INFORMATION TO USERS

This manuscript has been reproduced from the microfilm master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps. Each original is also photographed in one exposure and is included in reduced form at the back of the book.

Photographs included in the original manuscript have been reproduced xerographically in this copy. Higher quality 6" x 9" black and white photographic prints are available for any photographs or illustrations appearing in this copy for an additional charge. Contact UMI directly to order.

UMI

A Bell & Howell Information Company
300 North Zeeb Road, Ann Arbor MI 48106-1346 USA
313/761-4700 800/521-0600

Multiple Chemical Sensitivity:

A Test of the Olfactory-Limbic Model

by

Anne-Marie Brown-DeGagne

Submitted in partial fulfilment of the requirements for the degree of

Doctor of Philosophy

at

Dalhousie University

Halifax, Nova Scotia

(November 1997)

© Copyright by Anne-Marie Brown-DeGagne, 1997

National Library of Canada
Acquisitions and Bibliographic Services
395 Wellington Street
Ottawa ON K1A 0N4
Canada

Bibliothèque nationale du Canada
Acquisitions et services bibliographiques
395, rue Wellington
Ottawa ON K1A 0N4
Canada

Your file Votre référence

Our file Notre référence

The author has granted a non-exclusive licence allowing the National Library of Canada to reproduce, loan, distribute or sell copies of this thesis in microform, paper or electronic formats.

The author retains ownership of the copyright in this thesis. Neither the thesis nor substantial extracts from it may be printed or otherwise reproduced without the author's permission.

L'auteur a accordé une licence non exclusive permettant à la Bibliothèque nationale du Canada de reproduire, prêter, distribuer ou vendre des copies de cette thèse sous la forme de microfiche/film, de reproduction sur papier ou sur format électronique.

L'auteur conserve la propriété du droit d'auteur qui protège cette thèse. Ni la thèse ni des extraits substantiels de celle-ci ne doivent être imprimés ou autrement reproduits sans son autorisation.

0-612-36550-6

Canada

DALHOUSIE UNIVERSITY

FACULTY OF GRADUATE STUDIES

The undersigned hereby certify that they have read and recommend to the Faculty of Graduate Studies for acceptance a thesis entitled "Multiple Chemical Sensitivity: A Test of the Olfactory-Limbic Model"

by Anne-Marie Brown-DeGagne

in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

Dated: November 7, 1997

External Examiner

Research Supervisor

Examining Committee

Copyright Agreement Form
Dalhousie University

Date: 97/11/15

Author: Anne-Marie Brown-DeGagne

Title: Multiple Chemical Sensitivity:
A Test of the Olfactory-Limbic Model

Department of School: Department of Psychology

Degree: Ph.D. **Convocation:** October **Year:** 1998

Performance is herewith granted to Dalhousie University to circulate and to have copies for non-commercial purposes, at its discretion, the above title upon the request of individuals or institutions.

[redacted]
Signature of Author

THE AUTHOR RESERVES OTHER PUBLICATION RIGHTS, AND NEITHER THE THESIS NOR EXTENSIVE EXTRACTS FROM IT MAY BE PRINTED OR OTHERWISE REPRODUCED WITHOUT THE AUTHOR'S PERMISSION.

THE AUTHOR ATTESTS THAT PERMISSION HAS BEEN OBTAINED FOR USE OF ANY COPYRIGHTED MATERIAL APPEARING IN THIS THESIS (OTHER THAN BRIEF EXCERPTS REQUIRING ONLY PROPER ACKNOWLEDGEMENT IN SCHOLARLY WRITING) AND THAT ALL SUCH USE IS CLEARLY ACKNOWLEDGED.

Table of Contents

Table of Contents - Continued

List of Tables and Illustrations

Abstract

Thus far, three published studies have examined cognitive functioning in persons with Multiple Chemical Sensitivity (MCS). Cognitive impairments to substantiate the subjective complaints of individuals with MCS have not been found. No study, however, has yet examined the cognitive profile of MCS within the framework of Bell's Olfactory-Limbic Model. It predicts that cognitive weaknesses will be associated more with limbic (i.e., frontal and/or temporal lobe) regions of the brain than with non-limbic regions (i.e., posterior cortex). Matched MCS (N = 21), asthma (N = 21), and healthy control (N = 21) groups were tested on measures of cognitive functioning that have localizing value. Between-group comparisons showed that the MCS group performed as well as controls on all cognitive tasks. However, between-test comparisons showed that both the MCS and asthma groups performed significantly more poorly on tasks sensitive to frontal and temporal regions than to posterior regions. Subjective memory complaints were not related to memory task performance, but were related to anxiety and depression. Additional research is needed before concluding that the Olfactory-Limbic Model adequately describes the cognitive strengths and weaknesses of MCS. Confounding factors such as medication use, chronic illness, and environmental reactivity need to be considered. There is no evidence on norm-based cognitive measures that brain damage, per se, has occurred in MCS patients.

List of Abbreviations and Symbols Used

BAI = Beck Anxiety Inventory

BDI = Beck Depression Inventory

BFRT = Benton Facial Recognition Test

COWA = Controlled Oral Word Association

CNS = Central Nervous System

EI = Environmental Illness

MCS = Multiple Chemical Sensitivity

MOQ = Memory Observation Questionnaire

RMF = Recognition Memory Test For Faces

SOP = Self-Ordered Pointing Test

WAIS-R = Wechsler Adult Intelligence Scale-Revised

WMS = Wechsler Memory Scale

Acknowledgments

First, I thank my advisor Dr. Jeannette McGlone who has dedicated many hours to discussing research ideas, reviewing drafts of theses and papers, training me in clinical practice, and generally providing me with any number of opportunities to learn. Her knowledge, guidance, and expertise have been very much appreciated.

I feel fortunate to have also had the opportunity to work with my thesis committee members, Drs. Sherry Stewart and Richard Brown. Their comments on several drafts of this thesis helped me to clarify and expand upon my own interpretation of the findings. I thank them for the support they provided during several stages of the project.

Many groups within the community of Halifax took interest in this project and helped me to see it from start to finish. The Research Review Committee of the Environmental Illness Clinic, in particular Dr. Michelle Joffres and Tim Williams, reviewed the project proposal and provided me with valuable suggestions regarding subject recruitment and study design. In addition, the staff of the Environmental Illness Clinic graciously spread the word to potential study participants that I was conducting this study. The Asthma Self-Help Group, in particular Anna Freeman, also provided me with many contacts during this study's recruitment phase.

I also thank the many individuals who participated in this study. They not only gave up several hours of their time to complete the required tests and questionnaires, but they also took great interest in recruiting friends and family to participate. Their interest in my study was inspiring and I thank them for the time they spent discussing their research ideas.

I feel particularly fortunate to have known and worked with so many talented students in my program at Dalhousie University. I treasured the support and guidance I gained from them as a fellow student and look forward to many years as colleagues.

Finally, I thank my family whose relationships and outlook on life helped me to remember that, although academic accomplishments are important, friends and family are important too. I especially thank my husband Jean-Claude DeGagne. He, above all, has been my voice of reason during these past four years. His love, humour, and confidence in my ability to succeed have been wonderful.

