2000). The most problematic are the absence of appropriate control groups, the absence of a detailed description of quality control (reproducibility of the laboratory results) on the data, and the lack of a description of the statistical analyses performed on the data. The authors of the review conclude that, at present, the limitations of the studies do not permit any conclusions (a similar but slightly stronger view against an immunological explanation of MCS is formulated by (Kehrl, 1997).

MCS and other medical conditions

Airway inflammation has also been suggested as the cause of chemical sensitivity in MCS patients (Bascom et al., 1997; Meggs, 1995). Bascom argues that altered responsiveness of C-fiber neurons in the nasal mucosa causes the chemical sensitivity reported by MCS patients. Similarities between the reactive airways dysfunction syndrome (RADS) and the reactive upper-airways dysfunction syndrome (RUDS) and MCS have led Meggs to elaborate the hypothesis proposed by Bascom (Meggs, 1997a). Evidence for this was found in the form of heightened nasal resistance in MCS populations (Bascom et al., 1997; Doty, 1994), rhinoscopy (Meggs & Cleveland, 1993) and nasal biopsies (Meggs, Elsheik, Metzger, Albernaz, & Bloch, 1996). This evidence of possible airway inflammation in MCS patients unfortunately does not explain the diverse symptom pattern reported by most MCS patients. In order to account for this problem, Meggs suggests the mechanism of neurogenic switching (Meggs, 1997a). The basic idea is that, by means

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¹CD4 and CD8 are surface proteins found on T-cells (respectively called CD4+ and CD8+ T-cells) (Mitchell et al., 2000). T-cells are activated when they detect antigens and subsequently produce several regulatory mediators (cytokines). These cytokines control other cells participating in the immune response. Generally spoken, CD4+ T-cells initiate the immune response, while CD8+ T-cells function as suppressor cells (killing foreign antigens) and turn off the immune response.

of pathways from the initial site of inflammation through the central nervous system, inflammation can occur in other peripheral sites. Although such neurogenic switching is assumed in several allergies, there is currently no human evidence for such a mechanism in MCS (Ross et al., 1999; Guglielmi et al., 1994).

The psychiatrists

A number of authors have suggested the possibility of MCS sharing the same etiological mechanism as other medical or psychiatric conditions. Binkley & coworkers for example note the striking similarity between symptom patterns reported by patients with panic disorder and MCS patients (Binkley & Kutcher, 1997). Both report chest tightness, shortness of breath, mental confusion, etc. One study providing evidence for this hypothesis administered sodium lactate and a placebo (a saline solution) in five MCS patients (without any other medical condition) in a single-blind procedure (Binkley & Kutcher, 1997). All except one of these patients met the criteria for DSM-III-R panic disorder. All participants reacted significantly stronger to the sodium lactate injection than to the placebo solution, regarded by the authors as evidence for panic disorder-like features. However, one must note the relative specificity of the sodium lactate test (20% false positives) as mentioned by the authors. Also, all patients qualified for several DSM-III-R diagnoses, like depression and social phobia, and not exclusively for panic disorder.

The panic disorder hypothesis was put to test using a different panicogenic stimulus (a single breath inhalation of 35% CO₂ in oxygen mixture; Poonai et al., 2000). A total of 36 patients and 37 controls received a single-blind inhalation of the stimulus and of regular air. No difference between the groups was found on pulmonary measures, but MCS patients scored higher than controls on the Anxiety Sensitivity Index (i.e. a questionnaire assessing fear of panic-related sensations Reiss, 1991). Also, significantly more MCS (71%) patients satisfied the criteria for a panic attack after the challenge compared to controls (26%). Although these results support the possibility that a number of MCS patients suffer from panic disorder, some reticence is in order. The design included minimal randomization of the CO₂ and air trials (31 patients received the trials in the same order). MCS patients with panic disorder were excluded, but the authors do not mention if the selected MCS patients currently qualified for other DSM-IV diagnoses (exclusion criteria included only previous psychiatric diagnoses). Also, the mean ASI scores were within the range of a non-clinical population.

A more recent study provides further evidence for the panic disorder hypothesis (Binkley et al., 2001). From eleven MCS patients, DNA was checked for presence of panic disorder associated cholecystokinin B receptor alleles and compared with DNA from a matched control group. A higher prevalence of these receptor alleles

was found in MCS patients relative to the controls. The authors caution that these data need to be confirmed in a larger sample.

Besides panic disorder, several other psychiatric conditions have been considered as possible origins of MCS complaints. Black and coworkers have assessed several populations and checked for DSM diagnoses (Black, Rathe, & Goldstein, 1993; Black, 2000; Black et al., 2000; Black, Okiishi, & Schlosser, 2000). In all these studies, a large psychiatric comorbidity was found. Also, there are some case reports of successful outcomes of MCS patients by using selective serotonin reuptake inhibitors (SSRI) in treating panic disorder (Stenn & Binkley, 1998) or depression (Andin et al., 1997). The largest problem here is whether the psychiatric conditions cause or follow MCS. It has been suggested that existence of psychiatric problems prior to the onset of MCS points to a causal role, but this is highly speculative (it is not because psychiatric problems precede MCS that they are causal (Graveling et al., 1999)). Also, some authors argue that is very difficult to distinguish psychiatric pathology that was present prior to MCS development and psychiatric pathology that is a consequent of MCS, by means of often used diagnostic instruments (such as the MMPI-2; (Davidoff, Keyl, & Fogarty, 2000)).

The psychologists

One of the psychological theories put forward in the literature, is that MCS is an attributional syndrome (Gupta, Perharic, Volans, Murray, & Watson, 1997). The main thesis of this theory is that patients are initially exposed to some toxic event (although it is often difficult to establish post hoc if the event truly had toxic characteristics). This event elicits complaints and health concerns in the patients and causes them to consult a physician or seek information with the organization associated with the toxic event. Dissatisfied with the answers of both (physicians fail to detect a somatic cause for their symptoms; the organization or company involved in the toxic event dismisses their complaints), patients can express additional health concerns and search for information that can explain their problems. Sooner or later, they find information confirming their concerns (through the media, alternative practitioners, etc.), augmenting their fears and complaints.

There is currently some evidence for this theory. In a study of a claimed wood preservative poisoning (Gupta et al., 1997), 20 patients were retrospectively assessed and the scenario described above could be reconstructed. No toxicological problems were found in these patients, and they clearly attributed their symptoms to the wood preservative event. The problems with this study are of course the retrospective nature and the fact that psychiatric assessment was less than ideal (not standardized and only 70% of the patients were seen by a psychiatrist), and thus not excluding other explanations. Staudenmayer and Kramer report a similar

attributional explanation on a single case study of a woman showing seizures in response to the administration of chemical substances (Staudenmayer & Kramer, 1999). No physiological abnormalities could be found (even during the seizures, no change was observed in EEG patterns), leading the authors to conclude that the woman attributed her symptoms to chemical substances.

Dalton and Hummel proposed an information-processing account of MCS (Dalton & Hummel, 2000). Their thesis is that MCS patients are not more sensitive to odors than normals (see also the previous mentioned discussion of odor sensitivity), but that MCS patients differ in their processing of olfactory information. The authors review studies showing four non-sensory variables contributing to the perception and evaluation of odorous stimuli.

The first variable they deem important is the mental models people have about illness, anatomy and certain situations. It has been shown in other domains of psychology that mental schemata greatly influence the perception of stimuli. This hypothesis was tested using a paradigm in which subjects received information regarding the affective valence (either positive, neutral, or negative) of an odor prior to administration of that odor (i.e. acetone) in healthy adults (Dalton, Wysocki, Brody, & Lawley, 1997). The authors measured the perceived intensity of the odor, irritation, and health symptoms. They found a profound influence of information: the subjects in the negative group showed more symptoms and higher irritation ratings than the other two groups. A second variable influencing the processing of odors is the personality of the patient. The authors discuss one possible variable, Negative Affectivity (NA; a broad range of aversive mood states such as anger, disgust, fearfulness and depression). In a study with normal subjects divided in high and low NA (using the Positive and Negative Affectivity Scale; (Watson & Pennebaker, 1989), high NA participants reported higher symptom levels and irritation than low NA participants upon exposure to an odorous chemical, although no difference could be found in eye redness (a less demand sensitive measure of irritancy) between the groups. A third variable indicated by the authors is the role attention can play in the perception of odors. The amount of symptoms reported is strongly influenced by what aspects of the odor experience have received attention. For example, when exposed to a chemical, drawing the attention to the concrete sensory aspects of the experience (i.e. by using a diagram of where exactly in the nose the inflammation occurs) diminishes symptom reporting but not odor intensity ratings or eye irritation (Dalton & Hummel, 2000). A final variable is socially cued bias to perceiving odor characteristic. This variable is a variant of the first and the authors hypothesize that information delivered by peers has a profound influence on the reporting of odor characteristics by subjects. The authors conclude that hence there is evidence for a cognitive model of MCS (Spyker, 1995).

Besides the previous discussed theories, the vast amount of neuropsychologi-

cal observations in MCS patients has led several authors to assume a marked influence of psychophysiological variables on MCS pathology (Fiedler, Kipen, Deluca, Kelly–McNeil, & Natelson, 1994; Kipen & Fiedler, 1999). For example Lehrer has summarized some possibilities (Lehrer, 1997). He introduced the concepts of individual response stereotypy and situational response specificity in the MCS literature. Individual response stereotypy refers to the fact that some individuals react with specific psychophysiological responses to a number of stressors, while others do not. One person for example shows cardiovascular responses to stressors (whether it is a reaction time task or a scary movie), while another reacts mainly with a skin conductance response to the same stressors. According to the author, this could explain the wide range of symptoms found in MCS patients and the fact that there are substantial differences among MCS patients in what symptoms they report to exposure of a chemical substance. Situational response specificity refers to the fact that specific situations favor a certain type of response. For example, tasks that require a more active coping style (like a reaction time task) will elicit different psychophysiological responses (like increased heart rate and bronchodilatation) than tasks requiring a more passive coping (watching scary movies elicits responses like peripheral vasoconstriction and bronchoconstriction). Lehrer thus hypothesizes that MCS develops more easily in individuals whose individual response stereotypy greatly overlaps the situational response specificity of an exposure to chemical substances (either as a mass toxic exposure or a repeated low level exposure) (Lehrer, 1997). What process underlies the further elaboration of MCS is not yet clear according to the author. He proposes several possible mechanisms like sensitization, classical conditioning, or even the change of a homeostatic set point for arousal. One mechanism more extensively discussed by the author is the possible role of hyperventilation. Hyperventilation (breathing in excess of the metabolic need) can occur in response to many physical and emotional stressors and elicits typical complaints like headaches, dyspnea, shortness of breath, nausea, a feeling of suffocation, palpitations and panic (Folgering, 1999). The author suggests to investigate the occurrence of hyperventilation in MCS patients to test this hypothesis.

The latter hyperventilation hypothesis is supported by some studies. For example, Leznoff found in ten of eleven patients reacting to a challenge with a chemical substance, a lowered PCO_2 (end-tidal) after the challenge compared to prechallenge data, indicating that the patients had hyperventilated (Leznoff, 1997). This study is unfortunately limited by the amount of patients seen and the lack of control subjects. Also, it's not clear why the patients hyperventilated. The author argues that a direct neuropsychological mechanism is unlikely due to the nature of some of the chemical substances used to challenge the patients, but that the most likely cause is anxiety (see also the previous discussion on panic disorder). This explana-

tion has been questioned: the challenges could have caused pain sensations, known to be associated with hyperventilation and as such provide an alternative explanation for the hyperventilating of the patients (Meggs, 1997b). Also the patients were seen for insurance evaluation, possibly rendering the patients anxious and causing them as such to hyperventilate.

Conclusions

This overview shows that a vast number of specialisms have conducted and are conducting research in order to clarify Multiple Chemical Sensitivity. I believe that the most important message given by the literature is that there is not one all-embedding explanation. Miller's credo that only a theory that offers a complete explanation for the whole of the symptom pattern is to be considered, is appealing (Miller, 2001). But I believe that MCS is, as the same author argues, a collection of diseases. Although I would not go so far as to summon a new disease category, MCS is likely to be caused by several mechanisms and perhaps even different mechanisms in different patients with the same symptom pattern (as is the case in a quite a number of medical conditions).

A second important message emerging from the literature and logically following upon the previous opinion, is that some mechanisms are often complementary and not necessarily different. For example, the several psychological and psychiatric theories are not mutually exclusive. Even the more physiological theories are not incompatible with the psychiatric and psychological theories. The information-processing account of Dalton (Dalton & Hummel, 2000) for example does not exclude a sensitization model as proposed by Bell and coworkers (Bell et al., 2001).

1.3 A conditioning account of MCS

In the previous section on the current views on MCS etiology, I have omitted one large model which I intend to discuss in detail in this section. A conditioning account for MCS has been suggested more than a decade ago (Bolla-Wilson, Wilson, & Bleecker, 1988; Shusterman & Dager, 1991). Yet, very little experimental research has been conducted in order to scrutinize the conditioning account for MCS. The purpose of this section is twofold: in one subsection I will present the general idea and the current literature concerning the conditioning theory of MCS. In another subsection, I will elaborate on the research paradigm developed in our research group and the studies previously conducted that are relevant for the topic of this doctoral thesis.

1.3.1 MCS and conditioning in the literature

Basically, the initial exposure to a toxic chemical substance serves as an unconditional stimulus (US) eliciting various responses (unconditional responses; UR). Stimuli that are usually linked to a chemical substance (like the odor) then become conditional stimuli (CS) eliciting a conditional response (CR) similar to the UR in the absence of the US. Several observations are consistent with this view. For example the fact that MCS patients almost always react to odorous substances and not to odorless substances (Bolla-Wilson et al., 1988). Guglielmi and coworkers (Guglielmi et al., 1994) elaborated this model by proposing an adoption of the two-factor model of Mowrer (1974 in Guglielmi et al., 1994). In their view, the classical conditioning scenario accounts for the initial acquisition of the symptoms, while operant conditioning might explain the maintenance of the symptoms. The latter process entails that MCS patients avoid exposure to the offending chemical substances and, as such, prevent fear reduction. This in turn will reinforce the avoidance tendency and maintain the symptoms in MCS patients.

Evidence for a conditioning account in the literature mainly exists of case reports (Spyker, 1995) and indirect evidence from other illness research (for example conditioned immunosuppression and conditioned nausea in chemotherapy (Guglielmi et al., 1994); conditional allergic reactions and sensitization to drugs (Guglielmi et al., 1994; Siegel & Kreutzer, 1997)).

The conditioning account of MCS has received its share of criticism, but most issues raised in the literature can be answered by an elaborated conditioning model. What is criticized in the literature often stems from a degraded view on conditioning. Many critics (for example Staudenmayer, 1997) have identified the conditioning model for MCS with the prototypical diagram of Pavlov's dog salivation experiment. Although the essence of the idea is represented by this diagram, it is by no means complete. Several comprehensive conditioning models have been proposed, but a recent one by Davey could be of a particularly interest for MCS (although it originally dealt with phobias) (Davey, 1997). The remaining of this section will touch on some objections raised and how current conditioning ideas could answer these questions.

Based on the clinical observation that many MCS patients do not report a toxic exposure marking the beginning of their illness, a conditioning account has been dismissed because in these cases no US is present (Staudenmayer, 1997; Graveling et al., 1999). One can argue that a toxic exposure is not the only possible US in MCS. The research paradigm used in this doctoral thesis to investigate a conditioning account of MCS utilizes CO₂-enriched air as the US (see below). This is an operationalization of the idea that stress-induced hyperventilation could be the US in MCS. In one scenario, a stressful situation could provoke a hyperventilation

episode (Schottenfeld, 1987). Odors present at the time are salient cues and could, through this learning experience, become associated with the symptoms elicited by the hyperventilation episode (which overlap with MCS symptoms as noted by Lehrer, 1997, see also 1.2.2 on page 3). This hyperventilation could occur on only one occasion, but could also be more chronic, and hence provide the subject with multiple learning experiences. Odors could then elicit these symptoms without the necessity of hyperventilation (which also explains why MCS patients not necessary hyperventilate when exposed to offending chemicals).

1.3.2 A differential odor conditioning research paradigm

In this section, I will describe the details of a differential conditioning procedure and how this prototypical paradigm is translated to a research tool for investigating MCS. An overview will be presented of the studies conducted with this paradigm prior to the research reported in this doctoral thesis.

The procedure

Like the conditioning procedure described in the previous section, a differential procedure uses an unconditional stimulus (US; eliciting an unconditional response; UR), but instead of one, two conditional stimuli are used. One of these CSs is presented with the US (either simultaneous or sequential) according to some contingency schedule (reflecting the probability of the US given the CS and the probability of the US given the absence of the CS) and is called the CS+. The other CS is never administered with the US (or according to a contingency schedule where the probability for a US given a CS is less than in the schedule used for the CS+) and is called the CS-. After one or more trials of each type (CS+ US; CS- no US), both CS+ and CS- are administered without the US. Conditioning is then defined as the difference in response between the CS+ and CS- (conditional response; CR) (see Figure 1.1 on page 15).

To investigate MCS, a differential odor conditioning research paradigm was developed at our laboratory. Odors are used as CSs and the inhalation of CO₂-enriched air is utilized as the US. In the prototypical procedure (see Figure 1.2 on page 16), two odors are used, for example, ammonia (an unsavory smelling odor having a negative affective valence) and niaouli (smelling of eucalyptus and having a positive affective valence). One odor (CS+ odor) is consistently paired with CO₂-enriched air inhalation, while the other odor (CS- odor) is paired with air.

Three trials of each type are run. The order of administration is counterbalanced with the restriction that no more than two consecutive trials are of the same type. Together with a preceding air trial (used as an acquisition baseline), these

Figure 1.1: A conditioning procedure

six trials constitute the acquisition phase. After a pause, the test phase starts with an air trial (used as a test baseline) followed by presenting the CS+ odor and the CS- odor with air. During the trials, several respiratory related parameters are recorded: tidal volume (V_T), inspiratory (T_i) and expiratory time (T_e), fractional endtidal CO_2 ($FETCO_2$; percentage of CO_2 gas in the expired air at the end of the expiration). Of these primal parameters, breathing frequency (f ; $\frac{60}{T_i+T_e}$), and minute ventilation (V_E ; $f \times V_T$) are calculated. After each breathing trial, a questionnaire consisting of 16 symptoms often associated with CO_2 -enriched air inhalation and 5 non-related (dummy) symptoms, was presented.

The studies

The first study to use this paradigm intended to investigate the possibility of conditioning of respiratory responses (Van den Bergh, Kempynck, Van de Woestijne, Baeyens, & Eelen, 1995). The study also investigated the relationship between these respiratory responses and somatic symptoms. The US was 7.4% CO_2 -enriched air and ammonia and niaouli were used as CSs. The acquisition phase and the test phase were conducted on two consecutive days. Half of the participants received ammonia as the CS+ odor and niaouli as the CS- odor, and vice versa for the other half. Contrary to the prototypical procedure described above, participants received two baselines preceding both acquisition and test. The test phase in this study was a copy of the acquisition phase with the exception of the US administration.

Several observations were reported. For example, baseline measures of both physiological and symptom measures dropped from pre-acquisition to pre-test (probably due to habituation to the equipment). Also, odors provoked more symptoms than air (as noted on trials were the CS- odor was presented in the first trial follow-

Figure 1.2: The differential odor conditioning paradigm

ing baselines). When looking at the test phase, no conditioning effect (defined as a difference between CS+ odor test and CS– odor test; see above) for the symptoms appeared. But an interaction between the CS+ odor variable (what odor had been used in the acquisition phase as the CS+ odor) and the CS+ odor test / CS– odor test difference revealed a selective conditioning effect. When ammonia was CS+ odor (consistently paired with the US), participants reported more symptoms to the CS+ odor test compared to the CS– odor test. No such difference was found for niaouli CS+ odor. A similar pattern was found for breathing frequency but not for any other respiratory parameter.

A replication study was performed with patients reporting psychosomatic complaints instead of a student population (Van den Bergh, Stegen, & Van de Woestijne, 1997). In this study, a contingency awareness measure was conducted after the acquisition and test phase in order to assess the knowledge of the CS–US contingency. Also, in the last two trials of the test phase, the test for CS+ and CS– odor was replaced by the administration of two new odors. This allowed to ascertain any generalization effects from the CS to other odors. Some changes were made to the procedure (acquisition and test on the same day, and one baseline instead of two).

Contrary to the study previously described, a main conditioning effect appeared for the symptom scores. Patients reported more symptoms in test phase when the CS+ odor was presented compared to the CS– odor. This effect was mediated by which odor was used as the CS+ odor in acquisition: the conditioning effect appeared mainly for ammonia as CS+ odor in acquisition. The replication of the selective conditioning effect showed up not only for symptom reports but also for breathing frequency and tidal volume. These data were compared to a non-patient population and revealed an overall larger response on symptoms and a lower FETCO₂ in the patients. When confronted with new odors (as was previously mentioned, in the last two trials of the test phase, two new odors were administered), participants did not respond with a CR, indicating that for these odors, no generalization could be demonstrated.

An attempt was made to determine whether the previously found conditioning effects on symptoms were based on the conditioned physiology (and thus the bodily sensations experienced in the test phase) or rather on an activated memory representation of the acquisition phase (Van den Bergh, Stegen, & Van de Woestijne, 1998). In order to investigate this issue, a standard acquisition phase was conducted, but half of the participants received a distraction task intended to divert the attention away from the acquisition experience. As in the previously discussed study a main conditioning effect as well as a selective conditioning effect was found for the symptom reports, but only in the participants who did not receive a distraction task. No conditioning effects appeared for the respiratory measures. Distracting participants was hypothesized to tamper with the creation of a memory of the acquisition and as such no memory could be activated, resulting in the response pattern found in this study. The absence of a conditioned physiological response further supported this idea.

Extinction within the differential odor conditioning paradigm was investigated using two odors with a negative affective valence as CSs (instead of one positive and one negative as in the previous studies; (Van den Bergh et al., 1999)). Niaouli was replaced by butyric acid, a foul smelling odor (not unlike strong cheese). The reason for this switch was twofold. Firstly, the study could assess the influence of affective valence of the CSs on the selective conditioning effect found in the previous study. Secondly, the possible modulation of irritancy could be investigated. Ammonia is an irritant (but administered below irritancy thresholds) and, as previously mentioned, is perceived through two neural pathways, while this is not the case for butyric acid. Extinction was investigated by altering the standard test phase. After a baseline and the CS+ odor test and the CSodor test, half of the participants received the CS+ odor administered with air another five times (extinction group). The other half received five air trials instead (waiting group). Finally, all participants received a CS+odor test.

A main conditioning effect appeared for symptom reports, suggesting that the affective valence was crucial for obtaining a conditioning effect (conditioning has been attained only with odors with a negative affective valence). On the respiratory variables, conditioning appeared only on breathing frequency when ammonia was the CS+ odor in acquisition, suggesting a modulating effect of irritancy. In the extinction group, at the last CS+ odor test, no difference was found between the amount of symptoms reported to the CS+ odor compared to the amount reported to the CS- odor. However, this difference still existed in the waiting group, implying that in this group, no extinction occurred.

These studies with the differential odor conditioning paradigm provide some relevant findings for this doctoral thesis. First of all, it is possible to associate odors with a negative experience resulting in both symptom reporting and a physiological response (although both seem to develop rather independently of each other). Secondly, conditioning is obtained only when odors with a negative affective valence are used as CS+. Thirdly, although the study in question was not specifically designed to test generalization, it did not appear.

The paradigm and MCS

As was argued before, a skeletal view on conditioning can not account for a complex syndrome like MCS but a more elaborated model can, at the least partially, accommodate for most of the symptom pattern and the course of MCS. In this section I will summarize the features of the differential odor conditioning paradigm and two of the questions yet to be answered by research. These two questions have led to the studies reported in the remaining of this doctoral thesis.

The first question is based on the clinical observation that, although MCS patients are often exposed to only one or two chemicals, in due course they respond to an ever growing number of chemical substances (Fiedler & Kipen, 1997; Sparks et al., 1994). A question that was also raised regarding the TILT model by Graveling and coworkers (1999) (see also section 1.2.2 on page 3). A conditioning model of MCS can account for the “spreading” to other chemical substances through the phenomenon of generalization. In a previous study with the paradigm, generalization was not found (Van den Bergh et al., 1997). However, the main focus of this study was not generalization and as such did not explore multiple dimensions on which generalization could occur. The second chapter of this doctoral thesis will further elaborate on the possibility of generalization in the differential odor conditioning paradigm and present two studies that investigate this topic.

A second question concerns the fact that symptoms of MCS patients aggravate substantially after a certain time. Also, patients become often dysfunctional only after a certain amount of time has passed (Ziem & McTamney, 1997). Regarding

this phenomenon, US-revaluation will be considered as a possible mechanism in the third chapter of this doctoral thesis.

1.4 Conclusions

In this chapter, the nature of Multiple Chemical Sensitivity and the problems regarding the diagnostic criteria were presented. An all encompassing explanation for MCS was not revealed in the review of contemporary models. Several mechanisms should be considered in order to fully comprehend MCS. A conditioning account was subsequently introduced as a valuable model to fully encompass MCS. Subsequently, the differential odor conditioning paradigm was introduced as an operationalization of the conditioning model for MCS and several studies with this paradigm were presented. In the next chapter, generalization in the differential odor conditioning paradigm will be discussed.

Chapter 2

Post-conditioning phenomenon 1: Generalization

2.1 Introduction

As mentioned in the previous chapter, one of the clinical observations in MCS difficult to account for in most models, is the “spreading” of symptoms to a broad range of chemical substances. Initially, patients seem to react to one or only a few chemical substances, while, by the time they present themselves for treatment, they typically react to a whole range of chemical substances (Fiedler & Kipen, 1997; Sparks et al., 1994). Moreover, it has been established that these substances often are chemically unrelated (Cullen, 1987). Some mechanisms have been proposed in the models previously discussed (see 1.2.2 on page 3). The hypersensitivity concept put forward by the clinical ecologists for example, has no problem explaining the range of chemical substances to which MCS patients respond. As mentioned before, clinical ecology is unfortunately an unsubstantiated theory. Most of the other models mentioned have some difficulty in explaining this observation. Especially the sensitization model (Bell et al., 2001) and the TILT model (Miller, 1997) have been criticized on this point (Graveling et al., 1999). But also the immunological theories and psychiatric models must be accommodated in order to account for the spreading phenomenon.

A conditioning account on the other hand incorporates the spreading of symptoms to other than the initially involved chemical substances through the phenomenon of generalization. Generalization as a mechanism was already suggested by Bolla–Wilson and coworkers and later by Siegel and Kreutzer (Bolla–Wilson et al., 1988; Siegel & Kreutzer, 1997). Generalization can be defined as follows. Given the fact that a certain stimulus (CS) is conditioned to another stimulus (US) and elicits a conditioned response (CR), it has been observed that other stimuli than

the original CS also elicit a response similar to the CR. Of course, these other stimuli did not evoke a CR like response prior to the conditioning of the original CS. The intensity of this response to stimuli other than the original CS is determined by the similarity of these stimuli to the original CS on one or more dimensions. This phenomenon is called the generalization decrement for the particular stimulus. When all generalization stimuli including the CS are plotted against their responses, the resulting graph is called the generalization gradient for the CS. The larger the generalization to other stimuli, the “flatter” this generalization gradient will be.