Multiple Chemical Sensitivity: A Test of the Olfactory-Limbic Model

Chapter 1. Introduction

1.1 Multiple Chemical Sensitivity - Symptoms and Complaints

Multiple Chemical Sensitivity (MCS) is a term applied to individuals who experience a variety of symptoms when exposed to various environmental chemicals. Samples of such cases show a preponderance of middle-aged females who are well educated, in white collar professions, functioning at a relatively high level, and relatively free of a history of serious medical problems (Cullen, 1994). Individuals with this disorder note reactions, or sudden uncontrollable symptoms, in response to exposure to certain environmental stimuli. Provoking stimuli vary from person to person and include, among other substances, perfume, gasoline, smoke, cosmetics, food, water contaminants, and/or household cleansers (Meggs, Dunn, Block, Goodman, & Davidoff, 1996; Miller & Mitzel, 1995). Onset of the reactions may be insidious but often occurs in relation to some definable event such as a peak exposure to chemicals in the workplace, a large exposure to toxins in the environment, or exposure to fumes and other substances of a newly renovated building (Simon, Katon, & Sparks, 1990; Miller & Mitzel, 1995). Subsequent to the initial event, reactions typically involve several different systems such as respiratory, cardiac, gastrointestinal, musculoskeletal and dermal. Headache, fatigue, dizziness, weakness, irritability, memory loss, poor concentration, rashes, and upper respiratory difficulties are described as symptoms of MCS (Cullen, 1994). Most common, however, are those symptoms described as Central Nervous System (CNS) effects. CNS effects may include headache, dizziness, confusion, memory loss, and

sensory disturbances (Cullen, 1994, Miller & Mitzel, 1995).

1.2 Multiple Chemical Sensitivity - Definition

Labels such as "Environmental Allergy", "Chemical Hypersensitivity Syndrome", "Chemically Acquired Immune Deficiency Syndrome or Chemical AIDS", "Total Allergy Syndrome", "Mass Psychogenic Hysteria", "20th Century Disease", and "Multiple Chemical Sensitivity Syndrome" have all been applied to the disorder in which individuals experience heightened reactivity to low level chemicals. Each of these nosological labels reflects beliefs regarding the underlying cause and mechanism of the disorder. The lack of agreement on an operational definition, or even an appropriate label, for this condition has proved a hindrance to scientific analysis of the disorder and a limited understanding of the problem. To distinguish individuals with MCS from other individuals experiencing similar symptoms (e.g., fatigue, headache, dizziness, lack of concentration, memory loss) but labelled with diagnoses such as Chronic Fatigue Syndrome, an attempt has been made to define MCS in terms of attribution to environmental exposures (Guernsey, 1993).

Researchers such as Cullen (1987), Ashford and Miller (1991), and Nethercott, Davidoff, Curbow, and Abbey (1993), have acknowledged the importance of establishing a uniform case definition of the disorder. They have used the term Multiple Chemical Sensitivity Syndrome (MCS) and have developed operational definitions of this condition. Cullen (1987) defines MCS as:

"an acquired disorder characterized by recurrent symptoms, referable to

> multiple organ systems, occurring in response to demonstrable exposure to many chemically unrelated compounds at doses far below those established in the general population to cause harmful effects. No single widely accepted test of physiologic function can be shown to correlate with symptoms." (page 657)

According to this definition seven diagnostic features may be used in choosing cases. These features include the following (Cullen, 1987): (1) the disorder is acquired in relation to some documentable environmental exposure(s), insult(s) or illness(es); (2) symptoms involve more than one organ system; (3) symptoms recur and abate in response to predictable stimuli; (4) symptoms are elicited by exposures to chemicals of diverse structural classes and toxicologic modes of action; (5) symptoms are elicited by exposures that are demonstrable; (6) exposures that elicit symptoms must be very low, by which we mean many standard deviations below "average" exposures know to cause adverse human responses; and (7) no single widely available test of organ system function can explain symptoms.

MCS and disorders such as Environmental Illness, 20th Century Disease, Somatoform Disorder, and Post-traumatic Disorder (PTSD) are not, however, mutually exclusive. Cullen (1987) represents the overlap between MCS and other disorders through the use of Venn diagrams. In this conceptualization, MCS is contained within the broader spectrum diagnosis of "Environmental Illness" or "20th Century Disease", and overlaps slightly with Somatoform Disorder and PTSD. All individuals with MCS would also be classified as having Environmental Illness but only a portion of these individuals

would be considered to have a Somatoform Disorder. Similarly, only some individuals with MCS would be classified as having PTSD.[1]

Labelling an individual with MCS using Cullen's definition does not require objectively determining that exposures to chemicals cause symptoms and that symptoms recur and abate in response to predictable stimuli. Because the definition does not specify how reactivity to chemicals is assessed, the individual's self-report and attribution of reactions to chemicals is used in determining the presence or absence of the disorder (Doty, Deems, Frye, Pelberg, & Shapiro, 1988; Fiedler, Maccia & Kipen, 1992; Fiedler, Kipen, DeLuca, Kelly-McNeil, & Natelson, 1996).

Ashford and Miller (1991) believe that this reliance on self-report is insufficient. They propose a definition of MCS that is based on environmental testing.

> "The patient with multiple chemical sensitivities can be discovered by removal from the suspected offending agents and by rechallenge, after an

---

1

Changes in Criterion A for PTSD from the DSM-III-R to the DSM-IV (1994) increases the potential overlap between this disorder and MCS. According to the DSM-IV criterion A for PTSD, " the person has been exposed to a traumatic event in which both of the following were present: (1) the person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others, and (2) the person's response involved intense fear, helplessness, or horror. (Page 427-428). The preceding DSM-III-R criterion A stated that "The person has experienced an event that is outside the range of usual human experience and that would be markedly distressing to almost anyone, e.g., serious threat to one's life or physical integrity; serious threat or harm to one's children, spouse, or other close relatives and friends; sudden destruction of one's home or community; or seeing another person who has recently been, or is being, seriously injured or killed as a result of an accident or physical violence." (Page 250). The revised PTSD criterion A no longer requires the event to "be markedly distressing to almost everyone" or outside the range of usual human experience, and hence places greater emphasis on an individual's perception of the event rather than the actual event.

> appropriate interval, under strictly controlled environmental conditions. Causality is inferred by the clearing of symptoms with removal from the offending environment and recurrence of symptoms with specific challenge." (page 43)

Ashford and Miller's definition results in three main criteria to be used in selecting cases for research purposes (Ashford & Miller, 1991) and include: (1) Sensitivity to chemicals; (2) Sensitivity in one or more organ systems; (3) Symptoms and signs wax and wane with exposures. In contrast to Cullen (1987), these investigators do not believe that it is necessary to identify a chemical exposure associated with the onset of MCS in order to identify an individual with this disorder. Unlike Cullen (1987), Ashford and Miller (1991) outline neither criteria regarding the nature of the chemicals that provoke symptoms in an individual, nor the lack of tests available to explain the symptoms. However, similar to Cullen (1987), Ashford and Miller (1991) note that a definition of MCS should require sensitivity to chemicals, and recurring and abating of symptoms that involve more that one organ system. Ashford and Miller (1991) also note that preexistent or concurrent conditions such as asthma, arthritis, somatization disorder, or depression should not be used as exclusionary criteria.

In addition to the operational definitions provided by Cullen (1987) and Ashford and Miller (1991), Nethercott et al. (1993) have attempted to identify those diagnostic criteria used by experts as their major criteria for categorizing an individual as having MCS. One hundred and forty-eight American physicians were sent questionnaires assessing criteria used to diagnose MCS. Physicians were considered experts in the field

if they: published an article on the syndrome, served on a task force or committee regarding MCS, or were members of an editorial board, executive committee, or board of directors of a professional body concerned with MCS or a related topic. Fifteen different diagnostic criteria were provided in the questionnaire. The criteria were also grouped according to thematic content. Groupings consisted of: Nature of incitants provoking a response (2 criteria), Biological plausibility--identifiable exposure (3 criteria), Topology of responses (3 criteria), Persisting nature of perceived changes (1 criteria), Differential diagnosis (1 criteria), and Subjective responses and ameliorative actions of affected individuals (4 criteria). Each physician was asked to rate the criteria as major, minor or irrelevant in diagnosing MCS. Five of fifteen criteria were identified as major for diagnosing MCS by greater than 50% of the physicians. All five criteria were based on self-reports and included: (1) symptoms are reproducible with exposure; (2) condition is chronic; (3) low levels of exposure result in manifestations of the syndrome; (4) symptoms resolve with removal of incitants; and (5) responses occur to multiple, chemically unrelated substances.

According to the study conducted by Nethercott et al. (1993), current methods of diagnosing MCS in the clinic do not rely on environmental challenges. The criteria do, however, overlap with those proposed by Cullen (1987). At present, Ashford and Miller's (1991) operational definition of MCS requiring objectively identifying MCS through the use of environmental challenges is inconsistent with current practices of physicians who treat this disorder. Whether a given patient meets the operational definition of MCS outlined by Ashford and Miller (1991) can only be ascertained in centres specifically

designed to challenge individuals in controlled testing chambers. Thus far, however, results of double blind provocation studies have failed to find reliable reactions in individuals with MCS and food sensitivity (Jewett, Fein, and Greenberg, 1990; Staudenmayer, Selner, and Buhr, 1993). The failure of challenge studies to produce reliable patterns of symptom elicitation in individuals with MCS may indicate a role for expectancy (i.e., placebo response). If the unreliable responses are due to expectancy, then provocation challenges could be used to exclude those MCS cases who do not respond reliably (Staudenmayer et al., 1993). The requirement of provocation challenge to select cases is based on the assumption that only cases with a biological basis are "real" cases. At present, however, it is premature to use such challenge techniques to select cases for research purposes. Research has not been able to delineate if it is expectancy or the inadequate testing techniques that are producing the unreliable responses (Staudenmayer et al., 1993). Namely, provocation studies have been criticized for their inability to create adequately "clean" environments and for the lack of agreement regarding dose or duration of exposure (Jewett et al., 1990; Staudenmayer et al., 1993).

Cullen's definition of MCS is frequently identified as that used to select MCS cases in research settings (e.g., Doty et al., 1988; Fiedler et al., 1992; Fiedler, Kipen, & Kelly-McNeil, 1992; Fiedler et al., 1996; Sparks, Daniell, Black, Kipen, Altman, Simon, & Terr, 1994). This fact, together with the findings on current clinical practice from Nethercott et al. (1993), suggests that the use of Cullen's definition to identify cases for research purposes provides consistency not only across studies but between research and clinical practice as well.

Kipen, Hallman, Kelly-McNeil, and Fiedler (1995) developed a questionnaire called the Substance Checklist to assess the presence or absence of chemical sensitivity. The questionnaire consists of a list of 122 different substances. MCS is determined to be present or absent based on the number of different substances an individual endorses as provoking symptoms. Kipen et al. (1995) demonstrated that, although some individuals who do not have MCS (i.e., asthma, occupational and environmental complaints, and healthy controls) report reacting to a high number of substances (i.e., at least 23), as a group, individuals with MCS (i.e., Females: $\underline{M} = 41.8$; $SD = 5.5$; Males: $\underline{M} = 33.8$; $SD = 6.5$) reported significantly more substances that cause them to react than comparison groups (e.g., Female Asthmatics: $\underline{M} = 32.8$; $SD = 4.9$; Male Asthmatics: $\underline{M} = 18.6$; $SD = 4.6$; Female Surveillance Patients: $\underline{M} = 6.7$; $SD = 1.1$; Male Surveillance Patients: $\underline{M} = 3.8$; $SD = 0.4$). The Substance Checklist, therefore, can be used in conjunction with Cullen's criteria to provide greater sensitivity and specificity in choosing MCS cases (Kipen et al., 1995).

1.3 Theoretical Mechanisms of Multiple Chemical Sensitivity

By definition, the symptoms of MCS are elicited by environmental exposures to chemicals. However, the mechanism by which chemical exposure provokes symptoms of MCS is unclear. No one theory has been able to fully explain the phenomenon. Several theories, including psychogenic, psychophysiologic, and physiologic, have been proposed.

Psychogenic Theories

Several researchers believe that MCS is a manifestation of traditional psychiatric disorders such as depression, anxiety and somatization disorders and/or that MCS develops in individuals with predisposing psychiatric conditions (Black, Rathe, & Goldstein, 1990; Brodsky, 1983; 1987; Schottenfeld & Cullen, 1985; Simon, Katon, & Sparks, 1990; Staudenmayer, Selner, & Selner, 1993; Stewart and Raskin, 1985; Terr, 1986). Case histories, psychiatric and psychological measurement techniques, and medical assessments have all been used to examine psychopathology in MCS.

Two studies have used case histories to examine psychopathology in individuals reporting multiple symptoms attributable to the environment (Brodsky, 1983; Stewart & Raskin, 1985). Brodsky (1983) studied a sample of 70 individuals using a 2 to 3 hour psychiatric examination. All participants: 1) believed they had been injured by inhaling noninfectious, airborne substances in the workplace; 2) filed for Workers' Compensation benefits for the injury; and 3) showed no evidence on traditional physical and psychiatric examination of physical damage or physical functional impairment attributable to the alleged exposure in the workplace. Individuals were excluded if the claim of disability matched the evidence of physical impairment from exposure at work. The method by which claims were determined to match evidence of physical impairment was not outlined.

Based on the interviews with each participant, Brodsky (1983) concluded that the symptoms reported by the participants could best be understood in terms of somatoform

illnesses. The basis for this diagnosis was not outlined. According to the DSM-IV (1994), somatoform illnesses are defined by the presence of physical symptoms that suggest a general medical condition and are not fully explained by a general medical condition, by the direct effects of a substance, or by another mental disorder. Thus, the author's appraisal that most medical and psychiatric examinations of the participants failed to find any objective basis to substantiate the participants' claims of physical injury was likely paramount to the diagnosis.

Stewart and Raskin (1985) studied 18 patients with 20th Century Disease who had been referred by physicians or lawyers to a psychiatric service within a tertiary care hospital. Case histories were assessed by means of an unstructured psychiatric interview. Diagnostic criteria were not provided. All patients had been referred for psychiatric consultation and all were diagnosed by the authors with a recognizable psychiatric disorder. The authors reported that 7 of the patients exhibited somatoform disorders (i.e., 5 somatization, 1 conversion, and 1 hypochondriasis), 10 suffered from a psychosis or an affective or anxiety disorder (i.e., 1 schizophrenia, 2 atypical psychosis, 1 major depression, 2 dysthymia, 2 panic disorder, 2 generalized anxiety disorder), and 1 had a personality disorder (i.e., antisocial) and was malingering. Stewart and Raskin (1985) thus concluded that, "Twentieth century disease appears to be not a new illness but rather a fashionable name for a condition known to physicians for centuries." (Page 1006).

In addition to the case history studies, two studies used psychiatric or psychological measurement techniques to assess individuals with reported multiple symptoms attributed to the environment (Black et al., 1990; Simon et al., 1990). Black et

al. (1990) used the Diagnostic Interview Schedule to assess 23 individuals with Environmental Illness (EI) and 46 age and sex matched community controls. Individuals with EI were recruited from EI support groups, psychiatric and occupational medicine clinics, hospital newsletters and health food stores. Results from this study indicated that 15 of the 23 (i.e., 65%) EI subjects met criteria for a current or past mood (N = 9), anxiety (N = 10), or somatoform disorder (N = 4), compared with 13 of the 46 (i.e., 28%) controls. The researchers thus concluded that "patients receiving this diagnosis may have one or more commonly recognized psychiatric disorders that could explain some or all of their symptoms." (Page 3166).