In the next section, some theories about generalization will be presented. The remaining of the chapter will describe two empirical studies that have investigated the plausibility of generalization as a mechanism in our research paradigm for MCS.

2.2 Models of generalization

2.2.1 Generalization in the Rescorla–Wagner theory of conditioning

The Rescorla–Wagner model for conditioning has been fairly successful in explaining a wide range of conditioning phenomena. The topic of generalization was considered only some time after the presentation of the model (Rescorla, 1976). The pivotal assumption of their model is the restricted amount of conditioning a CS can gain from a particular US. As a consequence, when several CSs are presented, each can gain only a limited amount of conditioning, of which the sum does not exceed the asymptote of conditioning (λ) for the US. More formally stated, the amount of conditioning for a compound CS (AB) is equal to the sum of the amount of conditioning for each component of the compound ($V_{AB} = V_A + V_B$; V is the associative strength of a stimulus). When this compound CS is presented with a US, the change in associative strength for the components is thus determined not only by rate parameters of the CS (α) and US (β), but also by the total associative strength of the compound stimulus ($V_A = \alpha A(\beta - V_{AB})$; V_A is the change in associative strength for component A).

Starting from the observation that stimuli similar to the CS elicit a CR, it is assumed that these stimuli thus share a common element. So, for example, the CS A and a similar stimulus B could be looked upon as two compound stimuli AX and BX. X then comprises the common features of A and B. The amount of generalization should then be function of the salience of X. If stimulus A is then involved in a conditioning procedure, not only the associative strength of A is increased but also the associative strength of X (because A can be considered as AX and the model states that $V_{AX} = V_A + V_X$). Upon presenting stimulus

B (similar to A and thus considered as BX), a response is predicted because the associative strength of X renders the associative strength of BX non-zero ($V_{BX} = V_B + V_X$).

2.2.2 Generalization in the Pearce theory of conditioning

Part of the reason this model for conditioning has been formulated, is the inability of the Rescorla–Wagner model discussed in the previous section to account for a number of empirical observations (Pearce, 1987). The Rescorla–Wagner model nicely fits the generalization observations found in procedures where generalization is assessed by changing some feature of the CS. However, the model has trouble to account for observations found in procedures indirectly assessing generalization decrement through changes in the context rather than of the CS (such as one trial overshadowing and external inhibition). It is indeed the underlying assumption that the context in which a CS is presented, does not alter the associative strength of the CS, that discommodates the Rescorla–Wagner model.

Pearce has then formulated an alternative model that incorporates these observations (Pearce, 1987). The basic assumption is that one possesses a buffer of limited capacity in which the current pattern of stimulation is represented at all times. In classical conditioning, the CS is then not only the stimulus presented in the experimental procedure, but the entire content of the buffer prior to the presentation of the US. This CS is, as a result of this conditioning, committed to long term memory. If the content of the buffer changes from one trial to the next, a new CS–US association will be formed in long term memory. Also, upon presenting the CS, a comparison with representations stored in long term memory occurs. The more similar this new CS constellation is with these representations, the stronger the effect of the associative strength of the CS–US association will be on the CR.

Generalization from one or more stimuli to another stimulus is given a crucial position in this conditioning theory. It is proposed to define the difference between trials in function of the similarity (S) of the buffer content associated with these trials. This model then suggests that besides an excitatory associative strength acquired through conditioning, there exists an excitatory strength that has generalized from other stimuli present in the buffer for every CS. The latter is determined by the similarity with these other stimuli and their respective associative strengths.

Thus in this model, even if the same CS is used in acquisition as in test, a generalization decrement could occur resulting in a slightly decreased CR because the content of the buffer in acquisition could be slightly different from the one in test. On the other hand, a stimulus only remotely similar to the original CS could also elicit a, albeit small, CR because there will be an overlap in the buffer contents (for example because both stimuli are presented in the same experimental context).

2.2.3 An alternative yet complementary approach to generalization

It has been repeatedly found in the literature that the generalization gradient becomes flatter as the time between acquisition and testing increases (Riccio & Ackil, 1992). Two possible phenomena then can occur. Firstly, stimuli related to the CS, elicit a larger CR like response after an interval compared to immediate testing. Secondly, stimuli previously eliciting no response, do provoke a CR like response after an interval. Riccio and Ackil have proposed that retrieval failure of some attributes of the CS could be responsible for these phenomena (Riccio & Ackil, 1992). One possible explanation for this “forgetting” of stimulus attributes has been offered by (Estes, 1997). In this account, random perturbation of the memory trace over time could be responsible for the decreased retrieval performance.

Another account for this increase of generalization over time was discussed by Bouton and coworkers (Bouton, Nelson, & Rosas, 1999). They propose the “context change account of forgetting” to elucidate this phenomenon and possibly explain the retrieval failures noted above. Essentially, the context account of forgetting states that time induces a change in external as well as internal contextual cues. This “mismatch” between acquisition and test then causes retrieval failures resulting in a diminished recall of stimulus attributes, enhancing generalization. Riccio and coworkers noted more than a decade earlier that, regarding generalization phenomena, a context change account of forgetting leads to a peculiar paradox (Riccio, Richardson, & D.L., 1984). Stimuli become more interchangeable over time (increased generalization) because of forgetting of stimulus attributes, but the context change account of forgetting is based on the context becoming less similar and hence creating a mismatch between acquisition and test which results in retrieval failure. In other words, attributes of ordinary stimuli are forgotten over time while the same does not hold for contextual stimuli. Findings of contexts becoming more interchangeable however contradict these implications (Riccio et al., 1984). A context change account of forgetting then seems out of accord with the increase of generalization over time.

A conceptual solution for this paradox was proposed in the form of introducing time as a context (Bouton et al., 1999). Here, contextual cues are imbedded in temporal cues, which are considered insensitive to changes over time. This solution has not been readily accepted (see the ardent debate in Riccio, Richardson, & Ebner, 1999; Bouton, Rosas, & Nelson, 1999).

To summarize, the idea of forgetting of stimulus attributes is still a feasible manner to look at generalization, although a consensus has not yet been reached on the mechanisms behind this forgetting.

2.3 Experiment 1: Delayed testing and generalization

2.3.1 Introduction

The aim of the study presented in the following section is twofold. First, generalization was assessed on several physical dimensions of the odor stimuli used in our odor conditioning paradigm. Second, in view of the findings reported by Riccio and Ackil in the previous section, a delayed test of generalization was performed to ascertain possible changes in generalization over time (Riccio & Ackil, 1992). Both phenomena are valuable in elaborating our conditioning model for MCS.

2.3.2 Article

DEVRIESE, S., WINTERS, W., STEGEN, K., VAN DIEST, I., VEULEMANS, H., NEMERY, B., EELEN, P., VAN DE WOESTIJNE, K. P., & VAN DEN BERGH, O. (2000). GENERALIZATION OF ACQUIRED SOMATIC SYMPTOMS IN RESPONSE TO ODORS: A PAVLOVIAN PERSPECTIVE ON MULTIPLE CHEMICAL SENSITIVITY. *PSYCHOSOMATIC MEDICINE*, 62, 751-759.

Abstract

Objective Somatic symptoms in response to odors can be acquired in a Pavlovian conditioning paradigm. The present study investigated 1) whether learned symptoms can generalize to new odors; 2) whether the generalization gradient is linked to the affective or irritant quality of the new odors; and 3) whether the delay between acquisition and test modulates generalization.

Method Conditional odor stimuli (CS) were (diluted) ammonia and Niaouli. One odor was mixed with 7.4 % CO₂-enriched air (unconditional stimulus) during 2 min breathing trials (CS+ trial), while the other odor was presented with air (CS trial). Three CS+ and three CS trials occurred in a semi-randomized order (acquisition phase). The test phase implied one CS+ Only (CS+ without CO₂) and one CS test trial, followed by three trials using new odors (butyric acid, acetic acid, and citric aroma). Half of the subjects (n=28) were tested immediately, the other half were tested after one week. Ventilatory responses were measured during and somatic symptoms after each trial.

Results Participants had more symptoms to CS+ only exposures, but only when ammonia was used as a CS+. Also generalization occurred: more symptoms were reported to butyric and acetic acid but not to citric aroma, and only in participants who had been conditioned. Both the selective conditioning and the

generalization effect were mediated by negative affectivity of the participants. The delay between acquisition and test phase had no effect.

Conclusions Symptoms to odorous substances can be learned and generalize to new substances, especially in persons with high negative affectivity. The findings further support the plausibility of a Pavlovian perspective on multiple chemical sensitivity.

Keywords: classical conditioning, generalization, psychosomatic symptoms, multiple chemical sensitivity. NA = negative affectivity; CS = conditioned stimulus, US = unconditioned stimulus; UR = unconditioned response; CR = conditioned response; MCS = multiple chemical sensitivity; f = frequency; V_T = tidal volume; V_E = minute ventilation

Introduction

Multiple Chemical Sensitivity (MCS) is an acquired disease, implying symptoms in multiple organ systems that are elicited by chemicals at levels far below harmful doses. The symptoms may occur in response to various, chemically unrelated substances, and they typically include fatigue, malaise, dizziness, headaches, lack of concentration and respiratory problems (Cullen, 1987; Miller, 1997; Sparks et al., 1994). Several explanations, both physiological and psychological, have been put forward (see reviews Sorg, 1999; Fiedler & Kipen, 1997; Graveling et al., 1999). Numerous physiological studies have tried to identify a physical parameter systematically correlated with the symptoms, but up to now no consistent findings have emerged (Miller, 1997; Bascom et al., 1997; Cohn, 1994; Doty, 1994; Simon, Daniell, Stockbridge, Claypoole, & Rosenstock, 1993). Also neural sensitization has been suggested (Bell et al., 1992) Bell:1997b. Among the psychological explanations, Pavlovian conditioning has been advanced as a potential mechanism (Shusterman, 1992; Van den Bergh et al., 1995; Siegel & Kreutzer, 1997). Pavlovian conditioning implies that an originally neutral stimulus (conditional stimulus, CS) becomes associated with another stimulus (unconditional stimulus, US). This US elicits by itself a clear response (unconditional response, UR). This results in the CS becoming endowed with the capacity to elicit a conditional response, which is (often, but not always) similar to the UR. In this view, MCS symptoms may result from odors (CS) having been associated with a significant event for example, a toxic exposure whereby symptoms (UR) may subsequently become elicited by the odors only, and thus become CRs. Despite some case reports consistent with this view (e.g. Bolla–Wilson et al., 1988; Davidoff & Keyl, 1996; Davidoff et al., 1998), many criticisms have been raised as well (e.g. Staudenmayer, 1997).

Because experimental evidence is scarce, we developed a conditioning paradigm to test these assumptions in the laboratory. Harmless odorous substances (CSs) were presented in compound with CO₂-enriched air (US) in two-minute breathing trials. After three acquisition trials, the conditioning effects were tested by presenting the odors only. In a series of experiments, we observed an increased respiratory frequency, and elevated levels of somatic symptoms upon presenting the CS odor alone. This conditioning effect was selective: symptoms and respiratory responses were only learned to a foul smelling odor (ammonia) and not to a fresh smelling one (niaouli) as CS (Van den Bergh et al., 1995, 1997, 1998). When both CS odors were foul smelling (irritant ammonia and non-irritant butyric acid) conditioned symptoms emerged to both, suggesting that affective valence of the odors is critical and not irritancy (Van den Bergh et al., 1999). This selectivity in conditioning effects occurred despite roughly equal conscious awareness of the arranged contingencies between CS and US for both types of odors (ammonia and niaouli), suggesting that the critical processes were not identical to aware cognition. Compared to normals, the conditioning effects were overall stronger in a group of psychosomatic patients with hyperventilation related symptoms, in particular for the set of pre-existing symptoms (Van den Bergh et al., 1997). In addition, conditioning effects were overall stronger in normal subjects scoring high on neuroticism (negative affectivity) compared to normals scoring low (Van den Bergh et al., 1998; Van den Bergh et al., 1999). A straightforward Pavlovian extinction procedure, involving a series of unreinforced CS exposures, readily reduced the learned symptoms (Van den Bergh et al., 1999). Conditioned symptoms and altered respiratory behavior were also observed when mental images of situations were used as CSs rather than odors: merely evoking an image that was previously paired with a CO₂ challenge elicited increased symptoms and altered respiratory behavior, but only when the imagined situations were stressful (Van den Bergh et al., 1999).

This set of studies provided strong experimental evidence for the plausibility of a Pavlovian conditioning explanation of MCS. CO₂ inhalation as an US in our paradigm may act as a laboratory analogue for two types of USs in reality: first, it may mimic a toxic exposure; second, it may mimic the sensations of stress-induced hyperventilation. This latter argument may explain why a toxic exposure is not always found in a patient's history, and why stress may act as the major trigger of MCS in some cases (Sparks et al., 1994). Recent findings have indeed documented the presence of hyperventilation in some cases (Leznoff, 1997). However, if episodic hyperventilation would act as an US subserving learning mechanisms for symptoms, it is apparent that physiological indicators of hyperventilation need not always be found during symptom episodes.

An intriguing aspect of MCS is that symptoms of MCS tend to spread to many, often chemically unrelated substances. Patients respond to smoke, gasoline, clean-

ing products but also to perfume. This diversity in symptom-triggering substances could be explained by the concept of generalization. In the conditioning literature, this phenomenon refers to “the tendency to respond to stimuli other than the training stimulus that has been associated with reinforcement” (Riccio & Ackil, 1992, p. 433). Generally, the response strength tends to decline as test stimuli become increasingly different from the training stimulus (Riccio & Ackil, 1992; Rescorla, 1976; Pearce, 1987). The similarity between the training stimulus and the test stimuli is usually described along some physical or psychological dimension, but also the mere passage of time may affect the tendency to generalize to other stimuli (Riccio & Ackil, 1992; Zhou & Riccio, 1996). The mechanism behind this phenomenon is probably forgetting of stimulus attributes, which, as a consequence, allows more deviating stimuli to elicit a response.

In the present study, we tested the occurrence of generalization of learned symptoms and respiratory responses to other substances than the one used in the acquisition phase. As in our previous studies (see above), we used a differential conditioning procedure. This implied two odors (ammonia and niaouli), one of which was used in one group of subjects as a CS+ (the odor was presented in compound with the CO₂-enriched air) and the other as a CS (the odor was presented in regular room air). The specific combination was reversed in another group. In the test phase, we first tested the conditioning effect (one CS+ and one CS only), followed by three new odors differing along the dimension of affective valence (fresh vs. foul smelling) and along the dimension of irritancy (irritant vs. non-irritant). For half of the subjects, the generalization effect was tested immediately after the acquisition phase, for the other half, the test phase was run after one week. This delay was introduced in order to stimulate forgetting of the stimulus attributes, which has been shown to modulate generalization effects (Riccio & Ackil, 1992). In line with our earlier findings, we expected a selective conditioning effect: learned symptoms would only occur with foul smelling ammonia as the CS+ and not with neutral-positive smelling niaouli. Because affective valence of the CSs appeared critical for conditioning effects to emerge and not irritancy (Van den Bergh et al., 1999), we expected generalization along the affective valence dimension: more symptoms are expected to occur to foul smelling than to positive smelling substances, regardless of their irritant properties.

We also analyzed the impact of negative affectivity of the subjects. Negative affectivity (NA) or neuroticism is defined as a broad range of aversive mood states such as anger, disgust, fearfulness and depression (Costa & McCrae, 1988). High NA subjects have more psychosomatic symptoms in general (Watson & Pennebaker, 1989), which appears to be due to a greater interoceptive tendency and an inclination to interpret somatic sensations negatively (Stegen & Van den Bergh, Submitted). This variable appeared to modulate the conditioning effect in previous

studies: generally stronger effects were found in high NA subjects (Van den Bergh et al., 1998; Stegen & Van den Bergh, Submitted).

Method

Participants Fifty-six healthy students (23 men and 33 women, age between 18–26 yr.) voluntarily participated in this study. After completion of the experiment, they received 300 BEF (\$9, £6). Prior to participating, a brief health inquiry was administered to check for the presence of epilepsy, panic disorder, cardiac and respiratory diseases or for medication use that may suggest their presence. This led to the exclusion of 9 participants out of 65. An ethics committee approved the study.

Based on the Negative Emotionality Measure (NEM, range 0–14, see further), 30 participants were categorized as low NA (score lower than 7) and 26 participants as high NA (score equal or higher than 7). The distribution of high and low NA participants was roughly equal across the cells made up by crossing the between-subject variables (CS+ odor and delay; 7 of each in each cell), except for niaouli as a CS+ in the immediate condition : there were slightly more low NA participants (9 compared to 5 high NA participants).

Materials Odors and measures were identical with other studies of our group (see Van den Bergh et al., 1995, 1998; Van den Bergh et al., 1999). Only the most important and new features will be described here.

Odors Ammonia (NH₃) and niaouli (a volatile oil, containing 65 % eucalyptus) were used in the acquisition phase as CSs. In the test phase, three new odors were introduced: butyric acid, acetic acid and citric aroma. Butyric acid and acetic acid are both foul smelling, the first being a pure odor, the latter an irritant. Citric aroma was experienced as a positively valent odor. All irritants were administered below the irritancy threshold: ammonia and acetic acid were dissolved in water, respectively in a 0.4% and 5% concentration.

Subjective measures Before the experiment, we administered (besides the brief health questionnaire, see above), a symptom check list (39 daily life symptoms, see Wientjes, 1993), the Negative and Positive Emotionality Measure (NEM / PEM; Tellegen, 1982), the Positive and Negative Affect Schedule (PANAS; Watson, Clark, & Tellegen, 1988) and the Anxiety Sensitivity Index (ASI, Peterson & Heilbronner, 1988). The last three questionnaires are NA measures. The NEM was chosen based on a comparison of the three measures on internal consistency and correlations with symptom scores (Stegen & Van den Bergh, Submitted). In

addition, a median split of the NEM and the PANAS produced exactly the same composition of the two NA groups.

Symptoms after each trial were measured using the 16-item check list of our previous studies. Participants indicated the extent to which the symptoms were experienced (not at all, slight, medium, strong and very strong, respectively coded from 1 to 5). The sum of symptoms was used as a continuous variable. Based on data by Wientjes and Grossman, five symptom subsets were formed and analyzed separately (arousal, respiratory, cardiac/warmth, tingling sensations, unclassified) (Wientjes & Grossman, 1994). A sixth symptom subset, containing five items not sensitive to CO₂ inhalation, was added as a control set.

Physiological measures and apparatus All odors were administered through vaporization using a Devilbiss Nebulizer 646. The airflow was at a constant rate of 50 l/h. The CO₂-enriched air consisted of 7.5% CO₂, 21% O₂ and 71.5% N₂. After decompression, the CO₂-enriched air was led into a meteorological balloon which was connected to a valve allowing easy switching between CO₂-enriched air and regular room air. This valve was connected to a tube system ending in a double one-way valve, separating inspired and expired air. This double one-way valve was connected to a pneumotachograph (Fleish No 2, Switzerland), which fitted on a Rudolph mask. A small vinyl tube from the Nebulizer was attached to the side of the mask, allowing the odor to be mixed with the inspired gas mixture. At the other side of the mask, another small vinyl tube was connected to an infrared CO₂-monitor (Poet II, Criticare, USA) which sampled inspired and expired air (due to equipment failure, CO₂ data were unreliable and will not be discussed further). Airflow waveforms were sampled at a rate of 20 Hz using propriety software and stored on a PC. Off-line, a software program (Han, 1995) counted and removed pauses and irregularities from the datafile and extracted the following primary parameters per breathing cycle: inspiratory (T_i) and expiratory time (T_e), inspiratory (V_i) and expiratory volume (V_e).

Procedure

Participants were led into a waiting room to complete the questionnaires and to receive a written text explaining the purpose of the experiment: several gas mixtures would be administered and some of these mixtures could temporarily cause harmless symptoms like headache and shortness of breath. They would all disappear quickly after the trial. In addition, it was stated that the participants could stop the experiment at any time. A short description of the procedure was included. Next, they signed an informed consent form and were led into the laboratory. All trials were five minutes in duration. The first two minutes of a trial consisted of breath-

ing through the mask, followed by three minutes of rest during which participants completed the symptom list.

The acquisition phase (see Figure 2.1 on page 31) consisted of seven trials. Participants always started with a context exposure trial: only room air and no odor was breathed through the system. Next, six trials were run in a semi-randomized order. Three of them were CS+ trials: one odor (ammonia or niaouli) was mixed with the CO₂-enriched air. The other three were CS trials: the other odor was administered with room air. The trials were presented in a semi-randomized order with the constraint that no more than two trials in a row could be the same. Half of the participants received ammonia as CS+, while the other half received niaouli as CS+. Within each CS+ odor condition, half of the participants were randomly assigned to the immediate test condition: the test phase followed after a 20 min pause spent in the waiting room. The other half were assigned to the delayed condition: the test phase was run after one week.

The test phase consisted of six trials. Again, the first trial was a context exposure trial (room air, no odor). The following two trials were the CS+ and CS odor only (order was counterbalanced between-subjects). The remaining three trials were the new test odors: butyric acid, acetic acid and citric aroma. The order of presentation was semi-randomized between-subjects.

Before and after the acquisition phase and the test phase, all odors were presented in small containers. The participants lifted the lid and briefly inhaled the odor to rate the affective valence on a -5 to +5 Likert-type rating scale. Also, after the acquisition and test phase, the contingency awareness of the relation CS+/US was measured: the participants had to indicate which odor had caused the most symptoms in the previous phase. The answers were coded as 0 for wrong (e.g. answering ammonia when niaouli had been CS+), 2 for correct, and 1 for not knowing.

Data analysis and design

Analyses on subjective measures were run on the total symptom score per trial, and on the various subsets of symptoms separately (arousal, respiratory, cardiac/warmth, tingling sensations, unclassified and dummy symptoms). The two context exposure trials were analyzed in a CS+ odor (ammonia/niaouli) $\times$ Time of test (immediate/delayed) $\times$ NA (high/low) $\times$ Trial (one, two) design. The context data before acquisition and test were used as covariates for, respectively, analysis of the acquisition and test data. The acquisition trials were analyzed using a CS+ odor (ammonia/niaouli) $\times$ Time of test (immediate/delayed) $\times$ NA (high/low) $\times$ Conditioning (CS+/CS) $\times$ Trial (one, two, three) design. The test trials had a similar design, except that there was no Trial variable. For the analysis of the generaliza-

Figure 2.1: Experimental design. Boxes connected with single lines are sequential steps in the procedure while boxes connected with double lines represent randomized or semi-randomized events

tion effect, the variable Conditioning was replaced by Generalization odor (butyric acid, acetic acid and citric aroma). CS+ odor, Time of test and NA were between-subject variables, while Conditioning and Generalization odor were within-subject variables.

Several parameters were calculated from the raw physiological data: frequency per minute (f), tidal volume (V_T) and minute ventilation ($V_E = V_T \times f$). The analyses on means per trial were essentially the same as for the symptom score analysis, except that for each analysis an extra within-subject variable was added, Minute, because each trial consisted of 2 minutes breathing. Because breathing behavior is different for males and females, we included Gender as an additional variable. However, this extra between-subject variable caused an incomplete design as regards the distribution of NA. Therefore, the latter variable was left out of the analysis of the physiological data. This option was made, because NA, although substantially related to conditioning of symptoms, was unrelated to conditioning of breathing behavior in our previous studies (Van den Bergh et al., 1999). Greenhouse–Geisser corrections were used when appropriate to control for violations of the compound symmetry ANOVA assumption (McCall & Appelbaum, 1973).

Contingency awareness was analyzed using a Mann–Whitney U test. Odor evaluations were analyzed using a Moment (before/after acquisition /before/after test) $\times$ Odor (ammonia/ niaouli/acetic acid/butyric acid/citric aroma) ANOVA design.

Results

CONTEXT EXPOSURES

Subjective symptoms Participants reported overall more symptoms in the trial before the acquisition phase compared to the one before the test phase (Trial: $F(1,48) = 9.39$; $p < 0.01$). This effect was also observed in the arousal and cardiac/warmth symptom subsets (Trial: $F(1,52) = 29.02$; $p < 0.001$; and 4.99 ; $p < 0.05$, respectively), but not in the other subsets. This effect probably reflects habituation to the measurement context.

Physiological responses Women breathed faster with a lower volume and minute ventilation than men ($F(1,45)$, respectively, 4.16 (f); 17.71 (V_T) and 5.89 (V_M); all p 's < 0.05 or smaller). Unconditional odor effects. These effects were tested using the data from those participants starting the acquisition phase with a CS trial (see Van den Bergh et al., 1997)). As in our previous studies, no indication was found for different effects of the odors themselves, prior to using them as CSs.

Table 2.1: Subset and total symptom scores (mean & SD) during the acquisition phase

	CS+	CS–
1. Arousal	5.39 (2.49)	3.40 (0.60)***
2. Respiratory	9.17 (3.20)	4.97 (0.88)***
3. Cardiac / warmth	5.60 (2.44)	3.90 (1.20)***
4. Tingling	2.43 (1.13)	2.28 (0.77)*
5. Unclassified	5.94 (1.62)	4.81 (0.90)***
Total	28.53 (8.42)	19.35 (2.92)***
6. Dummy	5.81 (0.86)	7.07 (1.02)*

Note 1: * $p < 0.05$; *** $p < 0.0001$

Note 2: symptoms in set 1 : tension, anxious feelings, feelings of panicking; set 2 : fast breathing, smothering sensations, chest tightness, feelings of choking; set 3 : pounding heart, sweating, hot flushes; set 4 : tingling/numbness in extremities, in face; set 5 : lump in throat, headache, dizziness, cold chills; set 6 : joint pain, sleepy feeling, low back pain, stuffed nose, burning eyes

This was so for both symptoms and respiratory behavior.

UNCONDITIONAL ODOR EFFECTS

These effects were tested using the data from those participants starting the acquisition phase with a CS trial (see Van den Bergh et al., 1997). As in our previous studies, no indication was found for different effects of the odors themselves, prior to using them as CSs. This was so for both symptoms and respiratory behavior.

ACQUISITION

Subjective symptoms Participants reported overall more symptoms when breathing CO₂-enriched air compared to room air (Conditioning: $F(1,48) = 83.31$; $p < 0.00001$). This was found for all the symptom subsets (see table 2.1 on page 33). The participants became gradually less aroused (Trial effect for the arousal set: $F(2,96) = 4.03$; $p < 0.05$).

Depending on the CS+ odor, there was a difference in the response of the participants to CO₂-enriched air over trials (CS+ odor x Conditioning x Trial : $F(2,96) = 3.79$; $p < 0.05$). Symptom scores raised slightly over trials for the CS+ and decreased slightly for the CS, but only for niaouli as a CS+ odor. No NA effects were observed.

Physiological responses Participants had a higher tidal volume and minute ventilation on CS+ compared to CS trials ($F(1,46) = 73.11$; $p < 0.0001$ and $F(1,46) = 86.38$; $p < 0.0001$). However, this difference was modulated by the CS+ odor type: the frequency was only higher when ammonia was the CS+ and not when niaouli was CS+ (CS+ odor $\times$ Conditioning: $F(1,46) = 4.57$; $p < 0.05$). The participants also showed an increased frequency, tidal volume and minute ventilation from the first to the second minute during CS+, but not during CS trials (Conditioning $\times$ Minute : $F(1,46) = 14.72$ (f); 84.85 (V_T) and 154.79 (V_E), p 's < 0.001 or smaller).

TEST OF THE CONDITIONING EFFECTS

Subjective symptoms Replicating the selective conditioning effect found earlier (Van den Bergh et al., 1995, 1997, 1998), we observed more symptoms to the CS+ than to the CS- odor, but only when ammonia had been the CS+ odor (CS+ odor $\times$ Conditioning: $F(1,48) = 5.5$; $p < 0.05$). In addition, this effect was modulated by NA: the selective conditioning effect was found in high NA participants, but not in low NA (CS+ odor $\times$ NA $\times$ Conditioning : $F(1,48) = 6.20$; $p < 0.05$; CS+ odor $\times$ Conditioning in high NA : $F(1,48) = 10.37$; $p < 0.05$; in low NA $F(1,48) = 0.19$, see figure 2.2 on page 35).

This pattern of results was most prominently present in the respiratory symptom subset (CS+ odor $\times$ Conditioning : $F(1,48) = 4.91$; $p < 0.05$; CS+ odor $\times$ Conditioning $\times$ NA : $F(1,48) = 4.44$; $p < 0.05$). Participants reported themselves as more aroused in the immediate compared to the delayed test condition (Time of test : $F(1,47) = 4.93$; $p < 0.05$).

Physiological responses No (selective) conditioning effects were observed for respiratory behavior. A CS+ odor $\times$ Conditioning $\times$ Minute interaction ($F(1,41) = 5.05$; $p < 0.05$) showed that the volume for the CS+ raised from the first to the second minute, when ammonia was CS+ odor, which did not appear for niaouli, but the difference between CS+ and CS- within this interaction was not significant. Overall, participants breathed faster in the immediate condition compared to the delayed condition (Time of test : $F(1,40) = 8.11$; $p < 0.01$), but this was only so during the second minute of measurement (Time of test $\times$ Minute: $F(1,41) = 5.11$; $p < 0.01$).

TEST OF THE GENERALIZATION EFFECTS

Subjective symptoms Overall, butyric acid made participants report more symptoms than acetic acid or citric aroma (Generalization odor : $F(2,96) = 8.96$; p

Figure 2.2: The conditioning effect as a function of the odor acting as CS+ (ammonia or niaouli) on total symptom scores in participants scoring high and low for negative affectivity (NA) (Am CS+: ammonia CS+ in acquisition; Ni CS+: niaouli CS+ in acquisition)

< 0.001). However, participants who received ammonia as CS+ (that is, the group showing conditioning effects) reported more symptoms to butyric acid and acetic acid, but not to citric aroma, than participants for which niaouli had been the CS+ (those who did not show conditioning effects). However, this was only so when they were high on NA (CS+ odor $\times$ NA $\times$ Generalization odor: $F(2,96) = 4.80$; $p < 0.05$; for butyric acid: $F(1,47) = 7.27$, $p < 0.01$; for acetic acid: $F(1,47) = 4.61$, $p < 0.05$). Low NA participants did not show this effect (see figure 2.3 on page 36).

Again, this pattern of the data was most prominently present in the respiratory subset (see table 2.2 on page 37). The cardiac/warmth subset showed generalization for butyric acid only and not for acetic acid (see table 2.2 on page 37).

Physiological responses When ammonia had been used as a CS+ in the acquisition phase, the response to the generalization odors differed in the two minutes of measurement (CS+ odor $\times$ Generalization odor $\times$ Minute: $F(1,72) = 3.96$; $p < 0.05$): Acetic acid evoked a higher tidal volume compared to butyric acid in the

Figure 2.3: The generalization effect on total symptom scores for three new odors (butyric acid (Bu), acetic acid (Ac), and citric aroma (Ci)) in participants scoring high and low on NA (error bars denote standard error of mean)

second minute ($F(1,39) = 4.22$; $p < 0.05$; first vs. second minute of acetic acid breathing : $F(1,39) = 5.35$; $p < 0.05$). A decrease in tidal volume from the first to the second minute was found for citric aroma when niaouli had been the CS+ odor ($F(1,39) = 6.28$; $p < 0.05$). A similar CS+ odor $\times$ Generalization odor $\times$ Minute interaction was found for minute ventilation ($F(2,78) = 3.72$; $p < 0.05$). But here, we observed only a decrease from the first to the second minute for citric aroma when niaouli had been the CS+ odor ($F(1,39) = 5.91$; $p < 0.05$).

CONTINGENCY AWARENESS AND ODOR EVALUATIONS

Contingency awareness To test whether participants showed any difference in knowing which odor had been presented with CO₂-enriched air after the acquisition phase, Mann–Withney U-tests for several group comparisons were performed across the immediate and delayed test condition, because this distinction was not relevant at that moment. The participants showed no better contingency awareness of the CS-US relationship with ammonia as CS+ compared to niaouli as CS+. Also, high NA participants were overall not more aware than low NA partic-

Table 2.2: Subset and total symptom scores (means) for the generalization odors in low and high NA participants with ammonia or niaouli as CS+

	Low NA					
	Ammonia CS+			Niaouli CS+		
	Butyric acid	Acetic acid	Citric aroma	Butyric acid	Acetic acid	Citric aroma
Arousal	3.07	3.07	3.14	3.34	3.00	3.07
Resp.	4.86	4.50	4.50	4.85	4.41	4.45
Cardiac	3.64	3.79	3.79	3.88	3.60	3.58
Tingling	2.50	2.21	2.36	2.47	2.34	2.56
Unclas.	5.36	5.07	4.79	5.04	4.35	4.56
Total	19.43	18.64	18.57	19.59	17.70	18.21
Dummy	6.07	6.21	6.07	6.63	5.45	5.33

	High NA					
	Ammonia CS+			Niaouli CS+		
	Butyric acid	Acetic acid	Citric aroma	Butyric acid	Acetic acid	Citric aroma
Arousal	3.64	3.28	3.43	3.10	3.11	3.10
Resp.	6.21	5.42	4.79	4.56	4.43	4.81
Cardiac	4.07	3.50	3.86	3.49	3.53	3.53
Tingling	2.29	2.14	2.14	2.00	2.00	2.00
Unclas.	5.21	4.78	4.64	4.75	4.65	5.06
Total	21.42	19.14	18.86	17.90	17.71	17.50
Dummy	6.00	6.00	5.93	6.26	6.19	6.30

* $p < 0.05$ for the CS+ odor $\times$ NA $\times$ Generalization odor interaction

Symptom scores per row with the same symbol are significantly different

ipants. The data for ammonia as CS+ were: correct = 17 (8 low NA, 9 high NA), don't know = 8 (4 low NA, 4 high NA), incorrect = 3 (2 low NA, 1 high NA); for niaouli as CS+: correct = 17 (9 low NA, 8 high NA); don't know = 7 (5 low NA, 2 high NA), incorrect = 4 (2 low NA, 2 high NA). This means that participants in the condition where symptom learning occurred (ammonia CS+) were overall not more aware than those in the condition where no learning occurred (niaouli CS+). Therefore, our findings cannot be reduced to the effects of contingency awareness and/or demand characteristics¹.

¹Additionally, an ANOVA replacing NA by Contingency Awareness (yes/no) as independent variable did not yield a significant CS+ Odor $\times$ Contingency $\times$ Conditioning interaction ($p=.38$) for the symptom scores. However, looking at this interaction in each NA group separately showed it signif-

Odor evaluations Only an Odor main effect ($F(4|176) = 179,71$; $p < 0.0001$) appeared. Ammonia, acetic acid and butyric acid were all rated as negative odors. Ammonia and butyric acid were scored equally negative (respectively -3.48 and -3.31), while acetic acid was somewhat less negative (-1.36). Niaouli and citric aroma were rated positive (respectively 1.49 and 2.43), with citric aroma as most positive (Post hoc Tukey Honest Difference Test). Unlike in a previous study (Van den Bergh et al., 1999) no evaluative conditioning appeared (that is, a shift in evaluative judgment, depending on the conditioning manipulation).

Discussion

In this study, we replicated the selective learning effect found in earlier studies: when sensing an odor had been accompanied by a complex of symptoms caused by inhaling CO₂-enriched air, participants reported an elevated level of symptoms also when presented with the odor alone (Van den Bergh et al., 1995, 1997, 1998). However, this occurred only when the odor was foul smelling. A difference in conscious awareness of the contingency between the specific odor used as CS (ammonia or niaouli) and the experience of symptoms could not explain this selective conditioning effect. An exploratory analysis revealed that awareness of the CS-US relation was not sufficient in order to obtain conditioning, although it may have been necessary. Also this replicates earlier findings and shows that learning symptoms implies more basic processes than those reflected by aware cognition. The explanations that may account for this selective conditioning effect have been discussed elsewhere (Van den Bergh et al., 1995, 1997; Van den Bergh et al., 1999; see also Davey, 1995). The learned symptoms were not confined to sensations of arousal (which would merely document conditioned arousal), but were most prominently due to respiratory symptoms. This shows that the conditioning effects were quite specifically mimicking the unconditioned responses. The present study shows in addition that the learning effect on symptoms is quite stable: testing immediately or after one week did not affect the results.

Despite the learning effects on symptoms, there were no significant conditioning effects on breathing responses. These effects have been less reliable (they were found in studies Van den Bergh et al., 1995, 1997; Van den Bergh et al., 1999; Stegen, De bruyne, Rasschaert, Van de Woestijne, & O., 1999; but not in Van den Bergh et al., 1998; and the present study). Probably this is due to the use – for obvious ethical reasons – of a relatively weak US and a small number of learning trials.

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icant for the high NA participants ($F(1,40)=14.62$, $p < 0.001$) but not for the low NA participants ($p=0.15$), indicating learning in aware high NA participants and not in aware low NA or unaware participants.

In any case, it corroborates our earlier findings, showing that automatically activated memory representations of the acquisition experiences were responsible for the learned symptoms and not specific informational input from bodily responses (Van den Bergh et al., 1998).

Most importantly in the present context is that the learned symptoms appeared to generalize to new odors: only the participants showing conditioning effects also reported more symptoms to odors that had not been involved in the acquisition phase. Two aspects of this finding deserve particular attention. First, the generalization effect is confined to the negatively valenced odors, butyric and acetic acid, regardless of their potential irritancy. Overall then, it appears that the affective quality of the CSs is a critical cue for both the conditioning and generalization of symptoms. Second, the generalization effect was not modulated by the delay between acquisition and test. According to Riccio and Ackil (1992), generalization occurs because of the forgetting of stimulus attributes: No or little generalization occurs when testing follows immediately after acquisition, because stimuli attributes are “remembered” well. Introducing a delay between acquisition and test often produces more generalization. From this perspective, the fact that we already found a generalization effect after 20 minutes that was not affected by adding a delay of one week, may suggest either fast forgetting or poor learning about specific odor attributes. Because right after acquisition, 34 out of 56 participants correctly identified the CS+ odor among five odors presented in a row as the one that was associated with pronounced symptoms (15 did not know, and 7 were incorrect), it must be concluded that most participants clearly recognized the specific attributes. Moreover, the trials testing the conditioning effects (which were presented before the generalization odors) may be considered as “reminders” of the CS+ and CS– and, at the same time, serve as extinction trials. However, despite these possible counteracting effects, when an odor was presented 30 minutes later in a separate breathing trial, it appears that the participants’ responding was merely guided by an association between a (vaguely specified) negative odor and symptoms. Most of the available findings on the effect of delay on generalization pertain to other stimuli than odors. It is currently not clear what forgetting about stimulus attributes actually means for this class of stimuli. Other parameter values, if not other processes than those known for other classes of stimuli, may be involved in the present generalization effect.

The conditioning effects and, as a consequence, also the generalization effects were mainly observed in the participants scoring high on negative affectivity. Other experimental studies in our laboratory, specifically focusing on the mechanisms mediating between high negative affectivity and elevated symptom reporting during CO₂ inhalation, have shown that high NA subjects have a stronger attentional bias towards bodily sensations and are more inclined to contemplate about possible

negative health effects of the induced symptoms (Stegen et al., 1998; see also Pennebaker, 1994). However, the effect of NA on symptoms appeared to depend on the attentional demands of the ongoing events: a new and/or a strong respiratory challenge wiped out the NA effects on symptoms, because in those circumstances both high and low NA were attentionally involved with processing the events (Stegen et al., 1998). In conditions of minor challenges (breathing air Stegen et al., 1998, or when attentionally distracted during CO₂ breathing (Van den Bergh et al., 1998), the NA effects on symptoms showed up; for an extensive overview see Stegen & Van den Bergh, Submitted), probably because in those circumstances habitual differences in attentional direction among high and low NA show up. This may explain why in an earlier conditioning study of our group using distraction during acquisition, the conditioning effects reflected NA related differences that were already present during the acquisition phase (Van den Bergh et al., 1998). In the present study, NA effects only appeared in the test phase and not during acquisition, because the absence of distractive elements allowed both high and low NA participants to attend directly to the events in acquisition. The finding that the broader dimension of negative affectivity modulates the probability of both conditioning and generalization of symptoms to odors is particularly relevant for MCS-patients. They typically show a quite high psychiatric co-morbidity and stressful personal histories, pointing to the presence of high negative affect in those subjects (Bell, Baldwin, & Schwartz, 1998).

Our results further support the plausibility of a Pavlovian conditioning model for MCS: acquired symptoms can generalize to new odors, not having been involved in the acquisition context. Negative affective valence of the odors appeared to be a critical dimension along which both learning and generalization occurred. However clinical cases also report symptoms triggered by positively valent odors like perfumes. Several reasons may account for this discrepancy. For example, we used a weak US between acquisition and test. In real life, toxic exposures or hyperventilation episodes may provide much intenser sensations as USs, which may impact upon the generalization gradient. Also, the delay was chosen rather arbitrarily and, compared to real life situations, was relatively short. It is possible that longer delays and stronger USs will eventually trigger symptoms to stimuli that are qualitatively different from the original CSs. In addition, Davey (1997) argued that cognitive processes may strongly modulate learning and generalization processes. The simple *a priori* conviction held by a person that “we live in a chemically polluted environment, which gradually will compromise everybody’s health”, may potentially turn the evaluation of perfumes into a negatively valent stimulus. Such convictions may eventually help to spread generalization to other kinds of stimuli as well, such as foods. This is also relevant regarding possible treatments of MCS patients. Based on the conditioning account of MCS, for example, system-

atic desensitization (a well documented behavioral treatment technique, relying on extinction and counter-conditioning principles) has been applied to MCS. Positive effects with this technique have been documented in a number of cases (Spyker, 1995; Guglielmi et al., 1994; Stenn & Binkley, 1998). Our results suggest that merely applying such behavioral techniques to the original conditioned stimulus may not be sufficient.

2.4 Experiment 2: Distraction in a non-differential procedure

2.4.1 Introduction

In the previous experiment, a clear conditioning and generalization effect for the symptom scores was found. Based on the account of generalization proposed by Riccio and Ackil (1992) (see section 2.2.3 on page 23), it was hypothesized that the passage of time would enlarge the conditioning effect, but no such effect occurred. The mechanism behind this type of generalization would be the forgetting of stimulus attributes. When a stimulus different from the original CS, is presented at a moment later in time, participants elicit a CR-like response. This response would then be the result of a retrieval failure of the stimulus attributes of the CS (Riccio & Ackil, 1992).

In order to test this idea of retrieval failure, an attempt was made to interfere with the retrieval of the stimulus attributes in the test phase of the odor conditioning paradigm. It has been repeatedly shown that diverting the attention can partially impair memory retrieval (see for example Pashler, 1994; Meudell, Mayes, & MacDonald, 1994). To this effect, half of the participants received a task diverting the attention from the odor tests A Stroop-like task was chosen for this (its effectiveness to divert attention in the odor conditioning paradigm was shown in Stegen et al., 1998). Based on the previous mentioned generalization account of Riccio and Ackil Riccio & Ackil, 1992, it was hypothesized that in the participants receiving the distraction task, generalization would be larger compared to those not receiving the distraction task. In this study, a non-differential variant of the odor conditioning paradigm was used to verify whether the conditioning effects found in previous studies was dependent on the type of design (see experiment 1 discussed in the previous section and Van den Bergh et al., 1999). In the non-differential procedure, conditioning was tested between-subjects rather than within-subjects as in the differential variant. An experimental group of participants received the CS (ammonia) and the US (CO₂-enriched air) paired in one type of trial, while they received regular air in a second type of trial. A control group of participants received the CS in one type of trial, and the US in another type of trial. Condi-

tioning was then defined as a difference in response on the CS between these two groups of participants. Generalization was similarly defined as a difference in response between the experimental and the control group on the generalization odors (butyric acid and citric aroma).

Negative Affectivity was also analyzed in this experiment because of the mediation of the conditioning effect by NA found in the previous experiment (see section 2.2.3 on page 23). Therefore, participants were categorized as either low NA or high NA (see method section below for further details). It was hypothesized that high NA participants would show a larger conditioning effect than low NA participants.

2.4.2 Method

Participants

Forty-eight healthy subjects (31 women and 17 men, aged between 18 and 30 years old) took part in the experiment on a voluntary base. After completing the procedure and debriefing, 500 BEF was paid. All participants were subject to a health check: a questionnaire regarding instances of epilepsy, panic disorder, cardiac and respiratory diseases or any medication that could indicate such illnesses, was administered. 20 participants out of 68 were excluded from participating on these grounds. The study was approved by an ethical committee.

The Negative Emotionality Measure (NEM; Tellegen, 1982) was used to categorize all participants into either low Negative Affectivity (NA) or high NA, based on a median split of the NEM scores. The criterium for the former group was a NEM score of 6 or lower (maximum score is 14), for the latter group a NEM score of 7 and higher. The experimental condition had 4 low NA participants in the non-distraction group and 8 in the distraction group. For the control group this was respectively 8 and 5. The experimental condition had 8 high NA participants in the non-distraction group and 4 in the distraction group. For the control group this was respectively 4 and 7. In total there were 12 low NA and 12 high NA subjects in the experimental group, while the numbers for the control group were 13 and 11 respectively. The same numbers hold true for the distraction and non-distraction groups.

Materials

Odors Ammonia (NH_3) used as the CS in the acquisition phase. It was dissolved in a 0.8% concentration in water (which allowed a below irritancy threshold administration). Butyric acid (100%) and citric aroma (100%) were used as generalization odors in the test phase.

Subjective measures A number of questionnaires was presented to the participants prior to the procedure. As mentioned above, all participants received a health check questionnaire, screening for serious illnesses in the past, asthma, hay fever, bronchitis, hyperventilation, coronary disease, thyroid diseases, respiratory symptoms (such as coughing, wheezing, phlegm, and being out of breath easily) and any medication that could reveal any of these problems. Also, smoking and sport habits were assessed. Female participants were asked to indicate on a time schedule (partitioned in 4 periods of 1 week each) what moment they were at, in their menstrual cycle. A daily complaints questionnaire was administered consisting of 39 complaints to be scored on general occurrence (Wientjes & Grossman, 1994). Following these general questionnaires were two measures for negative and positive affectivity: the Negative and Positive Emotionality Measure (NEM/PEM) and the Positive And Negative Affect Schedule (PANAS) both in a state and trait version (Watson & Pennebaker, 1989).

The final questionnaire was the Anxiety Sensitivity Index (ASI; Peterson & Heilbronner, 1988) and administered as an alternative NA measure. Based upon previous comparisons of these measures, the NEM scores were chosen as measures of NA (Stegen et al., 1998).

After each breathing trial, a list consisting of 16 items which could be associated with the inhalation of CO₂-enriched air and 5 dummy items generally not associated with this type of inhalation, was administered (based on Wientjes & Grossman, 1994). Each item was scored by the participant on a 5 point scale (not at all, not much, average, a lot and very much, coded as 0 to 4). The sum of the 16 items was used as a continuous variable measuring the symptoms experienced by the participants.

Physiological measures and apparatus All odors were administered through vaporization using a Devilbiss Nebulizer 646. The airflow was at a constant rate of 50 l/h. The CO₂-enriched air consisted of 10% CO₂, 21% O₂ and 69% N₂. After decompression, the CO₂-enriched air was led into a meteorological balloon which was connected to a valve allowing easy switching between CO₂-enriched air and regular room air. This valve was connected to a tube system ending in a double one-way valve, separating inspired and expired air. This double one-way valve was connected to a pneumotachograph (Fleish No 2, Switzerland), which fitted on a Rudolph mask. A small vinyl tube from the Nebulizer was attached to the side of the mask, allowing the odor to be mixed with the inspired gas mixture. At the other side of the mask, another small vinyl tube was connected to an infrared CO₂-monitor (Poet II, Criticare, USA) which sampled inspired and expired air (due to equipment failure, CO₂ data were unreliable and will not be discussed further). Airflow waveforms were sampled at a rate of 20 Hz using propriety software and

stored on a PC. Off-line, a software program (Han, 1995) counted and removed pauses and irregularities from the datafile and extracted the following primary parameters per breathing cycle: inspiratory (T_i) and expiratory time (T_e), inspiratory (V_i) and expiratory volume (V_e).

2.4.3 Procedure

Participants were led into the room where the experiment was to be conducted. They received a number of questionnaires presented to them on a computer. After completing these questionnaires, a check was performed for relevant diseases (see materials section). Participants were then presented with a short explanation about the experiment, stating that several gas mixtures would be given to them and that these could elicit harmless symptoms which would quickly disappear after the end of the breathing trial. An informed consent was then presented and signed by the participants (the informed consent stated the possibility to stop the experiment at any time and the voluntariness of their participation).

Next, it was explained that they would receive a number of trials consisting of breathing through the mask for approximately one minute followed by a pause of approximately three minutes. In this pause, they were expected to complete a questionnaire about the trial.

One group (experimental group) then received nine breathing trials of which the first was a context exposure (only air was administered) followed by four trials whereby ammonia and 10% CO₂-enriched air were administered, and four air trials (these eight trials were semi-randomized: no more than two consecutive trials of the same type were allowed). The other group (control group) received an explicitly unpaired treatment: four ammonia and air trials, and four 10% CO₂-enriched air trials (again semi-randomized). After the acquisition phase, a 20 minutes pause followed, which participants spent in a waiting room. The test phase started with a context exposure trial, followed by three odor trials. In half of the subjects an attention distraction task was performed during the administration of the odors. This task consisted of evaluating two rectangles filled with numbers. In about half of the cases the highest number was to be reported, in the other cases the highest amount of numbers in a rectangle was to be reported.

Half of the participants received the CS test (ammonia) first, while the other half started with the generalization odors (butyric acid and citric aroma). All odors were administered without CO₂-enriched air. Participants were subsequently debriefed. They received information about what was presented (innocent odors) and about the inhalation of CO₂-enriched air and how this affected their breathing.

2.4.4 Design and analyses

Analysis on subjective measures were run on total symptom score per trial. The two context exposure trials were analyzed in a 2 (Condition: experimental or control) $\times$ 2 (Distraction: distraction or no distraction) $\times$ 2 (NA: high or low) $\times$ 2 (Trial: one or two) ANOVA. The context data before acquisition and test were used as covariates for, respectively, analysis of the acquisition and test data. The acquisition trials were analyzed using a 2 (Condition: experimental or control) $\times$ 2 (Distraction: distraction or no distraction) $\times$ 2 (NA: high or low) $\times$ 2 (Type of trial: odor or no odor) $\times$ 4 (Trial: one or two or three or four) ANCOVA. Test trials were analyzed using a similar design without the Type of trial and Trial variables. Generalization was analyzed using the same design with an Odor variable (butyric acid or citric aroma) added. Condition, NA, and Distraction were between-subject variables while the other variables were within-subject.

Several parameters were calculated from the raw physiological data: frequency per minute (f), tidal volume (V_T), and minute ventilation ($V_E = V_T \times f$). The analyses on means per trial were essentially the same as for the symptom score analysis, except that Gender (male or female) was included as an extra between subject variable. Due to incomplete design by adding this variable, NA was dropped from the analysis on the physiological data. This option was chosen, because NA, although substantially related to conditioning of symptoms, was unrelated to conditioning of breathing behavior in previous studies (see experiment 1 in section 2.3 on page 24; and Van den Bergh et al., 1999). Greenhouse–Geisser corrections were used when appropriate to control for violations of the compound symmetry ANOVA assumption (McCall & Appelbaum, 1973).

2.4.5 Results

Context exposures

Symptom scores No effects occurred on the symptom scores.

Physiological measures A main effect was found for Trial on breathing frequency, volume and on minute ventilation (respectively $F(1,39)=10.66$, $p < 0.01$, $F(1,39)=4.64$, $p < 0.05$, and $F(1,39)=14.28$, $p < 0.001$). Participants breathed faster but more shallow (lower volume), and showed a larger minute ventilation on the context exposure before test than on the context exposure before acquisition. This effect interacted with the distraction manipulation for breathing frequency, minute ventilation, and volume (respectively $F(1,39)=6.69$, $p < 0.05$; $F(1,39)=7.28$, $p < 0.05$; $F(1,39)=9.09$, $p < 0.01$). The effect of Trial was only found in the participants receiving distraction for breathing frequency and volume (respectively

$F(1,39)=16.87$, $p < 0.01$; $F(1,39)=17.91$, $p < 0.01$). For minute ventilation, the opposite was found, only participants in the non-distraction condition showed a larger minute ventilation on the context exposure before test.

Acquisition

Symptom scores A significant Condition $\times$ Type of trial interaction was found ($F(1,39)=47.02$, $p < 0.00001$) (see figure 2.4 on page 46). In the experimental condition, participants showed more symptoms on odor trials (these were accompanied by CO₂-enriched air) compared to no odors trials ($F(1,39)=32.23$, $p < 0.00001$). The opposite was true for the control condition (in which the no odor trials consisted of CO₂-enriched air inhalation) ($F(1,39)=16.12$, $p < 0.001$).

Figure 2.4: Symptom scores of the experimental and control group in function of function of the trial in acquisition (error bars denote standard error of mean)

Physiological measures A main effect of Gender showed up for volume and minute ventilation (respectively $F(1,38)=20.21$, $p < 0.0001$ and $F(1,38)=7.75$, $p < 0.01$). Males showed a larger volume and minute ventilation than females.