Simon et al. (1990) studied thirty-seven plastic workers who complained of physical symptoms attributable to their workplace. All subjects completed a structured diagnostic interview (Diagnostic Interview Schedule) and self-report measures of somatization and psychopathology (Symptom Checklist 90 - Revised, Personality Diagnostic Questionnaire, Whitely Index, Barsky Amplification Scale). Of the 37 individuals studied, 13 were considered to have EI as measured by a 4 item survey of symptoms occurring in response to common environmental exposures. Individuals were considered to have EI if they answered yes to three or more of the following questions: 1) Do you now need to follow any special diet because of chemical or food sensitivity?, 2) Do you now take special precautions in your home or home furnishings (furniture, drapes, carpets) because of chemical sensitivity?, 3) Do you now need to wear particular clothes because of chemical sensitivity?, and 4) Do you have trouble shopping in stores or eating in restaurants because of chemical sensitivity? Individuals with EI scored significantly

higher on all measures of prior psychopathology (i.e., DIS anxiety, depression, medically unexplained symptoms and somatization trait) and current measures of depression (i.e., SCL-90-R depression scale) than those without EI. Also, individuals with EI scored significantly higher on the Barsky Amplification Scale, the Whitely Index, and the SCL-90-R Somatization Scale than individuals without EI. The authors concluded, "these findings suggest that psychological vulnerability strongly influences chemical sensitivity following chemical exposure." (Page 901).

Schottenfeld and Cullen (1985), Staudenmayer et al. (1993) and Terr (1986) used medical and psychological measurements to assess individuals with multiple symptoms attributed to the environment. Schottenfeld and Cullen (1985) reviewed medical charts of an occupational medicine program and identified 21 patients who were severely disabled because of multiple or vague recurrent or persistent somatic symptoms for which no organic etiology had been determined. Based on review of their medical records, Schottenfeld and Cullen (1985) concluded that seven of the patients had atypical PTSD, three patients had typical PTSD, and the remaining 11 patients had somatoform disorders, according to DSM-III criteria. Atypical PTSD was considered to differ from typical PTSD only in aspects of the reexperiencing of the traumatic event. Namely, "in the typical form of the disorder, reexperiencing occurs in the form of repeated recall or recurrent, painful, intrusive recollections of the event or in dreams or nightmares about the event. In the atypical form, patients repeatedly reexperience the same bodily state or specific somatic symptoms initially experienced at the time of the event and do not report recollections of the event in words, thoughts, or images." (Page 199).

Staudenmayer et al. (1993) studied 63 patients with polysomatic symptoms attributed to sensitivity to multiple chemicals. For comparison, they also studied 64 control patients who had definable chronic symptoms, had an identifiable psychologic disorder on Axis I of the DSM-III-R (American Psychiatric Association, 1987), and whose complaints were not attributed to multiple chemicals or foods. Medical and psychological evaluations were completed. The psychological evaluation consisted of an undefined diagnostic interview and a self-report questionnaire on family of origin issues (Lazarus, 1980). Sexual abuse was defined as actual intercourse and physical abuse was defined as severe physical trauma with life-threatening intent. Thirty individuals in the experimental group and 36 controls then entered long-term psychotherapy. Among the individuals who entered long-term psychotherapy, the prevalence of physical and sexual childhood abuse was significantly higher among women who attributed their symptoms to environmental or chemically related illness (N=20) (50 % physical abuse, 60 % sexual abuse) than female controls (N=25) (12% physical abuse, 25% sexual abuse). The prevalence of physical and sexual childhood abuse did not significantly differ between men who attributed their symptoms to environmental or chemically related illness (N=10) (20% physical abuse, 10% sexual abuse) and male controls (N=11) (27% physical abuse, 0% sexual abuse). The authors thus concluded that "these data suggest that somatization may reflect sequelae of childhood abuse and may play an important role in the illness experienced by women who believe they are sensitive to environmental chemicals." (Page 538).

Terr (1986) analysed medical records, medical histories, and findings from

physical examinations and laboratory tests of 50 patients referred for evaluation of a clinical ecology diagnosis of environmentally induced illness caused by environmental chemicals and/or foods. Of the 50 patients studied, a subgroup of 31 individuals was identified in which multiple symptoms were evident. Terr (1986) reported that "these patients had clinical features of hypochondriasis, somatization, conversion hysteria, anxiety, depression and obsessive behavior...The subgroup of 31 patients with multiple symptoms most likely of psychological origin corresponds to the type of patient described repeatedly in the clinical ecology literature." (Page 149). Although the method by which these diagnostic features were assessed was not outlined, Terr (1986) may have used the DSM-III criteria as he references this source after making the above statement in the discussion.

Thus, these seven studies (Brodsky, 1983; Stewart & Raskin, 1985; Black et al., 1990; Simon et al., 1990; Schottenfel & Cullen, 1985; Staudenmayer et al., 1993; Terr, 1986) form a body of literature that states MCS is best understood as a form of psychiatric disturbance. Davidoff and Fogarty (1994), however, reviewed the research literature on psychogenic origins of multiple chemical sensitivity and noted several problems related to sample selection, measurement, and study design.

Sample selection problems were evident in several studies. First, Schottenfeld and Cullen (1985) used a chart review technique to select and review cases. Because information was limited to that reported in the charts, conclusions may not adequately reflect all pertinant facts regarding each case. Second, at least a portion of the chemically sensitive sample was recruited from psychiatric clinics in the studies conducted by Black

et al. (1990), Brodsky (1983) and Stewart and Raskin (1985). Selecting cases from psychiatric clinics potentially biassed the research towards finding psychiatric disturbances. Third, conclusions were based on findings of small sample sizes in the studies reported by Simon et al. (1990) and Stewart and Raskin (1985). Results from small sample sizes may not generalize to other MCS groups. Finally, all studies, with the exception of Simon et al. (1990), failed to assess the presence of chemical sensitivity by means of clear criteria. Selection criteria were vaguely described; criteria used to identify chemical sensitivities by clinical ecologists, physicians, or patients themselves were not identified.

A second problem evident in several of the studies related to the use of psychological measurement instruments that could not distinguish between psychopathology and unexplained medical symptoms. Davidoff and Fogarty (1994) noted this problem to be evident in the measures used by Simon et al. (1990), Brodsky (1983), Schottenfeld and Cullen (1985), Terr (1986) and Stewart and Raskin (1985). Davidoff and Fogarty (1994) concluded that, "given somatic symptoms usually inflate scores on tests of psychopathology, psychometric instruments that avoid questions about somatic symptoms.... are better choices for studying psychopathology in a condition presenting with medical symptoms." (Page 319). The outcome on psychometric instruments such as questionnaires, unstructured and structured interviews, as well as chart reviews could potentially be biased toward finding psychopathology in medical populations by the inclusion of somatic items.

Study design problems were observed in all studies described above. Cause and

effect relationships were proposed by the authors where none were justified. No study was designed to directly test a cause and effect relationship between psychopathology and MCS, yet the authors chose to discuss their data as supportive of psychogenic explanations. Davidoff and Fogarty (1994) noted that "plausible illness-related explanations for the psychiatric profile - for example, responses to environmental chemical triggers or adjustment to a chronic, distressing, and isolating illness - were not explored adequately by any author." (Page 320)

To date, research on the psychogenic origins of MCS has lead to the conclusion that MCS may best be understood as a psychiatric disorder (Hartman, 1995). This conclusion, however, is questionable given the flaws in sample selection, measurement, and study design evident in these studies. The conclusion that elevated levels of psychiatric symptoms are often observed in individuals with MCS is justified. However, the nature of these disturbances, including whether they are a cause of MCS, a result of MCS, or an effect of inappropriate measurement instruments, has yet to be adequately tested.