Also, a Condition $\times$ Type of trial interaction occurred for both volume and minute ventilation (respectively $F(1,39)=38.41$, $p < 0.00001$ and $F(1,39)=29.43$, p

Table 2.3: Means of symptoms scores of the experimental and control groups in function of the type of trial and whether or not they received the distraction task

Odor	Experimental group		Control group	
	No distraction	Distraction	No distraction	Distraction
Ammonia	5.29	4.06	5.69	4.4
Butyric acid	7.57	4.88	3.94	5.82
Citric aroma	2.34	1.19	2.25	3.68

< 0.00001). In the experimental condition, participants show a larger minute ventilation in the odor trials (accompanied in this condition with CO₂-enriched air) than on no odor trials ($F(1,39)=16.25$, $p < 0.001$). The opposite pattern appeared in the control condition: here, participants on the no-odor trials showed the largest minute ventilation ($F(1,39)=13.58$, $p < 0.001$).

Test conditioning

Symptom scores No conditioning effects appeared on symptom scores (see table 2.3 on page 47). Also, no effects of NA showed up.

Physiological measures A main effect of Distraction showed up for volume ($F(1,38)=4.12$; $p < 0.05$). Participants receiving distraction had a smaller volume compared to participants not receiving the distraction task. No effects occurred for frequency or minute ventilation.

Test generalization

Symptom scores A generalization odor main effect was found ($F(1,38)=12.31$, $p < 0.01$). Participants reported more symptoms on butyric acid compared to citric aroma. Also a Condition $\times$ NA $\times$ Generalization odor interaction appeared ($F(1,38)=7.07$, $p < 0.05$) (see figure 2.5 on page 48). Only high NA participants in the experimental group showed more symptoms to butyric acid compared to citric aroma ($F(1,38)=20.75$, $p < 0.01$). Contrast tests revealed no difference between the experimental and the control group on butyric acid for high NA participants. No further NA effects appeared.

Physiological measures No effects appeared for breathing frequency. An interaction between Condition and Generalization odor occurred for volume ($F(1,39)=13.99$, $p < 0.001$) and minute ventilation ($F(1,39)=4.57$, $p < 0.05$). Participants in the control group breathed deeper in response to butyric acid compared to citric aroma

Figure 2.5: Symptom scores of the experimental and control group in function of function of the trial in acquisition (error bars denote standard error of mean)

($F(1,39)=10.23$, $p < 0.05$). This was not so for minute ventilation. In the experimental group participants tended to do the opposite for volume ($F(1,39)=4.08$, $p=0.05$) but not for minute ventilation.

2.4.6 Discussion

The results of the context exposure analysis for the respiratory measures are the opposite of what is regularly found in the differential odor conditioning paradigm (Van den Bergh et al., 1997, 1998). Normally, participants respond less to the context exposure trial before test compared to the one before acquisition. It was hypothesized that in that case, participants were habituated to the experimental setup in the context exposure before the test phase, while the context exposure before acquisition represented a novel situation eliciting a larger response (see for example Bouton et al., 1999). In this experiment however, the distraction task was introduced in the context exposure trial for half of the participants. Hence, this task could render the context exposure before test a novel situation and subsequently elicit a larger response than the context exposure before acquisition. This is partially corroborated by the result that for breathing frequency and volume, the trial effect only appears in participants receiving the distraction task. For minute

ventilation however, the opposite was true. It is at present not clear how the latter can be accounted for.

In this non-differential variant of the odor conditioning paradigm, we find a clear effect of the CO₂-enriched air inhalation in acquisition. Due to the use of a different procedure compared to the standard differential odor conditioning paradigm, this shows up as an interaction between the type of trial and the condition participants were in. Participants clearly reported more symptoms in CO₂-enriched air trials than in room air trials whether an odor was administered or not. Also, in the former trials, minute ventilation and volume increased. This suggests that our US manipulation was successful, both in the experimental and the control group.

However, no conditioning effects were found. There was no difference between the experimental group and the control group, neither for the symptom scores, nor for the respiratory measures. These results are consistent with two other studies conducted at our laboratory with the non-differential variant of the odor conditioning paradigm (Winters et al., 2001). A possible explanation offered for the absence of a conditioning effect in the latter, was that in the differential procedure, the use of two odors (especially with an opposite affective valence) cues the participants more sharply to what features of the odor are critical in predicting the US. However, because this explanation is yet under investigation in our laboratory, it has to be concluded that at present no clear explanation for the difference in results between the differential and non-differential variants of our odor conditioning paradigm exists.

An effect of the distraction manipulation showed up for volume in the test phase: participants receiving the distraction task breathed more shallow compared to those not receiving the distraction manipulation. A similar main effect of distraction on the volume parameter was found in a previous study using the same task (Van den Bergh et al., 1998). A possible explanation could be that participants “held their breath” because of the concentration required for the distraction task. Similar decreases of volume have been reported during reaction time tasks requiring a certain amount of concentration (see for example Boiten, 1998) and in preparation.

Regarding the generalization odors, butyric acid elicited more symptoms than citric aroma. This effect only appeared in high NA participants in the experimental group, who responded particularly high to butyric acid. A possible explanation for this high mean might be an outlying participant. Indeed, one participant in that group had a symptom score 2.83 times the standard deviation of that group. According to Kirk (1995, p. 169) this is sufficient to be qualified as an outlier. However, this does not warrant an exclusion of this participant solely based on being an outlier, but it does offer an explanation as to why the mean of the high NA

group in the experimental condition is so high. Although the data at first glance suggest that there is a difference between the experimental and the control group on butyric acid in high NA participants implying a generalization effect (see figure 2.5 on page 48), this difference was not significant. In part, this difference can be accounted for by the outlying participant mentioned earlier.

To summarize, although a distinct effect was observed of the US-manipulation in the acquisition phase, no conditioning effect was found in this experiment. As was argued, probably this is due to a difference between the differential and non-differential variants of the odor conditioning paradigm, a difference yet to be further investigated. As a consequence generalization could not be assessed and further research is necessary to clarify the possibility of “the forgetting of stimulus attributes” account in the odor conditioning paradigm.

2.5 Conclusions

In this chapter, two studies were conducted in order to assess generalization in the odor paradigm. From the generalization account of Riccio and co-workers (Riccio & Ackil, 1992), the idea of time as another variable among which generalization could occur, was investigated in a first study. This study clearly showed the possibility of generalization in the odor conditioning paradigm, although it was found only along the affective valence dimension. The passage of time did not enlarge the generalization effect.

A second study then tested the “forgetting of stimulus attributes” account in a non-differential variant of the odor conditioning paradigm by partially disrupting the retrieval process in the test phase. Unfortunately, no conditioning effects were found and generalization could not be assessed. Similar results with this non-differential procedure suggest that the non-differential variant of the odor conditioning paradigm is not the most suited procedure to investigate generalization (Winters et al., 2001).

Although at present it is not entirely clear what underlies the generalization effect found in the first study, these results clearly show the possibility of generalization in a learning model of MCS. The delay did not modulate the generalization effect and together with the results of the second study, further research is required to fully investigate the “forgetting of stimulus attributions” account of generalization in the odor conditioning paradigm.

Parallel with these generalization studies, two studies on a second post-conditioning phenomenon, US-revaluation, were conducted and will be discussed in next chapter.

Chapter 3

Post-conditioning phenomenon 2: US-revaluation

3.1 Introduction

In the previous chapter, the phenomenon of spreading of symptoms to other chemical substances and the plausibility of generalization as its mechanism was discussed. In this chapter another clinical observation will be attended to. It has been noted that there often is a large interval between the time of onset and the moment MCS patients seek medical assistance. Also, MCS develops progressively towards disability (Ziem & McTamney, 1997). The symptoms of MCS patients seem to aggravate after a period of time. Often, MCS patients do not seek treatment until after they have received or searched for information regarding the possibility of a serious illness (see for example Dalton & Hummel, 2000, section 1.2.2 on page 3). One can assume that some or even most of these events happen once the initial relationship between the odor and the symptoms is established. In other words, after the acquisition of symptoms is complete, a number of events determine the responses of MCS patients to the chemical substances that trigger these responses.

In conditioning literature, a contemporary model has been proposed that enumerates a number of processes influencing the responses to CSs (Davey, 1997, see figure 3.1 on page 52). Although this model was originally formulated for phobias, it is also applicable to MCS. The model Davey formulates basically incorporates three issues. First, it has been established in classical conditioning that associations between the CS and the US are learned and that these associations mediate the CR. Second, many factors besides CS-US pairings influence the associative strength of the CS-US association. For example, any factor (like verbally transmitted information) influencing the CS-US contingency can affect the associative strength of the CS-US association. Third, and most relevant to this doctoral thesis, is that,

according to the author, the associative strength of the CS–US association is not the only determinant of the strength of a CR. Here, Davey’s model states that, before a CR is elicited, the US is evaluated. An important implication of this is that any factor changing the US representation, irrespective of the factor’s influence on the CS–US association, will influence the strength of the CR. One of these possible factors influencing the US-representation is socially or verbally transmitted information about the US and is particularly relevant for MCS.

Figure 3.1: A conditioning model by Davey (1997)

In this chapter, the feasibility of US-revaluation as a mechanism in MCS pathology will be considered. The next section provides an overview of the literature of US-revaluation in classical conditioning. The remaining of the chapter will be devoted to two experimental studies investigating US-inflation in our differential odor conditioning paradigm.

3.2 Evidence for US-revaluation

In this section, an overview of the literature on US-inflation will be given. Due to the large amount of research in the field of conditioning, this review is unfortunately not comprehensive. In a first subsection I will review some studies with animals, while in a second subsection an overview will be presented of some studies in a human population. A third subsection will provide some conclusions on the literature depicted in this section.

3.2.1 US-inflation in studies with animals

One of the earlier demonstrations of US-inflation originates from Rescorla (1974). Using a suppression paradigm¹ in rats, conditioning of a tone to an electrical stimulus was established. Next, preceded by a light, the electrical stimulus was administered in different magnitudes (varying from none to several orders stronger than the original stimulus). Rats receiving this US between the acquisition and test showed a larger CR compared to rats not receiving this manipulation. Also, the CR became larger with the magnitude of the US. It was hypothesized by the author that the observed effect was caused by a change of the US-representation. A replication study using higher order conditioning did not reveal a similar US-inflation effect.

A similar suppression paradigm was used to investigate US-inflation in both a sequential and a simultaneous conditioning procedure² (Sherman, 1978). Unlike the previously mentioned study a tone-light compound stimulus was used as CS. Also, the US administrations in between acquisition and test were not signaled by a light. US-revaluation was demonstrated in a first study using a forward sequential conditioning procedure. A second study using the simultaneous conditioning procedure suggested an influence of US alone presentations on the subsequently tested suppression. The author follows the reasoning of Rescorla (1974) concerning the change of the US-representation as the mechanism behind US-revaluation.

An alternative explanation was tested in a suppression paradigm (Bouton, 1984). The author notes that in US-reinstatement procedures, context plays an important role. US-revaluation could then be an indirect result of a CS-context summation

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¹In a suppression paradigm, the first step consists of the learning of a stable operant behavior (for example level pressing to obtain food). In a second step, a classical conditioning procedure is administered (for example a light followed by an electrical stimulus). In a final step, the first step is repeated while the CS conditioned in the second step is presented. The dependent variable in this paradigm is then the amount of suppression of the operant behavior caused by the administration of the CS conditioned in the second step.

²In a simultaneous conditioning procedure, the onset of CS and US coincide (as opposed to a sequential procedure where the onset of the US follows the onset of the CS).

effect. The author hypothesizes that, when following the acquisition phase, the US is presented alone, the participants also learn to fear the context in which this US is administered. When subsequently the CS is presented in this same context, this context fear could augment the CR, constituting the US-revaluation. In a first experiment testing this hypothesis, three groups of participants were used. A first group (no US group) functioned as a control group and received no US between acquisition and test. A second group (US same context group) received the US alone in the same context as acquisition and test, while a third group (US different context group) received the US-revaluation stimulus in a context different from acquisition and test. Besides the suppression ratio, a measure of context fear was administered. Concerning the latter, the US same context group showed a larger fear for the test context compared to the US different context group. Despite this difference, no larger US-revaluation effect was found in the US same context group than in the US different context group. Both groups did differ from the control group regarding the suppression ratio, suggesting a US-revaluation effect.

A second experiment to test the context summation hypothesis was conducted (Bouton, 1984). A similar design as the previous study was used, with the added manipulation of extinction of the context fear through a period following the US alone presentations in which no US was administered. The context fear measures indeed showed extinction. If a summation effect constituted the US-revaluation effect, then US-revaluation should be found only in groups with a context fear and not in groups with an extinguished context fear. In both the extinction and non-extinction group, an equally large US-revaluation effect was found, compared to no effect in the control group. The author concludes that the context summation hypothesis does not seem to hold for US-revaluation.

3.2.2 US-revaluation in studies with humans

The previous studies were all conducted on animals. There are some studies of US-revaluation in humans which will be reported in this section. One of the first studies was conducted by White and Davey (1989) a differential conditioning paradigm with skin conductance as the dependent variable. Neutral visual stimuli were used as CSs in the acquisition phase. The CS+ was followed by a non-aversive tone. Participants showed no difference between the CS+ and the CS- on skin conductance after this acquisition phase. Thereupon, an inflation manipulation was administered: a number of unannounced tones of increasing intensity were presented until an aversive volume was reached. A control group received the same number of tones but always with the same intensity. Next a test and extinction phase consisted of CS+ and CS- administrations (without the tones) to assess conditioning and US-inflation effects. Conditioning was found only in the groups receiving in-

creasing tone intensities and not in the control group. The authors concluded that participants, prior to the conditioned response, evoke a representation of the US. A US manipulation has changed this representation formed in the acquisition phase, and will consequently influence the magnitude of the CR. A replication study unfortunately could not reproduce this effect: no difference was found on skin conductance between the group receiving the US-inflation and the control group (de Jong, Muris, & Merckelbach, 1996).

US-inflation has also been considered within the field of evaluative conditioning (Baeyens, Eelen, Van den Bergh, & Crombez, 1992). In this study, a picture-picture paradigm is used. In acquisition, three types of stimulus pairs are administered based on previously conducted ratings of affective valence: neutral-neutral, positive-neutral, and negative-neutral. The positive and negative pictures are used as USs. Following the acquisition phase, one of the groups in this experiment received information about the personality of the persons on the pictures used as USs. When this information was incongruent with the affective valence previously given by the participants (for example, negative information on a formerly positively rated picture), they revalued the US correspondingly. This US-revaluation effect showed up for positive as well as for negative information.

A series of US-revaluation studies have been conducted using a remarkable differential conditioning paradigm (de Jong, Merckelbach, Koertshuis, & Muris, 1994). In a first study, US-inflation was investigated using physiological measures as well as a US expectancy measure (whereby participants indicated to what extent they expected the occurrence of the US). The acquisition phase consisted of six CS+ trials (a neutral visual stimulus paired with a mild electrical stimulus) and six CS- trials (a different visual stimulus). The US-inflation manipulation was the administration of four unannounced electrical stimuli with increasing intensity in half of the participants. A control group received four mild electrical stimuli of equal intensity. A test phase followed, existing of six CS- and six CS+ stimuli presented without the US. A US-inflation effect on skin conductance was found for the first trials administered in the test phase: conditioning was found largely in the participants receiving the US-inflation manipulation. No difference was found on the US expectancy measure between the US-inflation group and the control group (although the expectancy measure dropped faster in the latter group).

In an attempt to use a more ecologically valid procedure to investigate a model of phobias, only one US was presented in the US-inflation phase instead of several presentations. Also, phobic relevant visual stimuli were used as CSs as opposed to neutral stimuli in the previous study. At the end of the experiment, a visual-analogue scale was administered to measure the affective valence of CS+ and CS-. No US-inflation effects were found on the skin conductance measure, or on the affective valence measures. de Jong and coworkers concluded that the intensity of the

US probably was insufficient to result in a measurable change in the conditioning effect (de Jong et al., 1994).

A third study altered the paradigm in several ways. Erotic pictures were used as CSs, while the US became “to blush”. In the acquisition phase, CS+ pictures were consistently followed by a tone. The participants in the inflation group received, after the acquisition phase, a written text explaining that the tone measured “blushing” through an electrode attached to the participant. A control group received a similar text with the exception that the relationship between the tone and the electrode was not revealed. Following this phase, a test phase similar to the previous studies followed and, at the end, the tone was once more presented. Participants received some questionnaires regarding the significance of “blushing” to them and the affective valence of CS+ and CS-. Finally a contingency awareness measure was conducted. No US-inflation effects were found. But when the last two trials of the acquisition phase were compared to the first two of the test phase, a difference was found between CS+ and CS- on skin conductance but only in the US-inflation group. Also, a stronger skin conductance response was found on the final tone presentation relative to the first for the US-inflation group compared to the control group. No US-inflation effects appeared on the affective valence measures. Almost all participants were aware of the CS+ and tone contingency.

A fourth study replicated the third but used observers that were present during the experiment in order to augment the negativity of the “blushing” US (it was assumed that blushing in public is a more negative experience). The results were identical to the previous study, bringing the authors to conclude that US-inflation can be found in human participants under certain procedural conditions.

3.2.3 Conclusions

This small review has shown that US-inflation can be found both in humans and animals, albeit with varying success dependent on the paradigm and the measures used. One can also say that most authors conclude that the mechanism behind US-inflation is a revaluation of the US-representation and that alternative explanations such as investigated by Bouton (1994) have been refuted.

3.3 Experiment 3: Conditioning in an enhanced procedure

3.3.1 Introduction

One assumption that can be drawn from the literature review presented in the previous section, is that, in order to obtain a US-inflation effect, a CS-US associa-

tion must be learned. This assumption can be deducted from the fact that most authors agree on a change of the US-representation as the mechanism behind US-revaluation. Also, this assumption is consistent with the conditioning model by Davey presented earlier (see the introduction of this chapter; Davey, 1997). It is consequently hypothesized that a conditioning effect would suggest the learning of an association between the CS+ and the US.

The aim of this study was then to adapt the standard procedure in order to maximize the possibility of establishing a conditioning effect. To this effect, several changes were made to the procedure compared to the standard paradigm (see section 1.3.2 of the first chapter on page 14). First of all, butyric acid and niaouli were used as the CSs. Butyric acid has produced a conditioning effect on symptoms when paired with CO₂-enriched air in a previous study (Van den Bergh et al., 1999). Niaouli has proven to be consistent in failing to condition on symptoms when administered with CO₂-enriched air (experiment 1, see section 2.3 in the second chapter of this doctoral thesis on page 24; Van den Bergh et al., 2001). This configuration was chosen in order to be relatively certain of conditioning to butyric acid and not to niaouli on symptom scores. Possible generalization to ammonia and citric aroma could then be assessed, replicating the generalization effect found in experiment 1 (see section 2.3 in the second chapter of this doctoral thesis on page 24).

Second, bearing in mind the influence of contingency awareness as will be discussed in greater detail in the next chapter, two measures were taken to enhance contingency awareness. Prior to the acquisition phase, participants were informed that two air mixtures would be used and that one of them would be accompanied by the symptoms described in the informed consent previously administered. After the acquisition phase, contingency awareness was assessed as in the previous studies. Upon answering the question what odor caused the most symptoms in the acquisition phase, participants were informed whether their choice was correct and the actually used odor was pointed out to them if they were wrong. The effectiveness of such a procedure was inferred from the results of a study conducted by Grings and coworkers (Grings, Schell, & Carey, 1973). In this study, after a differential conditioning procedure with two CSs, participants were informed that the initial relationship between the CS+ and the US was no longer valid and that, as of then, the CS- predicted the occurrence of the US (in this case an electrical stimulus). No learning trials with this new contingency were conducted, but instead a series of extinction trials followed this information manipulation. The results showed that participants responded in the first extinction trials according to the contingency information they had received rather than to the contingency they had experienced.

Third, an expectancy measure was administered shortly after the beginning of

each trial. Participants indicated to what extent they expected symptoms to occur. This measure was partially used as an alternative and more concurrent measure of contingency awareness (Marinkovic, Schell, & Dawson, 1989; see also section 4.2 of the next chapter on page 74). It also is an alternative way of appreciating the association formed between the CS+ and the US.

Fourth, all participants received three texts between acquisition and test (see Appendix A). The first text described MCS as a syndrome and provided a description of the symptom pattern and the problems faced by MCS patients. The second text presented a case study. The last text stated the aim of the study and gave negative information on the air mixtures presented in the acquisition phase. These texts will be used in a subsequent experiment (see section 3.4 on page 63) to assess a possible US-inflation effect, but were included in this experiment to maximize the possibility to find a conditioning effect.

3.3.2 Method

Participants

Thirty-three volunteers took part in this experiment. Of these, twenty-two continued the experiment upon reporting no health complaints on a health checklist (see below). Participants received course credits in return.

Odors

Butyric acid (undiluted) and niaouli were used as CSs. Ammonia (NH₃, 0.8% diluted in water) and citric aroma were used as generalization odors.

Measures

Several questionnaires were administered prior to the experimental procedure. First, a health checklist was presented assessing a number of health problems: asthma, hay fever, bronchitis, hyperventilation symptoms, heart diseases, thyroid gland related problems, any other major diseases. The checklist also asked about some common symptoms associated with any of these diseases and about use of medication indicative of the latter. Finally smoking and sports habits were inquired upon. Second, female participants received a questionnaire about their menstrual cycle. Third, all participants received a list with general health symptoms (39 items based on Wientjes and Grossman (1994). Fourth, the Positive and Negative Affectivity Schedule was administered as a measure of Negative Affectivity (Watson & Pennebaker, 1989). Fifth and final questionnaire was the Anxiety Sensitivity Index (ASI; Peterson & Heilbronner, 1988).

After each trial, a symptom list consisting of sixteen items usually associated with the inhalation of CO₂-enriched air and five items (dummy items) usually not associable to CO₂-enriched air inhalation was administered. Participants' symptom level was rated from 0 to 4 (not at all, not much, average, a lot, very much). The sum of the sixteen non-dummy items was used as the dependent variable.

On each trial, an expectancy measure was administered. Ten seconds after the beginning of each trial, participants were asked to answer the question to what amount they expected symptoms to occur on a Likert-scale ranging from 0 ("not at all") to 100 ("very much"). This question was produced on a computer screen in front of the participants and they were instructed to continue breathing through the mask (see below) while answering this question.

The contingency awareness was assessed by presenting participants with small containers holding the odors. Upon sniffing at the odors, participants had to indicate what odor was accompanied by symptoms in the preceding acquisition phase. Afterwards, participants were informed whether their choice was correct and what had been the odor associated with the most symptoms.

3.3.3 Procedure

Participants started with filling out a number of questionnaires (see subjective measures above). After they were cleared for health problems, an informed consent was presented. This included the following information about the experiment. They would receive several substances of which some could temporarily provoke a number of somatic complaints. The experiment was approved by the ethical committee of the faculty. Thereupon, they were asked to sign a statement in which they acknowledged to participate voluntarily in this experiment. It was clearly stated that they could halt and exit the experiment at any time. Next, participants received information on the course of the experiment. Also, instructions were given on how to handle the nasal cannula and the breathing mask. Upon receiving instructions on the handling of the mask, they were informed that two air mixtures would be administered of which one would be followed by the symptoms described in the informed consent.

Next, the acquisition phase was conducted. Participants received an air trial as a baseline measure. The following six trials consisted of three CS+ trials (butyric acid and CO₂-enriched air for half of the participants, niaouli and CO₂-enriched air for the other half) and three CS- trials (niaouli and air for half of the participants, butyric acid and air for the other half). All combinations of trial-orders were used with the restriction that no more than two consecutive trials could be of the same type.

At the end of the acquisition phase, participants were asked to identify what

odor was paired with the most symptoms upon presenting these odors in small containers, in order to assess contingency awareness. Participants had thereupon a pause of fifteen minutes in which they were instructed to carefully read the three texts used as the US-inflation manipulation in a subsequent experiment (see experiment 4 section 3.4 on page 63).

The test phase started with an air trial as a baseline measure. Next, the CS+ odor and the CS- odor were administered with air. In half of the participants, the CS+ odor was presented first, while the other half received the CS- odor first. The final two trials consisted of the presentation of the generalization odors ammonia and citric aroma (reverse order of presentation in half of the participants).

Next to the regular respiratory measures on each trial and the symptom list at the end of each trial, the expectancy measure was administered 10 seconds after the beginning of each trial.

3.3.4 Design and analyses

The context exposure trials prior to acquisition and test were analyzed in a 2 (CS+ Odor: butyric acid or niaouli) $\times$ 2 (Context exposure trial: before acquisition or before test) ANOVA for both symptom scores and the expectancy measure.

The acquisition phase for both symptom scores and expectancy measure was analyzed in a 2 (CS+ Odor: butyric acid or niaouli) $\times$ 2 (Conditioning: CS+ or CS-) $\times$ 3 (Trial: 1 or 2 or 3) ANCOVA with the context exposure before acquisition as the covariate.

The test phase was analyzed in a 2 (CS+ Odor: butyric acid or niaouli) $\times$ 2 (Conditioning: CS+ or CS-) ANCOVA with the context exposure prior to the test phase as the covariate for both the symptoms scores and the expectancy measure.

The generalization effect was assessed in a 2 (CS+ Odor: butyric acid or niaouli) $\times$ 2 (Generalization odor: ammonia or citric aroma) ANCOVA with the context exposure prior to the test phase as the covariate. Both symptom scores and expectancy measures were analyzed in this way.

The CS+ odor variable was a between-subjects variable, while Conditioning and Trial were within-subjects variables.

3.3.5 Results

Context exposures

No effects appeared for the symptom scores. On the expectancy measure, an effect of Context Exposure Trial appeared ($F(1,20)=5.832179$, $p < 0.05$). Participants expected that more symptoms would occur on the context exposure trial prior to test compared to the one before the acquisition phase.

The acquisition phase

Participants reported more symptoms to the CS+ trials compared to the CS- trials ($F(1,20)=29.62$, $p < 0.0001$). This was also reflected in the expectancy measure: participants expected more symptoms to occur in the CS+ trials than in the CS- trials ($F(1,20)=9.51$, $p < 0.01$). Also, participants gradually expected more symptoms over trials ($F(2,40)=3.37$, $p < 0.05$). Post-hoc comparisons (Tukey honest significant difference test) revealed that participants expected more symptoms on the third trial than on the first trial. This pattern over trials differed for butyric acid and niaouli $F(2,40)=4.05$, $p < 0.05$) (see figure 3.2 on page 61).

Figure 3.2: Expectancy of symptoms in trial 1, 2, and 3 in function of the CS+ odor (Bu = butyric acid, Ni = niaouli (error bars denote standard error of mean)

The test phase

No effect on symptom scores appeared in the test phase. An effect of Conditioning was found on the expectancy measure $F(1,20)=7.94$, $p < 0.05$). Participants expected more symptoms on the CS+ odor test compared to the CS- odor test. Planned comparisons revealed that this was only so for participants receiving butyric acid as the CS+ odor ($F(1,20)=10.13$, $p < 0.01$) and not for those receiving niaouli as the CS+ odor (see figure 3.3 on page 62).

Figure 3.3: Expectancy of symptoms for butyric acid (Bu) and niaouli (Ni) in function of CS+ odor and CS- odor test (error bars denote standard error of mean)

Generalization An effect of generalization odors occurred on the symptoms scores $F(1,20)=4.51$, $p < 0.05$). More symptoms were reported to ammonia compared to citric aroma. No effects appeared on the expectancy measure.

Contingency awareness Fourteen out of twenty-two participants (63%) identified the correct odor in the contingency measure administered at the end of the acquisition phase. No difference was found between the ratio of correct and incorrect answers in participants receiving butyric acid as the CS+ odor compared to participants receiving niaouli (Mann–Whitney U test).

3.3.6 Discussion

Despite a clear effect of the US on symptoms in the acquisition phase, no conditioning effect appeared in the test phase on symptom scores. Participants did not report more symptoms to the CS+ odor test compared to the CS- odor test. These results suggest that the adaptations to the procedure did not yield the intended effects on conditioning.

On the expectancy measure, just as on the symptom scores, a clear influence of the US in the acquisition phase was demonstrated. However, contrary to the symptoms scores, a conditioning effect appeared on the expectancy measure in the

test phase. Participants expected more symptoms to occur when confronted with the CS+ compared to the CS-. The results further revealed that this was only so for butyric acid as the CS+ odor and not for niaouli.

Although the absence of a conditioning effect on symptom scores does not allow to conclude that the association between the CS+ and the US was learned, the results on the expectancy measure do. Therefore, the next study was conducted in order to assess a potential US-inflation effect.

3.4 Experiment 4: US-inflation through information

3.4.1 Introduction

In the review provided on the psychological models of MCS (see section 1.2.2 on page 3), both the attribution scenario suggested by Gupta and coworkers (Gupta et al., 1997) as well as the findings on cognitive processes presented by Dalton and Hummel (2000) are interesting.

In the case of Gupta's attribution model, it is suggested that upon experiencing complaints following a toxic exposure of some kind, health concerns develop in MCS patients. Often these concerns are not acknowledged by physicians or by the companies involved in the toxic exposure. Sooner or later these patients will encounter information confirming their suspicions about the malignant consequences of the toxic exposure. At this point it is often seen that the complaints of MCS patients aggravate and the search for recognition becomes more ardent. One could argue that in this case, the information contending the malignant effects of the toxic exposure revalues this toxic exposure as more harmful and with more consequences than previously assumed. Given the assumption of the conditioning model of MCS that the toxic exposure is the US, this scenario could be interpreted as a type of US-inflation.

The findings of Dalton and coworkers support the notion that information about stimuli can alter the way these stimuli are looked at. As discussed earlier, (see section 1.2.2 on page 3) they found that providing negative information about previously administered odors changed the way these odors were perceived (Dalton & Hummel, 2000). These results corroborate the possibility of information changing the way stimuli are regarded (see also the US-inflation studies by Baeyens et al., 1992, discussed in section 3.2.2 on page 54).

In view of these considerations, the study reported below was conducted to investigate the possibility of US-inflation as a possible mechanism for the aggravation of the symptom pattern of MCS patients as mentioned above. In this study, an information manipulation was used as a US-inflation. This information consisted of three texts (see the previous experiment, section 3.3.1 on page 56, and

Appendix A).

A standard differential odor conditioning procedure (see section 1.3.2 on page 14) was used. Half of the participants received the US-inflation information in the pause between the acquisition phase and the test phase, while the other half received no information. Ammonia and butyric acid were used as CSs. Based on a previous study conducted with the same CSs (Van den Bergh et al., 1999, and the previous experiment reported in 3.3 on page 56) conditioning is predicted irrespective of the CS+ odor. Regarding the US-inflation manipulation, it is hypothesized that the participants receiving this manipulation will show a larger difference between CS+ odor test and CS- odor test compared to participants not receiving the manipulation.

Aside from these manipulations, two odors were added after the CS+ odor and the CS- odor were tested with air in the test phase. Citric aroma and acetic acid were used to assess generalization in all participants. Also, participants were selected on NA. They were classified as either high or low on NA (see method section) prior to the start of the experiment. Previous studies have showed the mediation of the conditioning effects by NA (see for example experiment 1 reported in the second chapter). Therefore, this variable was included in the analysis in order to have an equal number of low and high NA participants, and as such assess modulation of the effects by NA.

3.4.2 Method

Participants

Seventy-seven healthy volunteers participated in this study. Fifty-six reported no health problems on a short health checklist (see subjective measures below) and completed the experiment, for which they received a fee of 500 BEF (approximately \$13, £9).

Odors

Ammonia and butyric acid were used as CSs in this experiment. Ammonia (NH_3) was administered in a diluted solution (0.8% in water), while butyric acid was administered undiluted. Acetic acid (5% diluted in water) and citric aroma were used as generalization odors (see procedure below).

Subjective measures

A health questionnaire was used to assess any health problems participants could have (see the previous experiment section 3.3.2 on page 58 for a more detailed account of this list). Female participants were asked in what week of their menstrual

cycle they were at the time of the experiment. Next, a list with 39 items concerning general health symptoms was administered (based on Wientjes & Grossman, 1994). The Positive and Negative Affectivity Schedule was administered as a measure of Negative Affectivity (Watson & Pennebaker, 1989). A median split on data acquired through various experiments in our laboratory of this measure ($N=929$), was used to determine whether participants were low or high NA. A PANAS score lower than 24 was considered low NA, while a PANAS score of 24 or more was considered high NA. A final questionnaire was the Anxiety Sensitivity Index (ASI; Peterson & Heilbronner, 1988).

After each trial, a symptom list consisting of sixteen items usually associated with the inhalation of CO_2 -enriched air and five items (dummy items) usually not associable to CO_2 -enriched air inhalation was administered. Participants' symptom level was rated from 0 to 4 (not at all, not much, average, a lot, very much). The sum of the sixteen non-dummy items was used as the dependent variable.

Physiological measures

All odors were administered through vaporization using a Devilbiss Nebulizer 646. The airflow was at a constant rate of 50 l/h for butyric acid, but the double of this rate for ammonia³. The CO_2 -enriched air consisted of 10% CO_2 , 21% O_2 and 69% N_2 . After decompression, the CO_2 -enriched air was led into a meteorological balloon which was connected to a valve allowing easy switching between CO_2 -enriched air and regular room air. This valve was connected to a tube system ending in a double one-way valve, separating inspired and expired air. This double one-way valve was connected to a pneumotachograph (Fleish No 2, Switzerland), which fitted on a Rudolph mask. A small vinyl tube from the Nebulizer was attached to the side of the mask, allowing the odor to be mixed with the inspired gas mixture. Participants wore a nasal cannula connected to an infrared CO_2 -monitor (Poet II, Criticare, USA) which sampled inspired and expired air. Airflow waveforms were sampled at a rate of 20 Hz using propriety software and stored on a PC. Due to a problem with the recording software, full physiological data was available for only a limited number of participants. The amount of available physiological data was considered insufficient for further analyses.

3.4.3 Procedure

The procedure was almost identical to the one described in experiment 3 (see section 3.3.3 on page 59). Therefore, a less detailed account of the procedure will be

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³The rate at which ammonia was nebulized was doubled in order to create an equally intense sensation as the other odors and was determined in a small pilot study.

presented in this section.

After completing the preceding questionnaires and complying to the informed consent, participants received information on the course of the experiment. Thereupon, they received instructions on the handling of the mask and nasal cannula.

Next an acquisition phase as in experiment 3 was run (see section 3.3.3 on page 59) with ammonia and butyric acid as the CSs. A pause of fifteen minutes, in which the adapted texts comprising the US-inflation manipulation (see Appendix A) were presented, followed the acquisition phase.

The test phase was conducted analogous to experiment 3 (see section 3.3.3 on page 59) with acetic acid and citric aroma as the generalization odors.

3.4.4 Design and analyses

The baseline trials prior to acquisition and test were analyzed in a 2 (CS+ odor: ammonia or butyric acid) $\times$ 2 (Information: yes or no) $\times$ 2 (NA: low or high) $\times$ 2 (Context exposure trial: 1 or 2) ANOVA.

The acquisition phase was analyzed in a 2 (CS+ odor: ammonia or butyric acid) $\times$ 2 (Information: yes or no) $\times$ 2 (NA: low or high) $\times$ 2 (Conditioning: CS+ or CS-) $\times$ 2 (Trial: 1 or 2 or 3) ANCOVA with the preceding air trial as the covariate.

The test phase was analyzed in a 2 (CS+ odor: ammonia or butyric acid) $\times$ 2 (Information: yes or no) $\times$ 2 (NA: low or high) $\times$ 2 (Conditioning: CS+ or CS-) ANCOVA with the preceding air trial as the covariate. Generalization was analyzed in a 2 (CS+ odor: ammonia or butyric acid) $\times$ 2 (Information: yes or no) $\times$ 2 (NA: low or high) $\times$ 2 (Generalization odors: acetic acid or citric aroma) ANCOVA with the air trial preceding the test phase as the covariate.

Of these variables, CS+ odor, Information, and NA were between subjects variables, while Conditioning, Trial, and Generalization odors were within subjects variables.

3.4.5 Results

Context exposures

A main effect for CS+ odor appeared ($F(1,43)=4.28$, $p < 0.05$). Participants receiving ammonia as the CS+ odor reported more symptoms on the context exposure trials than those receiving butyric acid.

The acquisition phase

A main effect for Conditioning showed up ($F(1,43)=46.98$, $p < 0.0001$). Participants reported significantly more symptoms to the CS+ than to the CS-. This

difference interacted with the information manipulation subsequently presented to participants ($F(1,43)=6.98$, $p < 0.05$) (see figure 3.4 on page 67). Contrasts⁴ were tested to assess whether there was a difference regarding the response to the CS+ odor between participants who would receive information and those not, but no such difference occurred.

Figure 3.4: Symptom scores in the information and no information groups in function of CS+/CS- (error bars denote standard error of mean)

The test phase

A main effect for CS+ odor was found in the test phase ($F(1,41)=6.22$, $p < 0.05$). More symptoms were reported to ammonia than to butyric acid. This effect interacted with conditioning ($F(1,42)=13.12$, $p < 0.001$). Only when ammonia was CS+ odor, a difference was found between CS+ odor test and CS- odor test ($F(1,42)=15.75$, $p < 0.001$) (see figure 3.5 on page 68). This effect was, however, the opposite of what was expected: more symptoms were reported to the CS- odor test than to the CS+ odor test. No effects of Information appeared.

⁴Perhaps post-hoc comparisons would have been more appropriate. Unfortunately, no consensus exists on what error term to use in post-hoc comparisons in an interaction with between-subjects and within-subjects variables (Winer, Brown, & Michels, 1991).

Figure 3.5: Symptom scores of CS+ odor in function of conditioning (Am = ammonia, Bu = butyric acid; error bars denote standard error of mean)

Generalization odors

A main effect for Generalization odors occurred ($F(1,42)=5.89$, $p < 0.05$). Participants reported more symptoms to acetic acid compared to citric aroma.

Contingency awareness

Overall, 27 out of 53 (51%) participants incorrectly identified the CS- odor as the odor associated with the most symptoms in the acquisition phase. Of the participants receiving ammonia as the CS+ odor in acquisition, only 9 out of 28 (32%) correctly identified ammonia as the CS+ odor. Significantly more participants (17 out of 25; 68%) receiving butyric acid, correctly chose this odor as associated with the most symptoms in acquisition (Mann-Whitney $U=224.5$, $p<0.05$). Of the participants receiving information, 13 out of 26 (50%) were aware of contingency. Similarly, 14 out of 27 participants not receiving the information manipulation (52%) were aware of the CS-US contingency. The ratio of aware and non-aware participants in the group receiving information is not significantly different from the ratio in the group receiving no information.

3.4.6 Discussion

A clear effect was found of the US manipulation in acquisition. Participants showed more symptoms to the CS+ trials compared to the CS- trials. Slightly odd is the finding that this effect seems to be larger in the participants subsequently receiving the US-inflation information than in the other participants. It is not clear as to why this a priori difference occurs.

In the test phase, a conditioning effect was found but only when ammonia was used as the CS+ odor. However, more symptoms were reported to the CS- odor test than to the CS+ odor test. Thus, participants receiving ammonia and CO₂-enriched air in the acquisition phase, reported more symptoms in the test phase to butyric acid, which was used as the CS- odor in the acquisition phase. The results thus show an opposite pattern of what is normally predicted and found in a differential conditioning procedure.

A possible explanation for these results might be found in the contingency awareness data. These results show that half of the participants identified the CS- odor as the odor accompanied by the most symptoms during the acquisition. When ammonia was used as the CS+ odor, the effect was even more pronounced: 68% of the participants identified butyric acid as the odor paired with the US, while in the acquisition phase, they reported more symptoms to ammonia (at that time accompanied by CO₂-enriched air). Possibly, participants reported symptoms in the test phase to the odor they believed to have caused the symptoms in the acquisition phase instead of to the odor administered with the CO₂-enriched air. This possibility is explored in the next section.

In the current analysis, no effect was found of the US-inflation manipulation. In the acquisition phase, the participants subsequently receiving the US-inflation information seem to have a larger response to the CS+ compared to those not about to receive this information, but this was not confirmed by the analysis. No such effect occurred in the test phase rendering an a priori group difference in symptom reporting unlikely (further supported by the fact that the response to the CS- in acquisition was almost equal for both groups).

3.4.7 Experiment 4 revised

Introduction

As mentioned in the discussion in the previous section, contingency awareness is hypothesized to mediate the reversed conditioning effect found in experiment 4. In order to test this hypothesis, experiment 4 was analyzed anew. Starting from the idea that participants respond to the stimulus they believe to be the CS+ rather than the odor actually used as the CS+, we recoded the variable CS+ odor to exactly this.

Table 3.1: Number of participants for ammonia perceived CS+ and butyric acid perceived CS+ in function of Information and NA (numbers in parentheses represent the number of participants for ammonia CS+ and butyric acid CS+ before recoding to perceived CSs)

Perceived CS+	Information		No information	
	Low NA	High	NA Low NA	High NA
Butyric acid	7(6)	9(6)	11(7)	5(6)
Ammonia	5(6)	3(7)	3(7)	7(7)

Thus, not the actual CS+ odor was used but the odor identified by the participants on the contingency awareness measure as eliciting the most symptoms. This odor will further be denoted as the perceived CS+ odor. In a similar way, the CS+ odor test becomes the perceived CS+ odor test. Using this perceived CS+ odor, the test phase was looked at again in an analysis similar to the one previously performed. The number of participants per condition after this recoding is depicted in table 3.1 on page 70.

Design and analyses

The symptoms in the test phase were analyzed in a 2 (Perceived CS+ Odor: ammonia or butyric acid) $\times$ 2 (Information: yes or no) $\times$ 2 (NA: low or high) $\times$ 2 (Perceived Conditioning: CS+ or CS-) ANCOVA with the preceding air trial as the covariate. The generalization effect for symptom scores was analyzed in a 2 (Perceived CS+ Odor: ammonia or butyric acid) $\times$ 2 (Information: yes or no) $\times$ 2 (NA: low or high) $\times$ 2 (Generalization odor: acetic acid or citric aroma) ANCOVA with the air trial preceding the test phase as the covariate.

Results conditioning

Perceived CS+ Odor interacted with Perceived Conditioning ($F(1,42)=7.11$; $p < 0.05$) (see figure 3.6 on page 71). Planned comparisons showed that only in participants perceiving butyric acid as the CS+ odor, a conditioning effect was found ($F(1,42)=9.5$, $p < 0.01$). No such effect appeared for ammonia perceived CS+ odor.

Results generalization

A main effect of Generalization odor appeared ($F(1,44)=6.08$, $p < 0.05$). Acetic acid elicited more symptoms compared to citric aroma. No other effects appeared.

Figure 3.6: Symptom scores for ammonia perceived CS+ and butyric acid perceived CS+ in function of CS+ and CS- (error bars denote standard error of mean)

Discussion

A clear conditioning effect appeared in participants who reported butyric acid as the odor associated with the most complaints in the acquisition phase. In contrast to the previous analysis of this experiment, these participants reported more symptoms in the CS+ odor test compared to the CS- odor test. Considering these results, the reverse conditioning effect found in this experiment is not that peculiar anymore. The previous analysis clearly showed that, during the acquisition phase, participants responded more in the CS+ odor trials than in the CS- odor trials. Yet, about half of the participants report the CS- as the odor accompanied by the most symptoms and subsequently report more symptoms to the CS- odor in the test phase. When assessing the conditioning effect using the odor perceived by the participants instead of the odor used in the acquisition, a regular difference is found between the CS+ odor test and the CS- odor test. Given the results of these two analyses, one could conclude that, although the data of the acquisition phase clearly show that participants respond to the CO₂-enriched air, the odor to which they conditioned is the one they believe caused the symptoms.

No generalization effect was found in this study. Participants perceiving bu-

tyric acid to be the CS+ odor (and subsequently showing a conditioned response to butyric acid) did not show a larger response to any of the generalization odors compared to participants perceiving ammonia as the CS+ odor (and who did not show a conditioning effect). Participants did respond more to acetic acid than to citric aroma, but this cannot be regarded as due to conditioning.

The main focus of this experiment was a US-inflation manipulation. Neither in the first, nor the second analysis, an effect of information was found. These results suggest that the US-inflation manipulation was not successful, or at least, did not reveal itself in the results. A first possible explanation is that the texts used for the US-inflation were not powerful enough to sufficiently alter the meaning of the US. Although the texts provided a negative context for the experiment, perhaps they were not focused enough on the US-experience itself, and as such failed to create a link with the US. Participants sometimes stated at the end of the experiment that they had not connected the texts with the events in the acquisition phase. Although this hardly can be considered as evidence for this explanation, it at least suggests that for some participants, the US-inflation manipulation did not work as intended.

A second possible explanation could be that the CS in our paradigm is associated only with the “emotional-affective” properties of the US and not with the “sensory-descriptive” properties of the US. Baeyens and coworkers have proposed this as a possible explanation for the absence of a US-inflation effect in an evaluative learning paradigm (Baeyens, Vanhouche, Crombez, & Eelen, 1998). The “emotional-affective” properties of a stimulus (for example foul smelling) are considered more general in nature than the “sensory-descriptive” features of a stimulus (which allow identification of a particular stimulus). Hence, if the CS is associated only with the former features, but not with the latter, information attempting to reevaluate the US will not be linked to the US used in acquisition, which will consequently not be reevaluated. However, because it is not clear whether the information in itself might not be powerful enough, it is difficult to assess this explanation. Future research would then comprise an adaptation of the US-inflation information in order to create a more powerful manipulation.

3.5 Conclusions

This chapter has discussed US-revaluation and presented evidence in the literature on behalf of this post-conditioning phenomenon. A conditioning model by Davey (1997) was proposed as relevant for both MCS and US-revaluation. It was concluded from this review that the US-representation was changed by the US-revaluation manipulation and that, according to the model of Davey, a CS-US association must be learned in order to find US-revaluation.

A first study was then conducted to attempt to maximize the possibility of finding conditioning on the symptom scores (as a measure of the learning of the CS–US association) by adding several adaptations to the standard conditioning paradigm. Although no conditioning effects were found on the symptoms scores, a clear indication that participants had learned the CS–US association was found on the expectancy measure.

Therefore, a second study assessing US-inflation was carried out. With MCS in mind, an information manipulation was chosen to operationalize US-inflation. The results of this study revealed a reversed conditioning effect possibly due to the contingency awareness as perceived by the participants rather than the actual used contingency. On that account, a revision of this experiment was performed using the perceived CS+ odor instead of the CS+ odor actually paired with the US in the acquisition phase. The results of this analysis showed a clear conditioning effect for participants perceiving butyric acid as the CS+ odor. Regarding the information manipulation, no US-inflation effects showed up. Further research will be needed to determine the reason of this non-effect (for example by enhancing the link between the information and the US-experience).

In the following chapter the role contingency awareness plays in the odor conditioning paradigm, will be further discussed.

Chapter 4

Contingency awareness

4.1 Introduction

In this fourth chapter, an article is presented on the influence of contingency awareness on three issues concerning our differential odor conditioning paradigm. Although it can be argued that contingency awareness actually is an acquisition phenomenon, the strong effect it had on the conditioning effect found in the third study reported in this doctoral thesis (see section 3.3 on page 56 in the previous chapter), warrants a more thorough investigation. The next section reconsiders three studies (one of which is discussed earlier in this doctoral thesis) and the influence contingency awareness has on the conditioning effect consistently found with the odor conditioning paradigm.

4.2 Article (submitted)

4.2.1 Introduction

Classical conditioning is a procedure to study the processes involved in learning in humans as well as in animals. The basic operationalisation consists of pairing a neutral stimulus with a stimulus (unconditioned stimulus; US) eliciting some response (unconditioned response; UR) on the measured dependent variable. This results in the organism responding to the originally neutral stimulus (now called the conditioned stimulus; CS) in a manner similar to the UR. A variant of this procedure is the differential conditioning procedure using two neutral stimuli, one paired with the US (CS+) and one not (CS-). After a number of pairings, administration of the CS+ without the US results in a conditioned response (CR) of the organism, while no or a significant smaller response on the dependent variable occurs for the CS-.

Contingency awareness, defined as the knowledge of the participant in a conditioning procedure of the association between the CS and the US, seems an important variable in obtaining a CR (Levin & Byers, 1987; Shanks & St.-John, 1994). A large and still continuing discussion exists on the nature of this variable. According to some authors, it is a necessary but insufficient condition (Shanks & St.-John, 1994). But not all hold the same opinion. Especially in the field of evaluative conditioning, there is a vast literature investigating the influence of contingency awareness (see for example Field, 2000; Purkis & Lipp, 2001, for studies showing contingency awareness to be necessary but insufficient in obtaining conditioning, but see De Houwer, Baeyens, & Eelen, 1995; Hammerl & Grabitz, 2000, for a different opinion).

One clear example of contingency as a necessary variable is the study by Marinkovic, Shell and Dawson (1989) on conditioning of skin conductance in a differential conditioning paradigm using odors as CSs and electric shock as US. The authors manipulated contingency awareness by giving different instructions to two groups of participants (one group was told that there existed a relationship between one odor and the US, while the other did not receive this information). A masking task was used in order to delay the appearance of awareness. The contingency awareness was assessed using two measures. One was a US expectancy measure after each trial and was considered a concurrent test of awareness. A second, more traditional, way of appraising awareness consisted of a post hoc recognition questionnaire. Participants were considered aware when they showed knowledge of the CS+ – US association (and of the absence of an association between the CS– and the US) on both measures. Participants were considered unaware when failing on both measures. They found that their instruction manipulation greatly overlapped with participants being aware versus unaware of the contingency awareness. A clear conditioning effect showed up on the skin conductance measure but only for the participants marked as aware of the CS–US relationship. Not only this, but more detailed analysis of the US expectancy measure showed that differentiation between the CS+ and the CS– on the skin conductance measure only appeared on trials following the onset of contingency awareness.

In regard of the previous literature, this article reconsiders three studies conducted in our laboratory using a differential odor conditioning paradigm (study 1: Van den Bergh et al., 1998; study 2: Van den Bergh et al., 1999; study 3: Devriese et al., 2000). In this paradigm we used two odors as CSs and the inhalation of CO₂–enriched air as US. Two studies (study 1 and 3) used ammonia (an odor having a negative affective valence) and niaouli (an eucalyptus like odor having a positive affective valence) as the CSs. The third study used ammonia and butyric acid (an odor having a negative affective valence). In all three experiments, contingency awareness was assessed using a recognition task. We will introduce the

details of the procedures in the method section.

The remainder of this introduction will focus on the three issues that will be discussed in this article. A first issue concerns the necessity and sufficiency of contingency awareness for conditioning. A second issue will discuss the possible mediation of the selective conditioning effect found in two studies previously mentioned. A third issue will treat the possible modulation of Negative Affectivity (NA, see below) effects by contingency awareness.

Considering the literature we reviewed, the first issue we would like to deal with is whether contingency awareness is a necessary condition and/or a sufficient condition for obtaining a classical conditioning effect in an odor-CO₂ paradigm using a differential procedure. Contingency awareness can be considered necessary only if conditioning cannot be found without participants being aware of the CS-US contingency. The critical test here is to search for a condition whereby participants are not aware of the contingency but do show conditioning. Unless such a condition can be found, contingency awareness can be considered to be necessary for conditioning. Contingency awareness is sufficient to obtain conditioning if, when participants are aware of the contingency, conditioning occurs. The critical test for sufficiency is then to search a condition whereby participants are aware of the contingency but do not show conditioning. If no such condition can be found, contingency awareness can be considered as sufficient to obtain conditioning.

To assess the first part of this issue, a test will be performed over all studies testing the conditioning effect and its possible interaction with contingency awareness. In order to conclude that contingency awareness is necessary, we should find that in the groups that are unaware of the contingency, no conditioning occurs. The second part of this issue, concerning the sufficiency of contingency awareness, will be tested by looking at the groups that are aware of the contingency. If the sufficiency hypothesis holds, these groups should show conditioning. Because the critical tests exist of finding conditions in which no contingency and conditioning (necessary) or contingency and no conditioning (sufficiency) occur, the analyses for the other issues discussed below will also be used to investigate this first issue.

The second issue we would like to consider in this part is the possible mediation by contingency awareness of a selective conditioning effect found in two studies. The two studies using ammonia and niaouli as CS odors found conditioning only in participants receiving ammonia as the CS+ odor (and niaouli as the CS- odor). The contingency awareness data collected in these experiments were mainly used as a control variable in order to test if one odor (ammonia) showed more contingency awareness than the other (niaouli), possibly explaining the difference in conditioning for the two odors. They were, however, not included in the main analysis as a potential mediating variable. Although no difference was found in the number of participants showing contingency awareness for different odors,

the effect of contingency awareness on the selective conditioning effect was not directly assessed in the previous mentioned studies. Therefore, we will perform an analysis over these two studies to assess the possible modulation of the selective conditioning effect by contingency awareness.

The third issue concerns Negative Affectivity (NA; depicted as a broad range of negative mood states such as anger, disgust, fearfulness and depression; Watson & Pennebaker, 1989). In study 3 we found conditioning only in participants scoring high on NA. One of the hypothesis in the literature (see for example Stegen, Van Diest, Van de Woestijne, & Van den Bergh, 2001) is that high NA participants might be more vigilant towards their bodily sensations (attentional bias). We would like to test whether this could mean that they more easily spot contingencies because they are more actively scanning their environment. For all three studies mentioned above, one of two questionnaires measuring NA was available. We will look at the possible relationship between NA and contingency awareness.

In the next section, we will discuss the details of the procedures employed in the studies and the method used to investigate these issues.

4.2.2 Method

Only features relevant for the present study are reported here. For full details on these experiments, we refer to the respective papers (Van den Bergh et al., 1998; Van den Bergh et al., 1999; Devriese et al., 2000).