Psychophysiologic Theories

Conditioning

Bolla-Wilson, Wilson, and Bleecker (1988) proposed a classical conditioning model to explain the development of MCS. Bolla-Wilson et al. (1988) hypothesized that conditioning was the causal mechanism for prolonged physical symptoms and sensitivity to common environmental substances. Initial pairings of an odour (conditioned stimulus)

with a toxicant (unconditioned stimulus) produced symptoms (unconditioned response). Subsequently, an odour would elicit symptoms (conditioned response) in the absence of any toxicant.

Bolla-Wilson et al. (1988) reported on two cases believed to highlight the potential for classical conditioning mechanisms to play a role in the development of MCS. In light of their conditioning model, they employed a cognitive-behavioural therapy approach with one of their cases to extinguish the conditioned response. Treatment involved restructuring his maladaptive negative cognitions which were related to the exposure in combination with systematic desensitization techniques. The authors report that some efficacy for systematic desensitization techniques to improve symptoms was found after two treatment sessions (i.e., the participant was then able to cut his grass and pump his own gas). However, after two sessions, the individual terminated therapy for unknown reasons, making preliminary information regarding long-term outcome of this technique unavailable.

Experimental studies have not yet been conducted to assess the classical conditioning model of MCS. Furthermore, the conditioning model needs to be modified to account for situations in which symptoms of MCS develop to substances that have minimal or no odour (Staudenmayer, 1997). The conditioning model proposed by Bolla-Wilson et al. (1988) cannot do so as presently described.

Physiologic Theories

Immune Theory

Clinical ecologists teach that MCS is due to exposure to environmental chemicals (Ashford & Miller, 1991; Bell, 1982; Randolph, 1978; Rea, 1978). Immunologic mechanisms have been proposed, but no supportive findings have been demonstrated in group studies (Fiedler et al., 1992; Simon, Daniell, Stockbridge, Claypoole, & Rosenstock, 1993; Terr, 1986).

Two case series (Fiedler et al., 1992; Terr, 1986) and one case-control study (Simon et al., 1993) have been conducted to assess the role of immunologic abnormality in MCS. Fiedler et al. (1992) studied 11 individuals selected from cases referred to their Environmental and Occupational Health Clinical Centre who met Cullen's (1987) definition of MCS and who did not have physical disorders or psychiatric conditions (past or present) that could explain their symptoms. Absence of physical or psychiatric disorders was determined by a self-report medical questionnaire. Immunologic evaluation (i.e., complete blood cell count, humoral immunity evaluation, Type I hypersensitivity evaluation, cell-mediated immunity evaluation) revealed that, "although there were scattered out of range values, no significant or consistent abnormalities of immunologic function were detected." (Page 533).

Terr (1986) reviewed 50 cases seeking Workers' Compensation benefits for symptoms they attributed to workplace toxicant exposures. Immunologic evaluations revealed that "serum levels of immunoglobulins and complement, and circulating lymphocyte, B-cell, T-cell, and T-cell subset counts were not significantly abnormal."

(Page 145).

Finally, Simon et al. (1993) used a case-control comparison design to assess immunologic factors in MCS. Forty-one individuals with chemical sensitivities and 32 control patients with chronic musculoskeletal injuries were assessed. Immunological assessments were performed by a commercial laboratory with special interest in the evaluation of chemical sensitivity. Personnel were blinded to case/control status. Simon et al. (1993) reported that "immunologic testing did not differentiate patients with chemical sensitivity from controls. The only difference noted (lower interleukin-1 generation among cases) appeared attributable to laboratory methods." (Page 97). Interleukin levels were later found to be associated with evaluation date and not with the presence of MCS. Thus, although immunologic mechanisms have been proposed to explain MCS, group studies have failed to demonstrate consistent abnormalities.

Neurotoxicological Theory

Bell (1982) proposed a mechanism of MCS that targets the limbic system. She termed this model the Olfactory-Limbic Model of MCS (Bell, Miller & Schwartz, 1992). This theory proposed that exposures to odours and respiratory irritants may precipitate both physiologic and psychological symptoms through interactions between the nervous and endocrine systems. Bell et al. (1992) proposed that neurotoxic chemicals target the brain's limbic system through the olfactory bulbs. Direct access to the limbic system may occur via the spinal fluid in the arachnoid spaces of the olfactory bulbs. The limbic system, located within the frontal and temporal lobes, includes the amygdala,

hippocampus, cingulate gyrus, fornix, and hypothalamus. Attentional processes, memory functions, affect and drive states, and olfaction are associated with the limbic system (Lezak, 1995).

Bell (1992) has derived several bases on which she believes the Olfactory-Limbic model is an adequate model of MCS. First, any model of MCS must consider the biological, psychological, and social factors involved in the disorder. It is too simplistic to state that the disorder is either psychogenic or physiological. Bell (1992) proposed that the CNS, in particular the olfactory and limbic systems, is the region in which to examine the convergence of biological, psychological, and social factors in MCS. She proposed the CNS, and especially the olfactory and limbic systems, based on six different points:

1. The CNS receives input and sends out information to many other systems.
2. Pesticides and solvents have effects on CNS functions.
3. Airborne chemicals interact with the brain through the olfactory system.
4. The limbic system regulates many different functions.
5. Unipolar and bipolar depression, panic and other anxiety disorders and schizophrenia may result from dysfunction of the limbic system.
6. Damage to the hippocampus is a feature of dementia.

Bell (1992) also noted that individuals who themselves or their family have histories of psychiatric disturbances may be most vulnerable to MCS. According to Bell (1992), the increased vulnerability in individuals with a history of psychiatric disturbance is due to their inherent brain dysfunction which make them more susceptible to low levels of environmental chemicals which in turn could worsen their dysfunction in brain

chemistry.

Olfactory pathway kindling and long-term potentiation are two mechanisms proposed to explain the phenomenon in MCS where an individual becomes sensitive to low dose exposures with symptoms in various body systems. According to Bell (1992), kindling "occurs when repeated subthreshold stimuli summate to trigger seizure activity in brain cells with previously normal activity." Long-term potentiation "involves persisting enhancement of synaptic response initiated by brief high-frequency stimulation of excitatory pathways at subictal levels." (Page 95). Bell noted (1992) that "it is also possible that chemical exposures which kindle certain limbic pathways could damage capacity for long-term potentiation in the hippocampus. Such events might in turn disrupt capacity for normal memory formation." (Page 96). The olfactory system affects limbic structures through its connections into the forebrain.

Bell et al. (1992) proposed that chemicals in the environment gain access to the CNS by way of the olfactory and limbic pathways. In the CNS, chemicals can induce long-term changes in limbic neuronal activity and overall cortical arousal levels. The changes in limbic neuronal activity and cortical arousal levels alter various behavioural and physiological functions within an individual to produce symptoms of MCS.

> "In the present model, subconvulsive chemical kindling in olfactory bulb, amygdala, and piriform cortex, as well as in hippocampus, would be the neurobiological mechanism that serves as amplifier for reactivity to low level chemical exposures and as an initial common pathway for a range of chemical phenomenology, including cognitive and affective dysfunctions.

> Derivative mechanisms would encompass neurophysiological (especially frontal and temporal dysfunctions), autonomic, endocrine, and immune pathways regulated by the limbic system and connected structures." (Page 221).

Rossi (1996) defines electrical kindling as, "the induction of generalized epileptic seizures following repeated electrical stimulation of brain tissue at levels initially insufficient to induce motor convulsions." (Page 89). Chemical kindling "refers to the induction of generalized motor seizures following repeated administration of chemical compounds at dose levels initially insufficient to induce motor convulsions." (Page 91). Adamec (1994) defines partial kindling as "repeated stimulation that lowers the electrical threshold to produce EEG seizures without producing motor convulsions." (Page 394).