Participants

All studies used healthy participants. We used locally recruited participants who responded on an advertisement spread throughout the city in study 1, while we used students enrolled in the university in the second and third study. All participants collaborated on a voluntary base. For reasons of compatibility of the procedures across experiments, we selected half of the participants from study 1 ($n=28$), all participants of study 2 ($n=64$) and study 3 ($n=56$). The analyses of the first and second issue are performed on the full dataset, comprised of 148 participants. The analysis for issue two is performed on the reduced dataset consisting of the studies using ammonia and niaouli as CSs ($n=84$).

Materials

ODORS

Study 1 and 3 use ammonia (NH_3 , a foul smelling odor) and niaouli (a volatile oil smelling of eucalyptus). Ammonia is an irritant (triggering the nervus trigeminus besides the olfactory nerve) but is administered below the irritancy threshold.

Study 2 used butyric acid (a foul smelling but non-irritant odor) instead of niaouli.

SUBJECTIVE MEASURES

Prior to the experiment, all participants received a number of questionnaires. Among others, all participants completed a questionnaire measuring Negative Affectivity. For study 1, this was the Dutch adapted version of the State and Trait Anxiety Inventory (STAI; Van der Ploeg, Defares, & Spielberger, 1980). For study 2 and 3, a Dutch translation of the Negative Emotionality Scale (NEM; Tellegen, 1982) was administered. Because there exists a high correlation between these two measures of NA (Watson & Pennebaker, 1989; Stegen et al., 1998), we used the results of these data to determine whether a participant was high or low on NA. The cutoff point for this dichotomy was based on a median split analysis of data collected in our laboratory on a normal population. For the STAI (normal population $n=343$) we found the median to be 32 (range from 12 to 64). Participants with a STAI score lower or equal to 32 were considered low on NA, while participants with a STAI score larger than 32 were considered high on NA. A similar analysis was performed for the NEM (normal population $n=585$). We found the median to be 6 (range from 0 to 14). Consequently, low-NA participants were defined having a score lower or equal to 6 and high-NA participants a score larger than 6.

After each trial, a questionnaire assessed the participant's symptoms. The questionnaire consisted of 16 symptoms frequently associated with CO₂-enriched air inhalation and 5 items (dummies) not frequently associated with CO₂-enriched air inhalation. The symptom score was the total of the 16 non-dummy items and was used as a continuous variable.

PHYSIOLOGICAL MEASURES

Odors were vaporized using a Devilbiss Nebulizer 646 at a rate of 50 l/hour. The CO₂-enriched air was composed of 7.5% CO₂, 21% O₂ and 71.5% N₂. Decompressed CO₂-enriched air was fed into a meteorological balloon. A Y-valve connected to the balloon allowed easy switching between room air and CO₂-enriched air. A tube departed from this valve and was connected to a double one-way valve (separating inspired and expired air). A Rudolph mask and a pneumotachograph (Fleish No 2, Switzerland) were mounted on the double one-way valve. A small vinyl tube linked the nebulizer with the mask, mixing the odor with the inspired air. Another vinyl tube linked the mask with a capnograph (Poet II, Criticare, USA) which sampled inspired and expired air (due to equipment failure in study 3, CO₂ data were unreliable in that study and will not be discussed further). Proprietary software sampled the airflow waveforms at a rate of 20 Hz. A software program (Han, 1995) counted and removed pauses and irregularities from the datafile and extracted the following primary parameters per breathing cycle: inspiratory (T_i)

and expiratory time (T_e), inspiratory (V_i) and expiratory volume (V_e).

Procedure

We will describe only the common procedural features across the experiments in this section (for full details, see the respective chapters). Participants filled out a number of questionnaires upon arrival (of which one was either the STAI or the NEM). After receiving information about the course of the experiment, all participants were asked to sign an informed consent. The information about the experiment mentioned the administration of several gas mixtures possibly causing harmless symptoms such as headache and shortness of breath. It was clearly stated that all symptoms would quickly disappear after the trial and that participants could stop the experiment at any time. Also, a short description of the procedure was provided.

Subsequently, participants were led to the experimental setup. All trials consisted of 2 minutes breathing during which physiological parameters were measured, followed by three minutes of pause during which they completed the symptom questionnaire. The acquisition phase started with a context exposure trial: participants breathed room air through the mask. Next, six trials followed. In three of these trials, odor 1 (in one half of the participants, odor 2 in the other half) was presented with CO₂-enriched air (further denoted as CS+ trials). The remaining three trials consisted of odor 2 (in one half of the participants, odor 1 in the other half) presented with room air (further denoted as CS- trials). No more than two consecutive trials were of the same type. Odor 1 was ammonia and odor 2 was niaouli (for study 1 and 3) or butyric acid (for study 2).

Following this acquisition phase, contingency awareness was measured using a recognition task. Participants briefly sniffed at small containers holding odor 1 and odor 2. They were then asked to identify the odor they perceived causing the most symptoms in the preceding trials. An answer was classified as correct when participants could identify the odor presented with the CO₂-enriched air and as wrong when they reported the odor presented with room air. Some participants reported that they had no idea what odor was associated with the symptoms. Because for some experiments and in some conditions no participants chose the wrong odor, we coded contingency awareness into “aware” (participants correctly stating the relationship between CS+ and US) and “unaware” (participants having no idea or being wrong about the relationship between CS+ and US).

All participants had thereupon a pause. Depending on the study, the duration of this pause was either 30 minutes (study 1 and 2), 20 minutes (half of the subjects in study 3), or one week (the other half of the subjects in study 3¹). Then, the test

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¹In study 3 Devriese et al., 2000 half of the participants received the test phase after one week as

phase started with a context exposure trial. Next, odor 1 and 2 were administered with room air. In study 2, four test trials were used (two for odor 1 and two for odor 2), while in the other studies, only two test trials were used (one for each odor). To be able to compare the test phase of this study with the other two studies, only the first trial for each odor was considered.

Data analyses and design

In order to investigate the several issues raised in the introduction of this paper, we have performed analyses per issue.

The first issue we looked at is the necessity and sufficiency of contingency awareness for obtaining a conditioning effect. We analyzed the test phase in a 3 (Experiment: study 1, study 2, or study 3) $\times$ 2 (Contingency awareness: aware or unaware) $\times$ 2 (Conditioning: CS+ or CS-) ANCOVA with the context exposure trial prior to the test phase as the covariate. This design was used both for the symptom scores and for the physiological parameters. We used planned comparisons to address conditioning within aware and non-aware participants.

The second issue regarding contingency awareness and the selective conditioning effect in the two studies in which the latter was found, was analyzed in a 2 (Experiment: study 1, or study 3) $\times$ 2 (CS+ odor: ammonia or niaouli) $\times$ 2 (Contingency awareness: aware or unaware) $\times$ 2 (Conditioning: CS+ or CS-) ANCOVA with the context exposure trial prior to the test phase as the covariate. Symptom scores and physiological parameters were analyzed using this design.

The third issue regarding the modulation of the conditioning effect by NA was analyzed using a 3 (Experiment: study 1, study 2, or study 3) $\times$ 2 (Contingency awareness: aware or unaware) $\times$ 2 (NA: low or high) $\times$ 2 (Conditioning: CS+ or CS-) ANCOVA with the context exposure trial prior to the test phase as the covariate. Again both symptom scores and physiological parameters were analyzed using this design.

Experiment, CS+ odor, Contingency awareness, and NA were between-subjects variables, while Conditioning was a within-subjects variable.

Results

ISSUE 1 CONTINGENCY AWARENESS AND CONDITIONING

part of the manipulation. Except for a larger period between acquisition and phase, these participants received an identical procedure as the other half. This delay manipulation did not mediate the conditioning or any other effect, hence all participants of study 3 were used in the analyses presented in this paper.

Subjective measures A clear conditioning effect was found ($F(1,142) = 15.33$, $p < 0.001$). Participants reported a larger response to the CS+ odor test than to the CS– odor test. Planned comparisons revealed that this difference only showed up in aware participants ($F(1,142)=24.77$, $p < 0.00001$) and not in non-aware participants (see figure 4.1 on page 81). The conditioning effect was different for the separate studies: study 1 and 2 revealed a difference between CS+ odor test and CS– odor test (respectively $F(1,142)=16.78$, $p < 0.001$; and $F(1,142)=6.62$, $p < 0.05$), but study 3 did not.

Figure 4.1: Symptom scores in participants aware and non-aware of the CS–US contingency in function of CS+ odor test and CS– odor test (error bars denote standard error of mean)

Physiological parameters A difference was found for tidal volume between the experiments ($F(2,134)=5.02$, $p < 0.01$). Participants in study 3 breathed more shallow than those of study 1 ($F(1,134)=7.94$, $p < 0.01$) and study 2 ($F(1,134)=6.19$, $p < 0.05$). A similar pattern of results was found for minute ventilation ($F(2,134)=5.86$, $p < 0.01$). Here also, study 3 showed a smaller minute ventilation in the participants than study 1 ($F(1,134)=6.16$, $p < 0.05$) and study 2 ($F(1,134)=10.04$, $p < 0.01$). We found that participants breathed deeper when they were aware of the CS–US relationship compared to when they were not ($F(1,134)=4.13$, $p < 0.05$). An analogous result was found for minute ventilation ($F(1,134)=4.19$, $p < 0.05$). No effects for breathing frequency appeared.

ISSUE 2 CONTINGENCY AWARENESS AND SELECTIVE CONDITIONING

Subjective measures Participants reported more symptoms on the CS+ odor test than on the CS– odor test ($F(1,76)=6$, $p < 0.05$). The conditioning effect was different for the two experiments: only in study 1 a difference was found between CS+ odor test and CS– odor test ($F(1,46)=6.69$, $p < 0.05$). The conditioning effect was mediated by the odor used as CS+ in acquisition ($F(1,76)=5.65$, $p < 0.05$). Only when ammonia was used as CS+ odor in acquisition, a conditioning effect appeared ($F(1,76)=7.92$, $p < 0.01$), but not when niaouli was used. No interactions with contingency awareness appeared, but when a priori tested, only contingency aware participants receiving ammonia as CS+ odor in acquisition showed a conditioning effect ($F(1,76)=3.73$, $p < 0.001$) (see figure 4.2 on page 82).

Figure 4.2: Symptom scores in participants aware and non-aware of the CS–US contingency in function of CS+ odor and Conditioning (Am = ammonia, Ni = niaouli; error bars denote standard error of mean)

Physiological measures We found a larger tidal volume in the first study compared to the third study ($F(1,68)=5.69$, $p < 0.05$). An analogous result was found for minute ventilation ($F(1,68)=5.86$, $p < 0.05$). No effects appeared for breathing frequency.

ISSUE 3 CONTINGENCY AWARENESS AND NEGATIVE AFFECTIVITY

Subjective measures No NA effects appeared. Participants reported more symptoms on the CS+ odor test than on the CS– odor test ($F(1,136)=11.39$, $p < 0.001$). This conditioning effect was different for the separate experiments ($F(2,136)=3.70$, $p < 0.05$): conditioning was found only in study 2 ($F(1,136)=16.51$, $p < 0.001$) and marginally in study 1 ($F(1,136)=3.72$, $p=0.055$), but not in study 3.

Physiological measures Tidal volume and minute ventilation differed for the three studies (respectively $F(12,128)=4.57$, $p < 0.05$ and $F(2,128)=5.11$, $p < 0.01$). Participants breathed more shallow in study 3 compared to study 1 ($F(1,128)=6.54$, $p < 0.05$) and compared to study 2 ($F(1,128)=6.07$, $p < 0.05$). A larger minute ventilation was found for study 2 compared to study 3 ($F(1,128)=9.6$, $p < 0.01$). We found a conditioning effect modulated by contingency awareness for breathing volume ($F(1,129)=5.65$, $p < 0.05$). Testing of the conditioning effect within the aware and non-aware groups revealed no significant effects. No effects appeared for breathing frequency.

4.2.3 Discussion

As mentioned in the introduction, a separate analysis was performed in order to test the first issue concerning the necessity and sufficiency of contingency awareness to obtain conditioning, but the analyses for issue two (regarding contingency awareness and the selective conditioning effect) and issue three (concerning contingency awareness and NA) would also be used. Therefore, we will first discuss the analyses performed for issue two and three, before turning to issue one.

Regarding the topic of the selective conditioning effect, we found an overall conditioning effect for the symptoms scores. This conditioning effect was found only in the first study and not in the third study. This is not surprising given the fact that in the individual studies, only study 1 showed an overall conditioning effect. The selective conditioning effect for the symptoms scores found in the separate studies was reproduced in this overall analysis: only when ammonia was used in the acquisition phase, we found a difference between CS+ odor test and CS– odor test. No conditioning effect was found when niaouli was used as the CS+ odor in the acquisition phase. This is in accordance with the result found in the original analyses of the separate studies that an equal amount of participants were aware of the CS–US contingency for ammonia CS+ odor as for niaouli CS+ odor (Van den Bergh et al., 1998; Devriese et al., 2000). We did perform an a priori test in order to check if aware participants receiving niaouli as the CS+ odor in the acquisition phase showed a conditioning effect, but this did not appear. In fact only participants aware of the contingency receiving ammonia as the CS+ odor showed conditioning, while non-aware participants did not. These results suggest that the

selective conditioning effect is not a concealed contingency awareness effect for the symptom scores.

The results for the physiological measures show a quite different pattern. No conditioning effects appeared and neither did any contingency awareness effects. In the original individual studies, a conditioning effect was found only for breathing frequency in study 2, and not for any other respiratory parameter or in any of the other two studies.

Concerning the issue on Negative Affectivity, the analyses performed revealed no NA effects. In the analyses presented in this paper, an overall conditioning effect for symptom scores was found, although further testing revealed it occurred only in study 1 and 2. Again this is consistent with the results of the separate analyses of the individual studies. The absence of a NA effect is slightly surprising given the fact that in two of the three individual studies, the conditioning effect was mediated by NA. The individual studies (study 1 and study 3) in which NA was a modulating factor, were both studies that used ammonia and niaouli as the CSs. Although participants in study 2 were preselected for high and low NA scores, no NA effects appeared, ruling out a difference in NA scores between the experiments as a possible explanation. In this study, ammonia and butyric acid were used as CSs. The difference between study 2 and studies 1 and 3, is the fact that the former used CSs with an equal (negative) affective valence while the latter used CSs with an opposite affective valence. To test this, we conducted an additional analysis on study 1 and 3, similar to the one used for issue two reported earlier but with NA added as a variable. We found the same pattern of results as in the analysis reported for issue two, but here two additional (NA) effects appeared. First of all, conditioning was mediated by NA ($F(1,76)=4.43$, $p < 0.05$). Only participants scoring high on NA showed a conditioning effect ($F(1,76)=21.65$, $p < 0.0001$). Secondly, the selective conditioning effect interacted with NA ($F(1,76)=5.12$, $p < 0.05$): only participants scoring high on NA who received ammonia as CS+ odor in acquisition showed a conditioning effect ($F(1,76)=46.83$, $p < 0.0001$).

It is not clear at present to us why a difference in conditioning for the symptom scores between high NA participants and low NA participants only occurs with CSs with an opposite affective valence. Previous research on NA in our laboratory would suggest an opposite effect (Stegen et al., 1998). In an ambiguous situation, a difference between NA should be the most distinct because here, high NA participants would rely more on schemas than on what they actually experience compared to low NA participants. Assuming that the ammonia and butyric acid design is more ambiguous than the ammonia and niaouli design, one would expect a NA effect here. Contingency awareness also does not seem to offer an explanation. High NA participants are not more aware of the contingency than low NA participants (Mann–Whitney n.s.) and there is no significant difference in the number of

aware participants versus unaware participants between the three studies.

Returning to the main issue of this paper, we will now discuss the evidence these analyses provide for the necessary but insufficient hypothesis regarding contingency awareness as put forward in the literature. To shortly recollect, in order for contingency awareness to be necessary, no condition must be found in which participants are not contingency aware but do show conditioning. The analysis performed for the first issue for the symptom scores support this hypothesis: no conditioning was found in the non-aware group. When we consider the other analyses, in not one group showing an absence of contingency awareness, a conditioning effect appeared. As in the previous analyses, no conditioning effects appeared for the respiratory measures. No interaction with contingency awareness was found for these measures, adding evidence to the necessity part of issue one: the non-aware participants did not show conditioning on the physiological measures.

Concerning sufficiency, no condition must be found in which participants report awareness without showing a conditioning effect. The overall analysis for issue 1 supports the sufficiency hypotheses. However, in the analysis for issue 2, participants receiving niaouli as the CS+ odor in acquisition who report contingency awareness, do not show conditioning. This suggests that contingency awareness alone is not sufficient in obtaining a conditioning effect. Also, on the respiratory measures, participants reporting contingency awareness did not show conditioning and as such, this adds evidence to the insufficiency hypothesis.

To conclude, the results of the analyses presented in this paper, support the “necessity but insufficient” hypothesis for contingency awareness in a differential conditioning procedure. Also the selective conditioning found in previous studies does not seem to coincide with a contingency awareness effect. NA effects do not seem to be modulated by contingency awareness but appear to depend on the affective valence of the used CSs.

4.3 Conclusions

An article concerning the modulation by contingency awareness of several results found with the differential odor conditioning paradigm, was presented in this chapter. Three issues were treated in this part. In a first issue, it was investigated whether contingency awareness was a necessary but insufficient condition to obtain a conditioning effect in the odor paradigm. The results clearly subscribe this hypothesis. At present, in no group of participants showing no knowledge of the CS–US relationship, a conditioning effect occurred, suggesting the necessity of contingency awareness in the odor conditioning paradigm. Conversely, in some groups of participants demonstrating knowledge of the CS–US relationship, no

conditioning effects appeared, rendering support for the insufficiency of contingency awareness to procure conditioning.

A second issue concerned the selective conditioning effect found with the differential odor conditioning paradigm. Here, no evidence was found of an influence of contingency awareness on the selective conditioning effect. Also, no mediation by contingency awareness of the NA effects found in previous studies with the odor conditioning paradigm, was found in a third issue.

The results presented in this chapter clearly advocate the inclusion of contingency awareness as a variable in the analyses of future research with the differential odor conditioning paradigm.

Chapter 5

Conclusions

In the introduction of this doctoral thesis, it was stated that, for science, a long way has to be travelled to come to an understanding of a pattern of symptoms reported by patients. In this final chapter, a summary and some concluding remarks will be presented. It will be left to the reader to determine whether the way has been shortened or rather prolonged.

In a first chapter, an overview was presented of the current scientific status of Multiple Chemical Sensitivity. From this, it was concluded that no unifying theory explains MCS to a full extent. Neither a mere physiological model, nor a mere psychological model succeeds in fully grasping the complexity of MCS. Nevertheless, a number of the theories and models presented, do offer some fair answers to a range of observations.

One of these models, a conditioning account of MCS, has been regarded as promising in elucidating MCS (Guglielmi et al., 1994; Siegel & Kreutzer, 1997). It has been emphasized that the critics of this model (for example Graveling et al., 1999) should consider a more elaborated view on conditioning instead of the often skeletal one used. The differential odor conditioning paradigm was developed in our laboratory as an operationalization of the conditioning account of MCS (Van den Bergh et al., 1999; Van den Bergh et al., 2001). In its prototypical form, odors are used as CSs and CO₂-enriched air as the US. Both questionnaires and respiratory measures are used as dependent variables. Among the basic findings with this procedure are a selective conditioning effect (conditioning appears only when odors with a negative affective valence are used; see for example Van den Bergh et al., 1995) and a dissociation between the conditioning effects found on the questionnaires and on the respiratory measures (see for example Van den Bergh et al., 1999). The intention of this doctoral thesis was to elaborate the conditioning account of MCS in order to incorporate two clinical observations in MCS patients. A first part of this doctoral thesis concerned the phenomenon of generalization to

account for the spreading of the symptoms of MCS patients towards an increasing number of chemical substances. A second part of this doctoral thesis looked at the possibility of US–inflation as a mechanism in explaining the aggravation of symptoms over time. In a third part, the modulation of the differential odor conditioning paradigm by contingency awareness was assessed. The remaining of this chapter will be devoted to discuss the results of the studies in light of the conditioning model of MCS.

Generalization was defined in Chapter I as the phenomenon whereby participants in a conditioning procedure respond to stimuli that are similar to the original stimulus used as the CS. This definition shows great overlap with the clinical observation of spreading of symptoms to an increasing number of chemical substances noted in MCS patients. Hence, generalization was a first post–conditioning phenomenon to be studied in reference to a conditioning account of MCS.

A number of theoretical accounts of generalization were presented and of these, the idea of the forgetting of stimulus attributes was retained and further investigated in the differential odor conditioning paradigm. In a first study, generalization was assessed along three dimensions: an affective valence dimension (positive or negative odors), an irritancy dimension (irritant or non–irritant odors), and a time dimension (immediately or after a delay). Although the first two dimensions are physical in nature and the third not, the Riccio and coworkers account of generalization proposes that the same mechanism underlies both types of dimension (Riccio & Ackil, 1992). Therefore, in a first study, generalization among these dimensions was investigated in the differential odor conditioning paradigm with ammonia and niaouli as the CSs. Butyric acid (negative affective valence, non–irritant), acetic acid (negative affective valence, irritant), and citric aroma (positive affective valence, non–irritant) were used as generalization odors and presented after the test of CS+ and CS– odors. Half of the participants received the test phase (comprised of CS+ and CS– odor test and the administration of the generalization odors) either immediately following the acquisition phase (bar a pause of 20 minutes), or after one week. The latter manipulation is the operationalization of generalization along the time dimension.

Besides a replication of the selective conditioning found in previous studies with this paradigm as mentioned earlier, a generalization effect was found along the affective valence dimension. The conditioned response to ammonia generalized to butyric acid and to acetic acid both in the immediate test and in the delayed test. Also, the conditioning effect as well as the generalization effect was found only in high NA participants. However, these effects only appeared on the symptom questionnaire and not on the respiratory measures.

These results have been extensively commented on in Chapter II, but, with regard to the fourth chapter on contingency awareness, it has to be added that also

in this experiment, the role of latter may not be underestimated. In the three analyses presented in Chapter IV which included the data of the first experiment, only participants aware of the contingency awareness showed the conditioning effect.

Because the results of the first generalization experiment yielded little support for the “forgetting of stimulus attributes” account of generalization, a second experiment was run with the specific intention to prevent a full retrieval of all stimulus attributes. To this effect, participants were given a distraction task shifting their attention away from the odor tests. In this study, a non-differential paradigm was used, partially to assess the conditioning effects in a variant of the standard odor conditioning paradigm. This latter manipulation did not result in a conditioning effect. Other attempts with the non-differential odor conditioning procedure were equally unsuccessful in this respect (Winters et al., 2001). This possibly points to the fact that the differential variant of the odor conditioning paradigm may have features critical in obtaining a conditioning effect. Therefore, the effect of the distraction manipulation could not be assessed in this experiment. Further research on this topic could hence include the use of the distraction task in the differential variant of the procedure possibly combined with a delay of the test phase in order to compare the difference between these two manipulations of disrupting an optimal retrieval of the stimulus characteristics.

A second part of this doctoral thesis was dedicated to the plausibility of the post-conditioning phenomenon US-revaluation in a conditioning account of MCS. It was hypothesized that US-inflation (as a form of US-revaluation) could be responsible for the exacerbation of the symptoms over time often reported by MCS patients. From the literature overview on US-revaluation presented in Chapter III, the idea that a US-revaluation procedure changes the representation of the US, was retained.

A first study was conducted to maximize the chances in obtaining a conditioning effect. The latter was regarded as an indication of the learning of the relationship between the CS+ and US. Therefore, a number of manipulations was added to the standard differential odor conditioning paradigm. Some of these additions tended to enhance the contingency awareness in the participants, bearing in mind the results of the analyses regarding the role of contingency awareness performed on previous studies and discussed in detail in the fourth chapter. Another addition, an expectancy measure administered at the beginning of each trial, was used as a more concurrent measure of contingency awareness. This measure also doubled as an additional indication of the learning of the relationship between the CS+ and the US besides a possible conditioning effect on the symptom scores.

The added optimizing features did not yield the expected result of an enlarged conditioning effect. At least not on the symptoms scores. A clear conditioning effect did appear on the expectancy measure, providing evidence for the learning

of the relationship between the CS+ and the US. Also the results of this measure showed that the conditioning effect only appeared for butyric acid used as the CS+ odor in acquisition and not for niaouli.

A second study was then conducted to investigate US-inflation in the odor conditioning paradigm. The optimizing features used in the previous study were dropped because they proved inefficiently in enlarging the conditioning effect on symptoms. Also, the expectancy measure was no longer administered. An information manipulation was chosen to operationalize US-inflation, because of the larger ecological validity for MCS compared to an administration of a larger percentage of CO₂-enriched air (which would be more in line with traditional US-inflation manipulations). Ammonia and butyric acid were chosen as CSs to maximize the number of conditioned participants and as such augmenting the chance to find a US-inflation effect.

The results of this study revealed a conditioning effect, but in the opposite direction of what was to be expected. Participants receiving ammonia as the CS+ odor in acquisition reported more symptoms to the CS- odor test than to the CS+ odor test. No effects of information appeared. However, half of the participants chose the wrong acquisition odor when asked what odor had been associated with the most symptoms in the acquisition phase. It was then hypothesized that participants responded to the odor they perceived to be the CS+ odor rather than the actual CS+ odor. Because of the rather surprising results on conditioning and the results of the contingency awareness measure, it was decided to revise this experiment. Instead of utilizing the actual odor used as the CS+, an analysis was performed with the perceived CS+ odor. This clearly showed a conditioning effect on the symptom scores when butyric acid was the perceived CS+ odor in acquisition. This time, participants reported more symptoms to the CS+ odor test compared to the CS- odor test. Again, no effect of information appeared in this analysis.

The last study clearly shows the influence of contingency awareness in the differential odor conditioning paradigm, but no effect of the information manipulation could be found. A number of possible explanations have been treated in the discussion of experiment 4 and will not be repeated here. Further research on this topic would then include a further development of the US-inflation information and possibly an attempt to establish a US-deflation effect, which would be particularly relevant concerning treatment options of MCS.

To conclude this doctoral thesis, I would like to add that the research presented here has addressed a number of questions regarding MCS, and to a certain extent, provided some answers. But it has also raised some other issues, such as the difference found between the differential and non-differential variant of the odor conditioning paradigm, and the difference in effects on the several measures (symptoms, expectancy, physiological) used, that should be attended to, inevitably,

in further research.

Chapter 6

Nederlandse samenvatting

Conditionering en Multiple Chemical Sensitivity

In dit proefschrift werd onderzoek voorgesteld naar twee post-conditioneringsfenomenen in een leermodel voor Multiple Chemical Sensitivity (MCS). In het eerste hoofdstuk werd ingegaan op wat Multiple Chemical Sensitivity is, wat de huidige wetenschappelijke stand van zaken is, en werd een leermodel voorgesteld voor Multiple Chemical Sensitivity.

Multiple Chemical Sensitivity is een syndroom waarbij patiënten een scala aan symptomen rapporteren wanneer zij blootgesteld worden aan chemische substanties. Typische symptomen gerapporteerd door patiënten zijn o.a. vermoeidheid, cardio-vasculaire problemen, respiratoire problemen zoals kortademigheid, en gastro-intestinale klachten. Tot op heden is er nog geen consensus bereikt over diagnostische criteria voor MCS. Wel bestaat er een afspraak over een werkdefinitie waarin vooral de lage dosis van chemische substanties waarop patiënten reageren, en de afwezigheid van andere stoornissen, centraal staan.

Wat betreft de etiologie van MCS is er op dit ogenblik geen consensus over een alomvattend model. Verschillende wetenschappelijke disciplines hebben echter wel modellen voorgesteld die momenteel onderzocht worden en waarvan er voor enkele reeds veelbelovende resultaten kunnen worden voorgelegd. Uit het overzicht dat geboden werd in het eerste hoofdstuk kwam vooral naar voor dat een louter fysiologische of louter psychologische verklaring er vermoedelijk niet in zal slagen MCS te vatten. Het lijkt dan ook plausibel dat, wat betreft MCS, verschillende mechanismen verantwoordelijk zijn voor de symptomen en dat niet elk mechanisme in elke patiënt een rol speelt in het symptomenpatroon.

In dit proefschrift werd gebruik gemaakt van een conditioneringsmodel voor MCS. Dit model werd in de literatuur reeds meermaals voorgesteld als vruchtbaar in het onderzoek naar MCS, maar weinig experimenteel onderzoek is hierover ver-

richt. In deze visie kunnen stress-genduceerde hyperventilatie of een blootstelling aan een toxische hoeveelheid van een chemische substantie als onvoorwaardelijke prikkel (OP) beschouwd worden. De geur van deze chemische substanties kan dan beschouwd worden als de voorwaardelijke prikkel, die geconditioneerd wordt op de OP. Het resultaat van het leren van deze associatie is dan dat patiënten symptomen vertonen wanneer zij geconfronteerd worden met die chemische substanties (VP).

In het eerste hoofdstuk werd een mogelijke operationalisatie in de vorm van het differentieel geurconditioneringsparadigma voorgesteld. Dit paradigma bestaat uit een differentiele conditioneringsprocedure waarbij geuren als voorwaardelijke prikkels (VP) gebruikt worden, en het inademen van met CO₂ verrijkte lucht als onvoorwaardelijke prikkel (OP). Zowel respiratoire metingen als symptoommetingen worden afgenomen en gebruikt als afhankelijke variabelen. In een acquisitiefase worden twee types van trials gebruikt: VP+ trials waarbij een geur (VP+ geur) consistent gevolgd wordt door met CO₂ verrijkte lucht, en VP– trials waarbij een andere geur (VP– geur) aangeboden wordt met lucht. In een daaropvolgende testfase worden beide geuren aangeboden met lucht. Conditionering in dit paradigma is dan gedefinieerd als een verschil in respons tussen de VP+ geur en de VP– geur in de testfase (waarbij de respons op de VP+ geur groter is dan deze op de VP– geur).

Verschillende studies met dit paradigma werden reeds uitgevoerd. Duidelijke conditioneringseffecten werden vastgesteld zowel voor de symptoommetingen als voor de respiratoire metingen, al zijn deze vaak onafhankelijk van elkaar. Deze effecten deden zich enkel voor wanneer de geuren (VP) een negatieve affectieve valentie hadden.

Het onderzoek in dit proefschrift heeft zich enerzijds toegespitst op het bekijken van generalisatie als mogelijk mechanisme voor de klinische observatie dat MCS patiënten na verloop van tijd op steeds meer chemische substanties gaan reageren. Anderzijds werd gekeken naar OP-revaluatie als mogelijk mechanisme voor de klinische observatie dat de symptomen van MCS patiënten na verloop van tijd steeds erger worden en vaak pas na enige tijd disfunctioneel worden.

Post-conditioneringsfenomeen 1: Generalisatie

De observatie dat MCS patiënten op steeds meer chemische substanties symptomen vertonen, heeft in de literatuur geleid tot het voorstellen van generalisatie als mogelijk mechanisme in een conditioneringsmodel voor deze observatie. Generalisatie kan als volgt omschreven worden: gegeven een VP die geconditioneerd is op een bepaalde OP en een onvoorwaardelijke respons (OR) uitlokt, dan stelt men

vast dat stimuli die gelijkend zijn aan de VP eveneens een op de OR gelijkende respons uitlokken.

In het tweede hoofdstuk werden een aantal modellen van generalisatie voorgesteld. Eén van deze modellen stelt kort samengevat dat het vergeten van stimulusattributen over tijd er voor zorgt dat andere stimuli dan de oorspronkelijke VP een respons uitlokken. Tijd wordt in dit model beschouwd als een andere maar even valabele dimensie als de meer gebruikelijke dimensies (zoals bijvoorbeeld de affectieve valentie van een prikkel) waarlangs generalisatie optreedt.

Uitgaande van dit idee werd een eerste studie opgezet met als doel generalisatie te onderzoeken in het geurconditioneringsparadigma langs drie dimensies: de affectieve valentie van de prikkels (aangenaam of onaangenaam), de irritantie (een geur wordt als irritant beschouwd wanneer hij, naast de geurzenuw, ook gepercipieerd wordt langs de trigeminale zenuwbundel) en over de tijdsdimensie.

Er werd gebruik gemaakt van het standaard differentieel geurconditioneringsparadigma waarbij ammoniak (een onaangenaam ruikende irritant) en niaouli (een aangenaam ruikende geur) werden gebruikt als VP, en met CO₂ verrijkte lucht als OP. Drie generalisatiegeuren werden aangeboden na de test van de VP+ geur en de VP- geur: boterzuur (een onaangenaam ruikende geur), azijnzuur (een onaangenaam ruikende irritant) en citroenaroma (een aangenaam ruikende geur). Als operationalisatie van de tijdsdimensie kregen de helft van de deelnemers de testfase pas na één week i.p.v. na een pauze van 20 minuten.

In deze studie werd ook Negatieve Affectiviteit (NA, een breed scala aan negatieve gemoedstoestanden zoals woede, angst en depressie) in ogenschouw genomen.

Een eerste resultaat dat in deze studie gevonden werd, was een selectief conditioneringseffect op de symptoommeting. Enkel deelnemers die ammoniak gekregen hadden als de CS+ geur in acquisitie, vertoonden een conditioneringseffect in de testfase. Dit effect werd niet gevonden voor de respiratoire metingen. Een tweede resultaat uit de studie was een generalisatie-effect langs de affectieve valentie dimensie. Deelnemers die geconditioneerd waren (met ammoniak als CS+ geur) vertoonden een grotere respons op de generalisatiegeuren met een negatieve affectieve valentie (boterzuur en azijnzuur) in vergelijking met deelnemers die niet geconditioneerd waren (met niaouli als CS+ geur). Generalisatie langs de irritantiedimensie of langs de tijdsdimensie werd echter niet vastgesteld. Er werd ook een duidelijke effect van NA gevonden op zowel het selectief conditioneringseffect als op het generalisatie-effect. Enkel deelnemers die hoog scoorden op NA vertoonden deze effecten.

Het gevonden selectief conditioneringseffect en generalisatie-effect verlenen verdere steun aan een conditioneringsmodel voor MCS.

In de eerste studie werd uitgegaan van het idee dat het vergeten van stimu-

luskenmerken het achterliggende mechanisme van generalisatie is en werd generalisatie over de tijdsdimensie nagegaan. Er trad echter geen generalisatie op langs deze dimensie. Het vergeten van stimuluskenmerken zou volgens het eerder genoemde model resulteren in het falen van het herinneren van stimuluskenmerken met het gevolg dat stimuli met gelijkende kenmerken eveneens een respons gaan uitlokken. In een tweede studie werd dit getoetst in het geurconditioneringsparadigma.

Er werd in deze studie gebruik gemaakt van een niet-differentiële vorm van het geurconditioneringsparadigma. In deze procedure werd gebruik gemaakt van een experimentele groep die in acquisitie enerzijds trials kreeg waarin de VP (ammoniak) steeds aangeboden werd met met CO₂ verrijkte lucht (OP), en anderzijds evenzoveel luchttrials kreeg. Een controle groep kreeg enerzijds trials waarbij enkel de VP aangeboden werd, en anderzijds trials waarbij enkel de OP aangeboden werd. In de testfase werd dan voor beide groepen de VP aangeboden met lucht en twee generalisatiegeuren (boterzuur en citroenaroma). Conditionering werd dan gedefinieerd als een verschil in respons op de VP in test tussen de deelnemers van de experimentele en de controle groep.

Om het falen van het herinneren van alle stimuluskenmerken te operationaliseren, werd gekozen om de deelnemers in test af te leiden via een distractietaak. Deze taak was bedoeld om te interfereren met het ophalen van alle stimuluskenmerken van de VP en als dusdanig de kans op generalisatie te vergroten. Concreet kreeg dus de helft van de deelnemers in de testfase deze distractietaak.

Alhoewel bij alle deelnemers een duidelijk effect van de OP werd vastgesteld in de acquisitiefase, trad er geen conditionering op in deze studie. Dit resultaat werd ook gevonden in twee andere studies uitgevoerd in onze onderzoeksgroep en suggereert een verschil tussen de differentiële en niet-differentiële vorm van het geurconditioneringsparadigma. Het onderzoek naar het waarom van dit verschil is momenteel nog lopende.

Het niet vinden van een conditioneringseffect hield dan ook in dat de vraagstelling rond het falen van het herinneren van stimuluskenmerken van de VP als mechanisme voor generalisatie in deze studie niet verder bekeken kon worden.

In dit hoofdstuk over generalisatie als mechanisme in een conditioneringsmodel voor MCS werd generalisatie in het geurconditioneringsparadigma aangetoond. Omwille van het uitblijven van een conditioneringseffect in studie twee is het momenteel niet duidelijk of het vergeten van stimuluskenmerken een mogelijke verklaring is voor het generalisatie-effect uit de eerste studie. Verder onderzoek zal dit duidelijk moeten maken.

Post-conditioneringsfenomeen 2: OP-revaluatie

Dit hoofdstuk behandelde een mogelijk mechanisme, OP-revaluatie, voor de klinische observatie dat de symptomen van MCS patiënten steeds erger worden en vaak pas na verloop van tijd disfunctioneel worden. Er werd vastgesteld dat MCS patiënten pas na een tijd medische hulp en informatie over hun problemen gaan zoeken, soms lang nadat ze een eventuele toxische blootstelling aan chemische substanties hebben gehad.

OP-evaluatie kan als volgt beschreven worden. Stel dat een bepaalde VP in een acquisitiefase geconditioneerd wordt op een bepaalde OP, zodat de VP een voorwaardelijke respons (VR) uitlokt. Wanneer nu na deze acquisitie fase een sterkere of zwakkere OP (OP-revaluatie manipulatie) wordt aangeboden, dan wordt vastgesteld dat de VR verandert in de richting van de OP-revaluatie manipulatie.

Het conditioneringsmodel voorgesteld in dit hoofdstuk stelt, kort samengevat, dat wanneer een VP aangeboden wordt, de OP gevalueerd wordt voordat een VR optreedt. Dit impliceert dat alle processen die deze evaluatie of de representatie van de OP beïnvloeden, eveneens een invloed zullen hebben op de sterkte van de VR. Eveneens volgt uit dit model dat de associatie tussen de VP en de OP geleerd moet zijn, wil een OP-revaluatie kunnen optreden. Een eerste studie werd uitgevoerd, gedeeltelijk om na te gaan of de VP-OP associatie geleerd werd in het geurconditioneringsparadigma. Daartoe werden een aantal aanpassingen aangebracht aan de standaard procedure. Deze aanpassingen dienden ook om de kans om een conditioneringseffect te bekomen, te maximaliseren. Eveneens werd een bijkomende meting afgenomen. Deze peilde naar de verwachting die deelnemers hadden omtrent het optreden van symptomen aan het begin van elke trial.

De resultaten van deze studie toonden aan dat de aanpassingen om het conditioneringseffect te maximaliseren weinig effect hadden. Op de symptoommeting werd geen conditioneringseffect vastgesteld, maar wel op de verwachtingsmaat. Dit suggereerde dat de VP-OP associatie wel degelijk geleerd was.

In een tweede studie werd OP-inflatie dan onderzocht als een vorm van OP-revaluatie. Hiervoor werd gebruik gemaakt van het standaard differentieel conditioneringsparadigma met ammoniak en boterzuur als VP. Drie teksten die informatie verschaffen over de negatieve gevolgen van de blootstelling aan de OP, werden gebruikt als OP-inflatie manipulatie.

In deze studie werd een omgekeerd conditioneringseffect vastgesteld. Deelnemers die ammoniak als VP+ geur (dus samen aangeboden met CO₂ verrijkte lucht in de acquisitiefase) gekregen hadden, reageerden sterker op de VP- geur (met lucht aangeboden in de acquisitiefase) dan op de VP+ geur in de test fase (beide geuren werden hier met lucht aangeboden). Omdat bleek dat ongeveer de helft van

de deelnemers na acquisitiefase in een meting van het contingentiebewustzijn de VP– geur hadden gedentificeerd als zijnde de geur die samenging met de gerapporteerde symptomen i.p.v. de VP+ geur, werd deze studie opnieuw geanalyseerd. In deze analyse werd niet de VP+ geur die in de acquisitiefase samen aangeboden werd met CO₂ verrijkte lucht gebruikt, maar de VP+ geur die door de deelnemers werd aangeduid als gepaard gaande met symptomen. Er werd opnieuw een conditioneringseffect vastgesteld, ditmaal in de verwachte richting, maar nu enkel voor de deelnemers die boterzuur percipieerden als de VP+ geur.

In geen van beide analyses werd een effect gevonden van de OP–inflatie informatie manipulatie. Een tweetal mogelijke verklaringen hiervoor werden besproken (de mogelijkheid dat de teksten onvoldoende krachtig waren en de mogelijkheid dat niet alle OP–stimulusattributen nodig om OP–inflatie vast te stellen, geëncodeerd werden).

Contingentiebewustzijn

In dit hoofdstuk werd ingegaan op de rol van contingentiebewustzijn in het differentieel conditioneringsparadigma. Drie studies uitgevoerd in onze onderzoeksgroep (waarvan één de in hoofdstuk II besproken studie 1 was) waarin gebruik werd gemaakt van het differentieel conditioneringsparadigma werden opnieuw geanalyseerd.

Drie vragen werden in dit hoofdstuk bekeken. Een eerste stuk onderzocht de hypothese dat contingentiebewustzijn een noodzakelijke maar onvoldoende voorwaarde is voor het vinden van conditionering in het differentieel geurconditioneringsparadigma. Daartoe werd gezocht enerzijds, wat betreft de noodzakelijkheid van contingentiebewustzijn, naar groepen van deelnemers die geen contingentiebewustzijn vertonen, maar waarin wel een conditioneringseffect gevonden kon worden. Anderzijds, wat betreft het onvoldoende zijn van contingentiebewustzijn, werd gezocht naar groepen van deelnemers die een correct contingentiebewustzijn rapporteerden, maar waarin geen conditioneringseffect kon worden aangetroffen. Uit de resultaten bleek dat contingentiebewustzijn een noodzakelijke maar onvoldoende voorwaarde is voor het vinden van een conditioneringseffect in het differentieel conditioneringsparadigma. Er werden namelijk geen groepen van deelnemers gevonden die zich niet bewust waren van de VP–OP relatie en toch conditionering vertoonden, maar er werden wel groepen van deelnemers gevonden die een correct contingentiebewustzijn rapporteerden en waarin toch geen conditioneringseffect gevonden kon worden.

Een tweede stuk onderzocht de mogelijke rol van contingentiebewustzijn in het selectief conditioneringseffect (het effect waarbij in het differentieel paradigma

enkel conditionering gevonden wordt voor negatief affectief valente geuren en niet voor positief affectief valente geuren). Een mogelijkheid is namelijk dat negatief affectief valente geuren als VP makkelijker leiden tot contingentiebewustzijn dan positief affectief valente geuren. Daartoe werden slechts twee van de drie studies gebruikt omdat in de derde studie twee negatief affectief valente geuren werden gebruikt en het selectief conditioneringseffect daar dus niet optrad. Uit de resultaten bleek dat het selectief conditioneringseffect geen gemaskeerd effect van contingentiebewustzijn was.

Een derde stuk behandelde de rol van contingentiebewustzijn in de NA effecten die gevonden werden in twee van de drie besproken studies. In deze studies werd gevonden dat hoge NA deelnemers makkelijker conditioneren dan lage NA deelnemers. Het is een mogelijkheid dat hoge NA deelnemers zich makkelijker bewust worden van de contingentie omwille van het feit dat zij actiever zoeken naar mogelijke negatieve situaties in hun omgeving dan lage NA deelnemers. De resultaten van deze analyse verstrekten echter geen steun aan deze hypothese. Opvallend was wel dat wanneer gekeken werd over de drie studies heen, er zich geen NA effecten voordeden wat betreft de conditioneringseffecten, maar wanneer er gekeken werd over de twee studies met een positief affectieve valente geur en negatief affectieve valente geur, NA wel interageerde met het conditioneringseffect.

Uit deze resultaten werd geconcludeerd dat in toekomstig onderzoek met het differentieel geurconditioneringsparadigma, contingentiebewustzijn zeker in beschouwing moet genomen worden.

Conclusies

Om kort samen te vatten, werd in dit proefschrift onderzoek naar een conditioneringsmodel voor MCS voorgesteld. Generalisatie en OP-revaluatie werden beschouwd als mogelijke mechanismen voor twee klinische observaties bij MCS patienten. Het onderzoek dat voorgesteld werd heeft een aantal vragen beantwoord, maar een aantal andere aandachtspunten zijn naar voor gekomen (zoals het verschil tussen de differentiele en niet-differentiele vorm van het paradigma). Verder onderzoek zal klaarheid moeten scheppen over het waarom van de deze fenomenen.

References

- Andin, P., Rnnbck, L., & Jrvholm, B. (1997). Succesful use of a selective serotonin reuptake inhibitor in a patient with multiple chemical sensitivities. *Acta Psychiatrica Scandinavica*, 96, 82–83.
- Baeyens, F., Eelen, P., Van den Bergh, O., & Crombez, G. (1992). The content of learning in human evaluative conditioning: Acquired valence is sensitive to US–revaluation. *Learning and Motivation*, 23, 200–224.
- Baeyens, F., Vanhouche, W., Crombez, G., & Eelen, P. (1998). Human evaluative flavor–flavor conditioning is not sensitive to post–acquisition US–inflation. *Psychologica Belgica*, 38(2), 83–108.
- Bascom, R., Meggs, W. J., Frampton, M., Hudnell, K., Killburn, K., Kobal, G., Medinsky, M., & Rea, W. (1997). Neurogenic inflammation: with additional discussion of central and perceptual integration of nonneurogenic inflammation. *Environmental Health Perspectives*, 105 Suppl 2, 531–537.
- Bell, I., Baldwin, C., & Schwartz, G. (1998). Illness from low levels of environmental chemicals: Relevance to chronic fatigue syndrome and fibromyalgia. *American Journal of Medicine*, 105, 74–82.
- Bell, I., Baldwin, C., & Schwartz, G. (2001). Sensitization studies in chemically intolerant individuals: Implications for individual difference research. *Annals of the New York Academy of Sciences*, 933, 38–47.
- Bell, I., Miller, C., & Schwartz, G. (1992). An olfactory–limbic model of multiple chemical sensitivity syndrome: Possible relationships to kindling and affective spectrum disorders. *Biological Psychiatry*, 32, 218–242.
- Bell, I., Rossi, J., Gilbert, M., Kobal, G., Morrow, L., Newlin, D., Sorg, B., & Wood, R. (1997). Testing the neural sensitization and kindling hypothesis for illness from low levels of environmental chemicals. *Environmental Health Perspectives*, 105(Suppl. 2), 539–547.

- Bell, I., Schwartz, G., Bootzin, R., & Wyat, J. (1997). Time-dependent sensitization of heart rate and blood pressure over multiple laboratory sessions in elderly individuals with chemical odor intolerance. *Archives of Environmental Health*, 52(1), 6–17.
- Binkley, K., King, N., Poonai, N., Seeman, P., Ulpian, C., & Kennedy, J. (2001). Idiopathic environmental intolerance: increased prevalence of panic disorder-associated cholecystokinin b receptor allele 7. *Journal of Allergy and Clinical Immunology*, 107(5), 887–890.
- Binkley, K., & Kutcher, S. (1997). Panic response to sodium lactate infusion in patients with multiple chemical sensitivity syndrome. *Journal of Allergy and Clinical Immunology*, 99(4), 570–574.
- Black, D. (2000). The relationship of mental disorders and idiopathic environmental intolerance. *Occupational Medicine: State of the art reviews*, 15(3), 557–570.
- Black, D., Doebbeling, B., Voelker, M., Clarke, W., Woolson, R., Barrett, D., & Schwartz, D. (2000). Multiple chemical sensitivity syndrome. *Archives of Internal Medicine*, 160, 1169–1176.
- Black, D., Okiishi, C., & Schlosser, M. (2000). A nine-year follow-up of people diagnosed with multiple chemical sensitivities. *Psychosomatics*, 41(3), 253–261.
- Black, D., Rathe, A., & Goldstein, R. (1993). Measures of distress in 26 "environmentally ill" subjects. *Psychosomatics*, 38(2), 131–138.
- Boiten, F. (1998). The effects of emotional behaviour on components of the respiratory cycle. 49(1–2), 29–51.
- Bolla-Wilson, K., Wilson, R., & Bleecker, M. (1988). Conditioning of physical symptoms after neurotoxic exposure. *Journal of Occupational Medicine*, 30(9), 684–686.
- Bouton, M. (1984). Differential control by context in the inflation and reinstatement paradigms. *Journal of Experimental Psychology: Animal Behavior Processes*, 10(1), 56–74.
- Bouton, M. (1994). Conditioning, remembering, and forgetting. *Journal of Experimental Psychology: Animal Behavior Processes*, 20(3), 219–231.
- Bouton, M., Nelson, J., & Rosas, J. (1999). Stimulus generalization, context change, and forgetting. *Psychological Bulletin*, 125(2), 171–186.

- Bouton, M., Rosas, J., & Nelson, J. (1999). Resolution now! reply to riccio, richardson, and ebner. *Psychological Bulletin*, 125(2), 190–192.
- Cohen, N., Kehrl, H., Berglund, B., O’Leary, A., Ross, G., Seltzer, J., & Weisel, C. (1997). Psychoneuroimmunology. *Environmental Health Perspectives*, 105(Suppl. 2), 527–529.
- Cohn, J. (1994). Multiple chemical sensitivity or multi-organ dysesthesia. *Journal of Allergy and Clinical Immunology*, 10, 953–954.
- Costa, P., & McCrae, R. (1988). Personality and adulthood: A six-year longitudinal study of self-reports and spouse ratings on the neo personality inventory. *Journal of Personality and Social Psychology*, 54, 853–863.
- Cullen, M. (1987). Multiple chemical sensitivities: summary and directions for future investigators. *Occupational Medicine*, 2(4), 801–804.
- Dalton, P., & Hummel, T. (2000). Chemosensory function and response in idiopathic environmental intolerance. *Occupational Medicine: State of the art reviews*, 15(3), 539–556.
- Dalton, P., Wysocki, C., Brody, M., & Lawley, H. (1997). The influence of cognitive bias on the perceived odor, irritation and health symptoms from chemical exposure. *International Archives of Occupational and Environmental Health*, 69(6), 407–417.
- Davey, G. (1995). Preparedness and phobias: Specific evolved associations or a generalized expectancy bias? *Behavioral and Brain Sciences*, 18, 289–325.
- Davey, G. (1997). A conditioning model of phobias. In G. Davey (Ed.), *Phobias: A handbook of therapy, research and treatment* (pp. 301–322). Chichester: John Wiley & Sons Ltd.
- Davidoff, A., & Keyl, P. (1996). Symptoms and health status in individuals with multiple chemical sensitivities syndrome from four reported sensitizing exposures and a general population comparison group. *Archives of Environmental Health*, 51(3), 201–213.
- Davidoff, A., Keyl, P., & Fogarty, L. (2000). Psychiatric inferences from data on psychologic/psychiatric symptoms in multiple chemical sensitivities syndrome. *Archives of Environmental Health*, 55(3), 165–175.
- Davidoff, A., Keyl, P., & Meggs, W. (1998). Development of multiple chemical sensitivities in laborers after acute gasoline fume exposure in an underground tunneling operation. *Archives of Environmental Health*, 53(3), 183–189.

- De Houwer, J., Baeyens, F., & Eelen, P. (1995). Verbal evaluative conditioning with undetected US presentations. *Behaviour Research and Therapy*, 32(6), 629–633.
- de Jong, P., Merckelbach, H., Koertshuis, G., & Muris, P. (1994). UCS–inflation and acquired fear responses in human conditioning. *Advances in Behaviour Research and Therapy*, 16, 131–165.
- de Jong, P., Muris, P., & Merckelbach, H. (1996). UCS inflation and human aversive autonomic conditioning. *Biological Psychology*, 43, 227–239.
- Devriese, S., Winters, W., Nemery, B., Veulemans, H., Eelen, P., & Van den Bergh, O. (2000). Generalisation in a differential odor conditioning paradigm in a model for multiple chemical sensitivity. *Psychosomatic Medicine*, 62, 751–759.
- Doty, R. (1994). Olfaction and multiple chemical sensitivity. *Toxicology and Industrial Health*, 10(4/5), 359–366.
- Estes, W. (1997). Processes of memory loss, recovery, and distortion. *Psychological Review*, 104(1), 148–169.
- Fiedler, N., & Kipen, H. (1997). Chemical sensitivity: The scientific literature. *Environmental Health Perspectives*, 105(Suppl. 2), 409–415.
- Fiedler, N., Kipen, H., Deluca, J., Kelly–McNeil, K., & Natelson, B. (1994). Neuropsychology and psychology of mcs. *Toxicology and Industrial Health*, 10(4/5), 545–554.
- Field, A. (2000). I like it, but i'm not sure why: can evaluative conditioning occur without conscious awareness. *Consciousness and Cognition*, 9(1), 13–36.
- Folgering, H. (1999). The pathophysiology of hyperventilation syndrome. *Monaldi Archive of Chest Disorders*, 54(4), 365–372.
- Graveling, R., Pilkington, A., George, J., Butler, M., & Tannahill, S. (1999). A review of multiple chemical sensitivity. *Occupational and Environmental Medicine*, 56, 73–85.
- Grings, W., Schell, A., & Carey, C. (1973). Verbal control of an autonomic response in a cue reversal situation. *Journal of Experimental Psychology*, 99(2), 251–221.
- Guglielmi, R. S., Cox, D. J., & Spyker, D. A. (1994). Behavioral treatment of phobic avoidance in multiple chemical sensitivity. *Journal of Behavior Therapy and Experimental Psychiatry*, 25(3), 197–209.