In the Olfactory-Limbic Model kindling is described as "partial" kindling. According to Bell (1992), exposure to chemicals does not actually produce seizures within individuals with MCS. Rather, it is hypothesized that exposure to chemicals sensitizes the brain so that small amounts of chemical exposure can produce neurobiological changes within the brain. Individuals most vulnerable to the process where environmental chemical impact on affective, cognitive, and somatic dysfunctions through kindling mechanisms are those with a genetic disposition to psychiatric disorders.

The Olfactory-Limbic Model is a neurotoxicological model of MCS. It suggests that exposure to solvents has subsequent effects on the limbic system. Little research has been conducted to directly test this model in a sample with MCS. However, research conducted on the effects of known solvent exposure on olfactory and limbic structures as

well as research conducted on olfactory function in MCS provides some insights into the hypothesized exposure to brain related processes of the Olfactory-Limbic Model.

Although it is at present unclear how chemical exposure might cause MCS, research on solvent exposure has been used to explain some of the processes involved in this disorder (Bell et al., 1992). Ryan, Morrow, and Hodgson (1988) speculated that solvent exposure may affect the rhinencephalic structures of the brain which are the evolutionary precursor of the limbic system. Ryan et al. (1988) studied 17 workers with a documented history of exposure to mixtures of organic solvents. The workers attributed changes in their memory, concentration, and mood to solvent exposure. A typical complaint of these workers was cacosmia, or a heightened sensitivity to odours. Stepwise multiple regression analyses indicated that cacosmia was associated with poor performance on tests of verbal and visual memory. Based on these findings, Ryan et al. concluded that, "it would not be at all surprising to find anatomical and physiological evidence of limbic lobe damage in individuals who have experienced chronic occupational exposure to mixtures of organic solvents." (page 1445)

Evidence to suggest that olfactory processes may be affected in individuals with MCS is available from studies conducted by Doty et al. (1988) and Meggs and Cleveland (1993). Doty et al. (1988) found increased nasal resistance in individuals with MCS relative to healthy controls matched on age, sex, ethnic background, and smoking habits. However, olfactory thresholds were equivalent in the MCS and control groups. Doty et al. (1988) concluded that their results did not support the hypothesis that MCS is associated with greater olfactory threshold sensitivity, but did suggest decreased nasal

airway resistance. Meggs and Cleveland (1993) noted findings of edema, excessive mucus, a cobblestone appearance of the posterior pharynx and base of the tongue, focal areas of blanched mucosa, and mucosal injection in 10 individuals diagnosed with MCS according to Cullen's definition who were assessed on rhinolaryngoscopy. However, no consistent pattern of abnormalities were found among patients in this study and no case-control comparisons were made.

The Olfactory-Limbic Model has several strengths. First, the theory does not necessitate the need to partial psychogenic processes from physiological processes. Second, it provides a testable model of MCS. Neuropsychological tests, and/or other neurological investigations, can be used to assess the proposed limbic dysfunction hypotheses. Finally, it attempts to encompass and explain the variability of symptoms of MCS and the mechanism by which symptoms are amplified. Thus, the Olfactory-Limbic Model is a testable theory of MCS that, if supported, would help explain both the physiologic and psychiatric symptoms of the disorder.

1.4 Cognitive Deficits in Individuals Exposed to Solvents

At present, the mechanisms involved in the development of MCS are not understood. Some parallels, however, have been drawn between MCS patients and patients who have been exposed to solvents (Fiedler et al., 1992). For example, individuals who have been exposed to solvents report some of the same symptoms as MCS such as changes in mood, concentration problems, memory deficits, and a variety of somatic complaints (Hartman, 1992; White, Feldman, & Travers, 1990; White & Proctor,

1992). Due to the similarities in experienced symptoms and the belief that MCS may be caused by exposure to environmental toxins, it would be important to know if cognitive difficulties experienced by solvent-exposed individuals may be evident in MCS.

Several studies have been conducted to assess cognitive deficits of individuals exposed to solvents and other environmental toxins (for a review see Hartman, 1995; White et al., 1990; White et al., 1992). Neuropsychological tests and test batteries have been used to assess deficits and severity of impairments in individuals exposed to solvents (Morrow, Robin, Hodgson, & Kamis, 1992; Morrow, Ryan, Hodgson & Robin, 1990; Otto, Molhave, Rose, Hudnell, & House, 1990; Ryan et al., 1988; Savage, Keefe, Mounce, Heaton, Lewis, & Burcar, 1988). In general, solvent exposure (e.g., dry cleaning fluid, paint removers, paints, auto and aviation fuels, and adhesives in the shoe and book industries) has been associated with memory, attention, visuospatial, and cognitive efficiency impairments (Hartman, 1992) as well as disturbances in mood and personality (e.g., increased depression and anxiety and interpersonal alienation; Morrow, Ryan, Goldstein, & Hodgson, 1989).

Ryan et al. (1988) assessed 17 nonexposed control subjects and 17 solvent exposed workers with complaints of either cognitive or affective changes on the Pittsburg Occupational Test (POET) battery. The POET is a neuropsychological test battery that was developed to detect neuropsychological impairments following documented toxin exposures (Ryan, Morrow, Bromet, & Parkinson, 1987). The battery consists of learning and memory tests (Verbal Learning, Symbol-Digit learning, Recurring Words Test, Incidental Recall Test), visuospatial tests (WMS Form I Visual designs - immediate and

delayed recall, WAIS-R Block Design, Embedded Figures Test), attention and mental flexibility tests (WAIS-R Digit Span and Digit Symbol, Trail Making part B), tests of psychomotor speed (Grooved Pegboard, Trail Making part A, time to complete Embedded Figures Test), a test of general intelligence (WAIS-R Information, Similarities, Picture Completion), and a test of malingering (Benton Visual Retention Test). The tests of the POET battery have been delineated into five neuropsychological factors: (1) Learning and Memory, (2) Visuospatial, (3) Psychomotor Speed and Manual Dexterity, (4) Attention and Mental Flexibility, and (5) General Intelligence. In addition to the POET battery, Ryan et al. (1988) measured cacosmia or "nausea, headaches, and subjective distress in individuals exposed to neutral environmental odours." (page 1442). The presence of cacosmia was assessed with a series of structured interview questions. Individuals were determined to be cacosmic if they reported heightened sensitivity to certain odors and indicated that such odours provoked feelings of nausea and a desire to avoid them. The purpose of their assessment was first to determine if solvent exposed workers who complain of cognitive changes actually differ in performance on a battery of neuropsychological tests from demographically similar non-exposed controls. The second purpose was to examine interrelationships between neuropsychological functioning and exposure-related variables, including cacosmia. Results indicated that solvent exposed individuals performed significantly more poorly than controls on four of the five POET factors using Hotelling's T squared statistic. The only factor displaying no group differences was General Intelligence. An assessment of the individual neuropsychological tests indicated that exposed subjects performed significantly more

poorly than controls on the following: Incidental memory, Verbal learning, Delayed symbol-digit, Immediate visual reproductions, Delayed visual reproductions, Block design, Embedded figures - time, Trail making - part A, Grooved pegboard - dominant, and Trail making - part B. When the Bonferroni correction for multiple variables was applied to the data, only scores on the Immediate Visual Reproduction, Delayed Visual Reproductions, Trail making - part A, and Trail making - part B subtests remained significantly lower than controls for the solvent exposed group. Using a stepwise multiple regression, it was determined that cacosmia negatively affected performance on the verbal learning and immediate visual reproductions tests.