- Gupta, K., Perharic, L., Volans, G., Murray, V., & Watson, J. (1997). Apparent poisoning by wood preservatives: An attributional syndrome. *Journal of Psychosomatic Research*, 43(4), 391–398.
- Hammerl, M., & Grabitz, H. (2000). Affective–evaluative learning in humans: a form of associative learning or only an artifact? *Learning and Motivation*, 31(4), 345–363.
- Han, J. (1995). *Breathing patterns in anxiety disorders: is there a hyperventilation syndrome?* Unpublished doctoral dissertation, University of Leuven.
- Kehrl, H. (1997). Laboratory testing of the patient with multiple chemical sensitivity. *Environmental Health Perspectives*, 105(Suppl. 2), 443–444.
- Kipen, H., & Fiedler, N. (1997). Introduction and overview. *Environmental Health Perspectives*, 105(Suppl. 2), 405–407.
- Kipen, H., & Fiedler, N. (1999). Invited commentary: Sensitivities to chemicals – context and implications. *American Journal of Epidemiology*, 150(1), 13–16.
- Kipen, H., Fiedler, N., Maccia, C., Yurkow, E., Todaro, J., & Laskin, D. (1992). Immunologic evaluation of chemically sensitive patients. *Toxicology and Industrial Health*, 8(4), 125–135.
- Kirk, R. (1995). *Experimental design: Procedures for the behavioral sciences* (3 ed.). Pacific Grove, CA: Brooks/Cole.
- Kreutzer, R. (2000). Idiopathic environmental intolerance: Case definition issues. *Occupational Medicine: State of the art reviews*, 15(3), 511–528.
- Lehrer, P. (1997). Psychophysiological hypotheses regarding multiple chemical sensitivity syndrome. *Environmental Health Perspectives*, 105(Suppl. 2), 479–483.
- Levin, A., & Byers, V. (1987). Environmental illness: a disorder of immune regulation. *Occupational Medicine*, 2(4), 669–681.
- Leznoff, A. (1997). Provocative challenges in patients with multiple chemical sensitivity. *Journal of Allergy and Clinical Immunology*, 99(4), 434–437.
- Marinkovic, K., Schell, A., & Dawson, M. (1989). Awareness of the CS–UCS contingency and classical conditioning of skin conductance responses with olfactory CSs. *Biological Psychology*, 29, 39–60.

- McCall, R., & Appelbaum, M. (1973). Bias in the analysis of repeated-measures designs: Some alternative approaches. *Child-Development*, 44(3), 401–415.
- Meggs, W. (1995). Multiple chemical sensitivities: Chemical sensitivity as a symptom of airway inflammation. *Clinical Toxicology*, 33(2), 107–110.
- Meggs, W. (1997a). Hypothesis for induction and propagation of chemical sensitivity based on biopsy studies. *Environmental Health Perspectives*, 105(Suppl. 2), 473–478.
- Meggs, W. (1997b). Psychogenic versus biologic basis for chemical sensitivity. *Journal of Allergy and Clinical Immunology*, 100(6), 855–856.
- Meggs, W., & Cleveland, C. (1993). Rhinolaryngoscopic examination of patients with the multiple chemical sensitivity syndrome. *Archives of Environmental Health*, 48, 14–18.
- Meggs, W. J., Elsheik, T., Metzger, W., Albernaz, M., & Bloch, R. (1996). Nasal pathology and ultrastructure in patients with chronic airway inflammation (rads and ruds) following an irritant exposure. *Journal of Toxicology and Clinical Toxicology*, 34(4), 383–396.
- Meudell, P., Mayes, A., & MacDonald, C. (1994). Dual task performance in amnesic and normal people: does resource depletion cause amnesia? *Cortex*, 30(1), 159–166.
- Miller, C. (1997). Toxicant-induced loss of tolerance – an emerging theory of disease. *Environmental Health Perspectives*, 105(Suppl. 2), 445–453.
- Miller, C. (2001). The compelling anomaly of chemical intolerance. *Annals of the New York Academy of Sciences*, 933, 1–23.
- Mitchell, C., Donnay, A., Hoover, D., & Margolick, J. (2000). Immunologic parameters of multiple chemical sensitivity. *Occupational Medicine: State of the art reviews*, 15(3), 647–665.
- Pashler, H. (1994). Dual-task interference in simple tasks: data and theory. *Psychological Bulletin*, 116(2), 220–244.
- Pearce, J. (1987). A model for stimulus generalization in pavlovian conditioning. *Psychological Review*, 94(1), 61–73.
- Pennebaker, J. (1994). Psychological bases of symptom reporting: Perceptual and emotional aspects of chemical sensitivity. *Toxicology and Industrial Health*, 10(4/5), 497–511.

- Peterson, R., & Heilbronner, R. (1988). The anxiety sensitivity index: construct validity and factor analytic structure. *Journal of Anxiety Disorders, 1*, 117–121.
- Poonai, N., Antony, M., Binkley, K., Stenn, P., Swinson, R., Corey, P., Silverman, F., & Tarlo, S. (2000). Carbon dioxide inhalation challenges in idiopathic environmental intolerance. *Journal of Allergy and Clinical Immunology, 105*(2), 358–363.
- Purkis, H., & Lipp, O. (2001). Does affective learning exist in the absence of contingency awareness? *Learning and Motivation, 32*, 84–99.
- Reid, S. (1999). Multiple chemical sensitivity – is the environment really to blame. *Journal of the Royal Society of Medicine, 92*, 616–619.
- Reiss, S. (1991). Expectancy model of fear, anxiety, and panic. *Clinical Psychology Review, 11*(2), 141–153.
- Rescorla, R. (1974). Effect of inflation of the unconditioned stimulus value following conditioning. *Journal of Comparative and Physiological Psychology, 86*(1), 101–106.
- Rescorla, R. (1976). Stimulus generalization: Some predictions from a model of pavlovian conditioning. *Journal of Experimental Psychology: Animal Behavior Processes, 2*(1), 88–96.
- Riccio, D., & Ackil, J. (1992). Forgetting of stimulus attributes: Methodological implications for assessing associative phenomena. *Psychological Bulletin, 112*(3), 433–445.
- Riccio, D., Richardson, R., & D.L., E. (1984). Memory retrieval deficits based upon altered contextual cues: A paradox. *Psychological Bulletin, 96*(1), 152–165.
- Riccio, D., Richardson, R., & Ebner, D. (1999). The contextual change paradox is still unresolved: Comment on bouton, nelson, and rosas (1999). *Psychological Bulletin, 125*(2), 187–189.
- Ross, G. (1997). Clinical characteristics of chemical sensitivity: An illustrative case history of asthma and mcs. *Environmental Health Perspectives, 105*(Suppl. 2), 437–441.
- Ross, P., Whysner, J., Covello, V., Kushner, M., Rifkind, A., Sedler, M., Trichopoulos, D., & Williams, G. (1999). Olfaction and symptoms in the multiple chemical sensitivities syndrome. *Preventive Medicine, 28*, 467–480.

- Schottenfeld, R. (1987). Workers with multiple chemical sensitivities: a psychiatric approach to diagnosis and treatment. *Occupational Medicine*, 2(4), 739–753.
- Shanks, D., & St.-John, M. (1994). Characteristics of dissociable human learning systems. *Behavioral and Brain Sciences*, 17(3), 367–447.
- Sherman, J. (1978). US inflation with trace and simultaneous fear conditioning. *Animal Learning and Behavior*, 6(4), 463–468.
- Shusterman, D. (1992). Critical review: The health significance of environmental odor pollution. *Archives of Environmental Health*, 47, 76–87.
- Shusterman, D., & Dager, S. (1991). Prevention of psychological disability after occupational respiratory exposures. *Occupational Medicine*, 6(1), 11–27.
- Siegel, S., & Kreutzer, R. (1997). Pavlovian conditioning and multiple chemical sensitivity. *Environmental Health Perspectives*, 105(Suppl. 2), 521–526.
- Simon, G., Daniell, W., Stockbridge, H., Claypoole, K., & Rosenstock, L. (1993). Immunologic, psychological, and neuropsychological factors in multiple chemical sensitivity: A controlled study. *Annals of Internal Medicine*, 19(2), 97–103.
- Sorg, B. A. (1999). Multiple chemical sensitivity: potential role for neural sensitization. *Critical Review of Neurobiology*, 13(3), 283–316.
- Sparks, P. (2000). Idiopathic environmental intolerances: Overview. *Occupational Medicine: State of the art reviews*, 15(3), 497–510.
- Sparks, P., Daniell, W., Black, D., Kipen, H., Altman, L., Simon, G., & Terr, A. (1994). Multiple chemical sensitivity syndrome: A clinical perspective. *Journal of Occupational Medicine*, 36(7), 731–737.
- Spyker, D. (1995). Multiple chemical sensitivity: Syndrome and solution. *Clinical Toxicology*, 33(2), 95–99.
- Staudenmayer, H. (1997). Multiple chemical sensitivities or idiopathic environmental intolerances: Psychophysiologic foundation of knowledge for a psychogenic explanation. *Journal of Allergy and Clinical Immunology*, 99(4), 434–437.
- Staudenmayer, H., & Kramer, R. (1999). Psychogenic chemical sensitivity: Psychogenic pseudoseizures elicited by provocation challenges with fragrances. *Journal of Psychosomatic Research*, 47(2), 185–190.

- Stegen, K., De bruynne, K., Rasschaert, W., Van de Woestijne, K., & O., V. (1999). Fear-relevant images as conditioned stimuli for somatic complaints, respiratory behavior, and reduced end-tidal pCO₂. *Journal of Abnormal Psychology*, 108(1), 143–152.
- Stegen, K., Neujens, A., Crombez, G., Hermans, D., Van de Woestijne, K., & Van den Bergh, O. (1998). Negative affect, respiratory reactivity, and somatic complaints in a CO₂ inhalation paradigm. *Biological Psychology*, 49, 109–122.
- Stegen, K., & Van den Bergh, O. (Submitted). Negative affectivity and psychosomatic symptoms.
- Stegen, K., Van Diest, I., Van de Woestijne, K., & Van den Bergh, O. (2001). Is there a stronger attentional focus to internal stimuli in persons with negative affect? *Cognition and Emotion*, 15(6), 813–829.
- Stenn, P., & Binkley, K. (1998). Successful outcome in a patient with chemical sensitivity. *Psychosomatics*, 39(6), 547–550.
- Tellegen, A. (1982). *Brief manual for the differential personality questionnaire*. Unpublished manuscript, University of Minnesota.
- Van den Bergh, O., Devriese, S., Winters, W., Veulemans, H., Nemery, B., Eelen, P., & Van de Woestijne, K. (2001). Acquiring symptoms in response to odors : A learning perspective on multiple chemical sensitivity. *Annals of the New York Academy of Sciences*, 933, 278–290.
- Van den Bergh, O., Kempynck, P., Van de Woestijne, K., Baeyens, F., & Eelen, P. (1995). Respiratory learning and somatic complaints: A conditioning approach using CO₂-enriched air inhalation. *Behaviour Research and Therapy*, 33(5), 517–527.
- Van den Bergh, O., Stegen, K., & Van de Woestijne, K. (1997). Learning to have psychosomatic complaints: Conditioning of respiratory behavior and somatic complaints in psychosomatic patients. *Psychosomatic Medicine*, 59, 13–23.
- Van den Bergh, O., Stegen, K., & Van de Woestijne, K. (1998). Memory effects on symptom reporting in a respiratory learning paradigm. *Health Psychology*, 17(3), 241–248.
- Van den Bergh, O., Stegen, K., Van Diest, I., Raes, C., Stulens, P., Eelen, P., Veulemans, H., , Van de Woestijne, K., & Nemery, B. (1999). Acquisition and

- extinction of somatic symptoms in response to odors: A pavlovian paradigm relevant to multiple chemical sensitivity. *Occupational and Environmental Medicine*, 56, 295–301.
- Van der Ploeg, H., Defares, P., & Spielberger, C. (1980). *Handleiding bij de Zelfbeoordelingsvragenlijst ZBV. Een Nederlandstalige bewerking van de Spielberger State Trait Anxiety Inventory STAI-DY*. Swets & Zeitlinger.
- Watson, D., Clark, L., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: the panas scales. *Journal of Personality and Social Psychology*, 54, 963–1070.
- Watson, D., & Pennebaker, J. (1989). Health complaints, stress, and distress: exploring the central role of negative affectivity. *Psychological Review*, 96, 234–254.
- White, K., & Davey, G. (1989). Sensory preconditioning and UCS inflation in human fear conditioning. *Behaviour Research and Therapy*, 27, 161–166.
- Wientjes, C. (1993). *Psychological influences upon breathing: Situational and dispositional aspects*. Unpublished doctoral dissertation, Catholic University of Tilburg, Soesterberg.
- Wientjes, C., & Grossman, P. (1994). Overreactivity of the psyche or the soma? interindividual associations between psychosomatic symptoms, anxiety, heart rate, and end-tidal partial carbon dioxide pressure. *Psychosomatic Medicine*, 56(6), 533–540.
- Winer, B., Brown, D., & Michels, K. (1991). *Statistical principles in experimental design* (3 ed.). McGraw-Hill.
- Winters, W., Devriese, S., Eelen, P., Veulemans, H., Nemery, B., & Van den Bergh, O. (2001). Symptom learning in response to odors in a single odor respiratory learning paradigm. *Annals of the New York Academy of Sciences*, 933, 315–318.
- Zhou, Y., & Riccio, D. (1996). Manipulation of components of context: The context shift effect and forgetting of stimulus attributes. *Learning and Motivation*, 27, 400–407.
- Ziem, G., & McTamney, J. (1997). Profile of patients with chemical injury and sensitivity. *Environmental Health Perspectives*, 105(Suppl. 2), 417–436.

Appendix A

TEXT 1

In samenwerking met het Laboratorium voor Longtoxicologie en dat van Arbeids- en Milieugeneeskunde doet het laboratorium voor Ergonomie en Gezondheidspsychologie onderzoek naar MCS.

Wat is MCS

MCS staat voor Multiple Chemical Sensitivity of meerdere chemische gevoeligheid. Dit syndroom is in België nog maar weinig gekend, maar in de USA is het een “hot topic” omdat naar schatting ongeveer 3 tot 5% van de bevolking er last van zou hebben.

Allerlei klachten kunnen optreden: ijlheid en duizeligheid, hartkloppingen en pijn in borststreek, concentratieproblemen, vermoeidheid, gebrek aan eetlust, hoesten, etc. Maar ook hoofdpijn, uitgesproken geurperceptie, tintelingen in de handen of het gezicht en nog een aantal andere niet-specifieke klachten. Ze worden bijna altijd uitgelokt door contact met chemische stoffen en daarom zoekt men de oorzaak in de al maar toenemende chemische pollutie in de moderne maatschappij. Denken we maar aan PCB's en dioxines, maar ook aan kleur-, smaak- en bewaarestoffen die via de industrie in ons eten terechtkomen, aan het overmatig gebruik van vaatwas-, kuis- en reinigingsproducten in huis, aan de toenemende luchtvervuiling door uitlaatgassen van auto's, verbrandingsovens, fabrieken, aan pesticiden en bestrijdingsmiddelen in onze landbouw, aan nieuwe plasticsoorten zoals polymeren in allerlei gebruiksvoorwerpen (zelfs in speelgoed), aan nieuwe isolatiematerialen in onze huizen (bv. poly-urethaan), enz.

Door een “overdosis” aan chemische producten in ons milieu zouden sommige mensen een overgevoeligheid ontwikkelen, zodat ze op de duur zelfs geen alledaagse onschadelijke geuren (zoals bv. parfums) meer kunnen verdragen of al

klachten krijgen bij het inademen van met uitlaatgassen licht vervuilde stadslucht.

Lees nu het verhaal van Eric in de bijgevoegde UZ–gezondheidsbrief en daarna het doel van deze studie.

TEXT 2

Nr 89
Februari 1999

Gezondheidsbrief

UNIVERSITAIRE ZIEKENHUIZEN K.U. LEUVEN • NIEUWSBRIEF OVER ZIEK ZIJN, VOORKOMEN EN GENEZEN

VERDER IN DIT NUMMER

4 Bij de dood van twee kinderen

5 Vitiligo, storende witte vlekken op de huid

8 KORT :
- Astma en toch een medaille
- Een brutale aanleiding om te stoppen met roken

DE BIJSLUITER :

De breekbare nek-wervels

10 Welke gevolgen ?

11 Na een val, altijd opletten !

11 Heelkundige en andere behandelingen

Abnormaal ziek door chemische stoffen

Sommige mensen beweren dat ze overmatig gevoelig zijn voor allerlei chemische stoffen. Deze zouden bij hen een hele reeks klachten veroorzaken. Een aantal mensen spreekt zelfs van allergie, maar dit is erg twijfelachtig. De typische symptomen van een allergische reactie ontbreken immers meestal. Dit betekent echter niet dat er geen probleem is, integendeel.

In deze tijden van milieuvervuiling heeft het begrip 'chemische stof' voor veel mensen een zeer negatieve bijklank gekregen. Dit is begrijpelijk, maar tegelijk ook bizar, want het is niet duidelijk wat met die woorden bedoeld wordt. Sommigen mensen verwijzen ermee naar stoffen die industrieel vervaardigd worden en dit in tegenstelling tot stoffen die uit de vrije natuur afkomstig zijn. De bijhorende veronderstelling is dan vermoedelijk dat de ene slecht en de andere goed zijn. Dit is echter enigszins kortzichtig, vermits ook veel natuurlijke stoffen schadelijk of zelfs ronduit gevaarlijk zijn voor de gezondheid.

Bovendien bestaan er ontzaglijk veel verschillende chemische stoffen en hebben ze zeer uiteenlopende invloeden op het menselijke lichaam. Sommige zijn giftig, zelfs in een minimale dosis. Andere zijn onschuldig of hebben zelfs een gunstig effect, bv. voedings- of geneesmiddelen (tenminste in de juiste dosis).

Toch beweren sommige mensen dat ze overgevoelig zijn voor *chemische stoffen*. Deze veroorzaken bij hen uiteenlopende klachten; van duizeligheid, ademnood, hartkloppingen tot chronische vermoeiheid, mentale problemen, enz. Een kort verhaal helpt duidelijkheid brengen.

Het verhaal van Eric

Eric klaagt reeds enige tijd dat hij zich niet goed voelt wanneer hij blootgesteld wordt aan chemisch ruikende producten. Wanneer hij in een lokaal komt waar recent zulke producten gebruikt werden, krijgt hij last van ijlhoofdigheid, evenwichtsstoornissen, beklemming en ademnood, wordt het hem zwart voor de ogen, wordt hij mistroostig, vloekt alle kracht uit hem weg, enz. Deze toestand houdt enige uren aan en na-dien voelt hij vaak hoofdpijn opkomen die soms enkele dagen aanhoudt. Liefst blijft hij dan thuis. Hij woont in een landelijke gemeente. Hij werkt graag in de tuin en voelt zijn krachten dan snel terugkomen. "De natuur geneest zichzelf", zegt hij.

De problemen begonnen 5 jaar geleden. Eric werkte als bediende op een bedrijf dat siliconen aanmaakt. Hij moest onder meer geregeld naar de ateliers en magazijnen voor controles en adviesverlening. Alle werknemers uit de ateliers en magazijnen moesten geregeld op medisch onderzoek, Eric dus ook. Er werden nooit ernstige problemen gemeld.

De klachten bij Eric kwamen geleidelijk op. Eerst waren ze nog draaglijk, maar ze werden steeds meer hinderlijk. Tegelijk begon bij alle geuren te mijden die hem de klachten bezorgden. Hij bleef zoveel mogelijk weg uit de ateliers en magazijnen, wat uiteraard zijn werkstoede. Hij meld-

IN VOLGENDE NUMMERS

- Ziek door stress ?
- Schimmels in huis
- Niet-ingedaalde teelballetjes
- Hoe verwijder ik een splinter ?

Gezondheidsbrief

de zich ook geregeld ziek. Uiteindelijk nam het probleem zulke vormen aan dat hij ontslagen werd.

Sindsdien is hij werkloos, maar het probleem is er niet op verbeterd. Allerhande producten die volgens hem een chemische geur hebben, moesten het huis uit. Verf, bruine zeep, brandalcohol, poetsmiddelen, toiletblokjes en zelfs parfums; het is allemaal giftig. Als er gepoetst wordt, gaat hij het huis uit, zulke vormen heeft zijn vermijdingsgedrag aangenomen.

Die verhouding kan extreem lijken, maar het is het niet. Er zijn er nog andere, meer of minder ernstig, maar nagenoeg allemaal vertonen ze een gelijkaardig patroon.

Op een of andere wijze ontstaat bij deze mensen op een gegeven moment de indruk dat zij klachten krijgen wanneer ze blootgesteld worden aan chemische stoffen. De klachten kunnen van de meest uiteenlopende aard zijn. De lijst is dan ook indrukwekkend lang: duizeligheid, verwarren, geheugenverlies, wisselvallige emoties, prikkelbaarheid, karakterlele en persoonlijkheidsveranderingen, algemene verzwakking, lusteloosheid,

vermoeidheid, gebrek aan eetlust, ademnood, hoesten, hartkloppingen, pijn in de borststreek, prikkende ogen, spanningen, hoofdpijn, misselijkheid, concentratiestoornissen, een verstoorde spijsvertering, spierpijn, enzovoort.

Men vindt bij een lichamelijk onderzoek geen enkele afwijking of stoornis die de klachten kan verklaren. Alle organen en weefsels werken normaal.

Gewoonlijk blijft de hinder in de beginperiode nog beperkt, maar doorgaans is er een **tendens tot vergroting**. De klachten nemen toe en ontstaan op steeds meer stoffen terwijl dit oorspronkelijk slechts op enkele stoffen was. Vaak reageert men ook op stoffen die geen enkel verband met elkaar hebben. Uiteindelijk krijgt men zelfs problemen met stoffen die door de meerderheid van de bevolking zonder moeite verdragen worden, zoals bv. parfum, poetsluchtjes, een flard sigarettenrook (dit neemt niet weg dat veel mensen zich kunnen ergeren aan zulke luchtjes).

Sommige mensen hebben voortdurend last van deze klachten. Bij anderen komen en verdwijnen ze naargelang de blootstelling.

Tegelijk met de uitbreiding van de klachten begint men de mogelijke blootstelling vaak te **vermijden** en dit vermijdingsgedrag kan ook stelsmatig uitbreiden.

Lastige mensen

Mensen met angst voor chemische stoffen staan vaak bekend als **lastige mensen**. Ogenschijnlijk is er immers niets mis met hen. De arts kan geen duidelijke problemen vinden.

Vaak lopen ze ook verschillende artsen langs, zeker wanneer ze geen arts vinden die geneigd is hen op hun woord te geloven of wanneer ze een arts treffen die kritisch staat tegenover hun klachten.

Wanneer ze een arts vinden die in de richting van overgevoeligheid en allergische reacties begint te zoeken, verleent deze daarmee als het ware "het bewijs" dat er wel degelijk iets ernstigs met hen aan de hand is.

Deze wirwar van klachten wordt vaak in één adem vernoemd met andere problemen waarvoor op het eerste gezicht evenmin een duidelijke

verklaring is, zoals het chronisch vermoeidheidssyndroom, spanningsstoornissen, enz.

Soms wordt er ook naar verbanden gezocht met aandoeningen waarvoor men nog geen definitieve verklaring heeft, zoals sommige maag- en darmklachten, multiple sclerose, enz. Zulke verbanden blijven nagenoeg steeds beperkt tot vage veronderstellingen zonder harde bewijzen.

Het is te eenvoudig om al deze problemen onder de mat te vegen met de noemer *mode*, maar de algemene belangstelling, bv. in kranten of op tv, oefenen er zonder twijfel invloed op uit.

Dit neemt niet weg dat chemische stoffen wel degelijk problemen kunnen veroorzaken, zoals bv. een vergiftiging, aantasting van de zenuwen, enz. Het **organisch psychosyndroom voor solventen** bv. wordt veroorzaakt door oplosmiddelen zoals die in verf terug te vinden zijn. Dit syndroom gaat gepaard met een onomkeerbare hersenbeschadiging die vergelijkbaar is met een voorloper van seniliteit en dementie. Deze beschadiging is echter aantoonbaar.

Welke verklaring?

Er bestaat onenigheid over de oorsprong en de mechanismen achter de klachten waar deze mensen mee worstelen. De verklaringen kunnen in grote lijnen in twee groepen onderverdeeld worden.

Lichamelijke verstoring

Volgens sommige onderzoekers zijn bepaalde mensen extra gevoelig voor allerlei chemische stoffen. Zulke stoffen komen tegenwoordig nagenoeg overal in kleine hoeveelheden voor, bv. in de lucht, in de voeding (o.a. via verpakkingsmiddelen), enz. Vooral de lange blootstelling en het gezamenlijke effect van de opgestapelde stoffen zou voor de problemen zorgen.

Deze theorie is weliswaar populair, maar er is geen degelijk bewijs voor geleverd. Bovendien komt dit verklaringsmodel niet altijd overeen met de vaststellingen, zoals bv. met het feit dat de klachten nagenoeg alleen feller worden als de chemische stoffen waargenomen kunnen worden. Stoffen die niet ruiken en onzichtbaar zijn, leveren immers zelden problemen op.

Geen allergie

De mensen met dergelijke problemen spreken zelf vaak van overgevoeligheid of van allergische reacties ("Ik ben er allergisch voor."). Een allergie is echter een zeer specifieke soort van reactie waarbij in het bloed typische stoffen gevormd worden. Deze worden bijna nooit teruggevonden in het bloed van mensen met een abnormale angst voor chemische stoffen. Buiten de enkele, eerder zeldzame uitzonderingen, is er bij deze mensen bijgevolg zeker geen sprake van een allergie.

Dit is niet zo eigenaardig. Bij een allergie is men doorgaans immers overgevoelig voor één specifieke stof en soms ook nog voor stoffen die zeer sterk op die eerste stof gelijken. Allergische reacties voor zeer veel stoffen van de meest uiteenlopende aard zijn niet bekend.

TEXT 3

Doel van deze studie

Wij gaan jou in deze studie chemische luchtsamenstellingen laten inademen. Deze wekken in hoge concentraties bij iedereen klachten op, maar bij MCS-patiënten soms ook al in lage concentraties, waarbij normaal nog geen klachten optreden. De concentratie die wij zullen gebruiken ligt daar tussenin. De klachten die zouden kunnen ontstaan gaan al na een paar minuten over, en de gassen zijn toxicologisch onschadelijk (het experiment werd goedgekeurd door de ethische commissie). En van de gasmengsels bevat stikstofhydride en ruikt eerder slecht.

We hebben deze concentraties ook al getest bij MCS-patiënten. In dit onderzoek willen wij onderzoeken welke effecten deze chemische mengsels hebben bij een normale populatie. Een ademhalingsbeurt duurt telkens iets meer dan een minuut en de registratie gebeurt d.m.v. een masker. De proefleider geeft aan wanneer je het masker mag afzetten. Nadien moet je telkens invullen of en welke klachten je zoal gevoeld hebt tijdens of vlak na de adembeurt. De proefleider zal altijd aangeven wanneer het masker terug mag opgezet worden.