In 1990, Morrow et al. assessed 32 workers with a history of exposure to mixtures of solvents and 32 age and education matched controls on the POET battery. Based on the results of multivariate analyses of between group differences on each of the five neuropsychological factors of the POET, Morrow et al. (1990) concluded that solvent exposed individuals differed from controls on four of the five factors. Solvent exposed individuals performed significantly more poorly than normal controls on the Learning and Memory, Visuospatial, Psychomotor Speed and Manual Dexterity, and Attention and Mental Flexibility factors. Similar to the findings of Ryan et al. (1988), no significant differences were found between the groups on measures of General Intelligence.

Morrow et al. (1992) assessed memory and attention functioning in 40 workers exposed to organic solvents and 40 controls matched on age, education and Wechsler Adult Intelligence Scale - Revised (WAIS-R) Information. Tests included: Verbal-Verbal Paired Associate Learning Test, Symbol Digit-Paired Associate Learning Test, Wechsler

Memory Scale (WMS) - Logical Memories, Visual Reproductions, WAIS-R Digit Span, and the Four-Word short-term memory test. Morrow et al. (1992) found that the exposed group performed significantly more poorly on tests of digit span, learning and recall than the control group. If initial learning was considered, long-term recall was not impaired. The authors concluded that the memory systems most affected by solvent exposure were short-term and working memory, but not long-term memory. Morrow et al. (1992) also noted that "the poorer performance by exposed subjects on the attention and memory measures is not surprising, given that several authors have speculated that medial temporal structures, including the limbic system and basal ganglia, may be particularly compromised following solvent neurotoxicity." (Page 10).

The reviewed studies on cognitive deficits in solvent exposure indicates that groups exposed to solvents may experience problems in a variety of domains. Typically, deficits in initial learning of material was observed. No deficits in long-term memory were evident across studies.

As mentioned, individuals who have been exposed to solvents report some of the same symptoms as MCS such as changes in mood, concentration problems, and memory deficits (Hartman, 1992; White et al., 1992; White et al., 1990). However, as noted by Fiedler et al. (1992), the symptom complex, chronicity of symptoms, and the exposure history differ between solvent exposure and MCS. Chronicity of symptoms is similar between MCS and solvent exposure in that MCS patients and solvent exposed individuals report their symptoms dissipate when exposure has ended (Fiedler et al., 1992). Differences between MCS and solvent exposure are evident, however, in the fact that

MCS patients report their symptoms recur when they are exposed to any number of substances from a diverse group of chemically unrelated substances in very low concentrations. Exposure histories differ in that solvent exposed workers have long durations of exposures (e.g., several years)(Morrow et al., 1990; Ryan et al., 1988; Savage et al., 1988). Additionally, solvent exposed workers are typically blue collar workers, and males who have had opportunities to handle and inhale neurotoxins. MCS patients tend to be white collar workers, and females (Cullen, 1994). In MCS, history of exposure to toxins has been less well defined; it tends to be based on attribution rather than validated by objective measurement.

Thus, there are some similarities between MCS and symptoms due to solvent exposure. However, the range of symptoms, chronicity of symptoms, exposure history, and current substances that induce symptoms differ between MCS and solvent exposure. Controlled scientific studies using operational definitions of MCS and appropriate control groups need to be conducted. At present it is premature to assume that individuals with MCS will demonstrate equivalent cognitive deficits to those observed after solvent exposure. The solvent exposure literature, may however, provide some guidance to expected deficits in MCS if it indeed does become known that MCS results from exposure to environmental solvents.

1.5 Cognitive Deficits in Individuals with MCS

Although individuals who have been diagnosed with MCS complain of impairments in memory and attention (Bell, 1992; Miller & Mitzel, 1995), there currently

exists a limited body of research assessing neuropsychological performance in MCS. To date, three published group studies have been conducted to determine if individuals with MCS perform poorly on neuropsychological tests (Fiedler et al., 1992; 1996; Simon et al., 1993). Fiedler et al. (1992) assessed 11 patients that met Cullen's criteria (1987) for MCS. The 11 patients were selected from a group of 25 individuals referred to an Environmental and Occupational Health Clinic for evaluation of chemical sensitivities. The sample consisted of 3 men and 8 women with a mean age of 42 and 43 years, respectively. Their education ranged from 12 to 16 years with men having an average education of 15 years and females an average of 14 years. Patients in their study were required to be free of physical problems and psychiatric histories or current psychiatric diagnoses that could account for the development, breadth, and severity of their symptoms. Physical and psychiatric status was determined by a self-report medical questionnaire. Patients were also required to report being in good health before their initial environmental exposure.

The neuropsychological screening of individuals in Fiedler et al.'s study (1992) consisted of seven tests assessing memory, concentration, and estimated level of pre-morbid ability. Tests of concentration included Digit Span (forward and backward), Digit Symbol, and the Stroop Colour-Word test. Tests of memory included the total score from the California Verbal Learning Test (CVLT), and Visual Reproduction (immediate and delayed). The Wide Range Achievement Test - Revised (WRAT-R), a measure of reading ability, was also used as an estimate of pre-morbid functioning because it is believed that certain verbal skills remain intact despite exposure to neurotoxins (Hartman,

1992). A criterion of two standard deviations below the mean achieved by the standardization sample for each particular test was used to determine if an individual was impaired. An exception to this rule was the Stroop test. Published cutoff scores were used to indicate impairment on this measure (Trenerry, Crosson, DeBoe, et al., 1989).

Fiedler et al. (1992) determined that 4 out of 11 individuals with MCS would be classified as impaired on the CVLT. The authors noted that two others also performed poorly on the CVLT (<10th percentile) but did not reach the criterion of 2 standard deviations below the normative mean. The authors stated that "poor performance in all cases seemed to be related to difficulty in learning the information in the first place rather than in remembering it. This may be reflective of impairment in attending to a relatively more difficult learning task." (page 534 - 535). Results on all other concentration, memory, and reading tests revealed no consistent impairments across subjects.

Fiedler et al. (1992) concluded from their results that individuals with MCS demonstrate poor memory performance consistent with some form of CNS dysfunction. The poor memory performance of individuals with MCS was also noted to be consistent with findings among solvent exposed individuals. They note another similarity among MCS patients and solvent exposed individuals in that both report cacosmia (i.e., olfactory hypersensitivity with headaches, dizziness, and feelings of nausea). Cacosmia is thought to be mediated by the frontal and temporal lobes as well as the olfactory nerves and bulb (Harrison & Pearson, 1989). Verbal memory is also mediated by the temporal lobe and has been associated with cacosmia among solvent exposed workers (Ryan et al., 1988). For these two reasons, Fiedler et al. (1992) speculated that the temporal lobe may be

implicated in MCS.

The study by Fiedler et al. (1992) was the first case series to assess neuropsychological deficits in individuals diagnosed with MCS. An increased understanding of neurocognitive deficits in MCS can be drawn from this study based on its attempt to operationally define MCS using Cullen's (1987) criteria, and on its selection of a relatively homogeneous group of individuals with this disorder. However, a number of questions regarding cognitive functioning in MCS remained. First, no control group was used to compare results on neuropsychological measures. Rather, normative sample means were used to assess impairment. The one memory test where impairments were indicated was the CVLT. However, the CVLT is a test normed on a relatively small, well educated, sample (Delis et al., 1987). Although Fiedler et al. (1992) also had a relatively well educated group of subjects, the sample upon which the CVLT was normed necessitates the use of a control group to ensure representativeness. Second, the observation that the verbal memory deficits seen in the group of MCS patients are consistent with disruptions of temporal lobe functioning warrants further consideration. Verbal memory is mediated by the temporal lobes, but more specifically is often associated with left temporal lobe lesions (Frisk & Milner, 1990; 1991; Milner, 1958; 1972). The right temporal lobe has been linked to memory for material that is difficult to verbalize (e.g., faces, complex designs) (Lezak, 1995). In addition, results indicated that poor performance among MCS patients was related to difficulty in encoding or learning the information initially rather than disruption in recalling information. Individuals with temporal lobe lesions experience difficulties with memory, both in terms of learning and

recall (Frisk & Milner, 1990; 1991; Milner, 1958; 1972). Other deficits related to temporal lobe lesions include problems with immediate recall (Barr, Goldberg, Wassertein, & Novelly, 1990) and increased numbers of intrusion errors (Hermann, Wyler, Bush, & Tabatabai, 1992).

The second group study that assessed neuropsychological deficits in MCS was conducted by Simon et al. (1993). Forty-one patients with chemical sensitivity were recruited from an allergist's practice. The researchers employed their own operational definition of MCS to select cases. In order to be eligible for the study, it was required that: illness duration be greater than or equal to three months, symptoms be present in at least three organs including the CNS, and reported sensitivity be to four or more substances from a list of fourteen common exposures. Controls were 34 patients with musculoskeletal injuries, matched for sex and a 5 year age range to the MCS patients. Attention and memory assessment of each individual included tests of immediate and 30-minute recall for verbal and visual information (the Logical Memory and Visual Reproduction subtests of the WMS-R), tests of visuomotor speed and flexibility (Trails A and B), a test examining verbal list learning and memory (the Rey Auditory-Verbal Learning Test (RAVLT), a test evaluating auditory attention and concentration (WAIS-R Digit Span), and a test of concentration and visuomotor speed (WAIS-R Digit-Symbol).

Simon et al. (1993) reported that the mean performance scores for cases and controls fell within an average range (+ or - one standard deviation for normative age group). However, a few differences were noted to be statistically significant between individuals with MCS and controls. First, cases ($M = 22.8$, $SD = 6.4$) showed

statistically poorer immediate verbal recall on the Logical Memory subtest of the WMS than controls (M = 26.0, SD = 6.3). Delayed recall of verbal and visual information (i.e., the proportion of initially memorized information remembered after a 30 minute delay) did not differ between cases and controls. The authors also noted that cases showed slightly poorer performance than controls on one of the five initial trials and on the postdistraction trial of the RAVLT. However, data are not provided on any of the initial five trials and the difference between cases and controls on the distraction trial failed to reach significance (p = .06).

Simon et al. (1993) also administered psychological tests in order to determine the presence of psychiatric symptoms. Psychological evaluations included the Hopkins Symptom Checklist - 90 (SCL - 90), a self-report measure of psychiatric symptoms, and the Diagnostic Interview Schedule (DIS). Diagnoses assessed by the DIS included panic disorder, generalized anxiety, depression, and somatization. When an analysis of covariance was conducted to adjust Logical Memory scores for psychological distress (i.e., SCL-90 total score and depression scores), the differences between cases and controls were no longer significant. The exact nature of this analysis (i.e., scores entered into analysis) was not reported. The authors concluded that the small differences in memory performance may have reflected psychological distress.

More recently, Fiedler et al. (1996) studied 23 individuals with MCS, 13 individuals with Chemical Sensitivities (CS), 18 individuals with Chronic Fatigue Syndrome (CFS) and 18 normal controls. The purpose of the study was to determine the characteristics that differentiated their clinic samples (i.e., MCS, CS, and CFS) and to

compare psychiatric and neuropsychological complaints of their clinic samples to their control group. All groups were matched for age, sex, and education.

The 23 individuals with MCS were selected from a group of 53 patients referred for evaluation of chemical sensitivities. All participants in this group met Cullen's definition of MCS (see Appendix A). The 13 individuals with CS, were also selected from the original group of 53 patients referred for evaluation of chemical sensitivities. They met the criteria for MCS with the exception of being able to identify a clear onset of their symptoms. Individuals were excluded from participating in the MCS and CS groups if they had other preexisting explanatory medical conditions (e.g., chronic fatigue), had a history of psychiatric hospitalization, or were involved in a legal case related to their exposure. The 23 individuals with CFS were referred to the study by a director of a CFS centre and all met Centres for Disease Control criteria for the disorder (i.e., debilitating fatigue lasting at least 6 months that reduces activity 50% below premorbid levels; and 8 minor symptoms - mild fever, sore throat, muscle weakness, painful lymph nodes, myalgia, severe fatigue after mild exercise, headaches, and neuropsychological complaints). The 18 healthy controls were recruited from a general internal medicine clinic population and from newspaper advertisements.

The neuropsychological measures administered in this study included tests of concentration (computerized Simple Reaction Time, computerized Continuous Performance Test, Stroop Color-Word Task), tests of visuomotor skills (Digit Symbol, computerized Hand-Eye Coordination, Grooved Pegboard), and tests of memory (California Verbal Learning Test (CVLT), Continuous Visual Memory Test (CVMT),

Visual Reproduction I and II). All participants also completed a questionnaire that assessed the number of substances to which they reacted (Substance Checklist, Kipen et al., 1995), the Structured Clinical Interview of the Diagnostic and Statistical Manual, 3rd Edition, Revised (SCID; all scales with the exception of the somatoform scale), the Minnesota Multiphasic Personality Inventory-2, and the somatization section of the Diagnostic Interview Survey (DIS-III-A). The somatization section of the DIS-III-A was used to provide a measure of lifetime prevalence of somatization disorder as the authors felt that a history of somatization disorder was particularly important to consider in individuals with MCS.

Univariate Analyses of Variance examining group differences on each measure revealed no significant differences on the neuropsychological measures with the exception of the visual memory test (CVMT). The MCS group had a significantly higher rate of false alarms than the normal and CS groups. However, multiple regression analyses revealed that reading achievement (WRAT-R), age, health concerns, and membership in the CS group were the variables that accounted for a significant amount of the variance in the CVMT total score.

The three published group studies assessing cognitive deficits in MCS suggest that, in general, the memory and concentration complaints of individuals with MCS are not consistent with findings from objective neuropsychological tests, once emotional distress and demographics (e.g., age, education) have been factored into the outcome measure. However, no study to date has selected tests based on theoretical predictions of cognitive deficits. Bell et al. (1992) outlined a theoretical mechanism by which the

limbic system is the targeted area in this disorder. More specifically, she hypothesized that the frontal and temporal lobes might be the regions of the CNS most affected in MCS. This Olfactory-Limbic Model thus provides a theory on which to base test selection and hypotheses regarding cognitive performance. No study has yet been conducted to test the Olfactory-Limbic Model's predictions of focal cognitive deficits.

1.6 Use of Cognitive Tests to Localize Brain Dysfunction

The ability to localize function in the human cerebral cortex has been an area of interest for neurobiologists, neuroanatomists and neuropsychologists (Damazio & Geschwind, 1985; Haxby, Grady, Ungerleider, & Horwitz, 1991; Kertesz, 1983; Kiernan, 1981; Phillips, Zeki, & Barlow, 1984; Yeo, Turkheimer, & Bigler, 1990). Localization of cognitive function to specific regions of the human cerebral cortex has been studied with the use of techniques such as the focal lesion and brain imaging methods.

Groups of patients with cerebral lesions of the same region have been studied to observe the consequences of loss of function thought to be associated with that region. Conclusions based on this technique, however, must take into account the theoretical and technical problems associated with it (Kertesz, 1983). First, the focal lesion method cannot distinguish whether the behavioural changes are due to the damaged area functioning without some of its components or are a result of intact regions of the brain taking over functions previously performed by the damaged region. Second, a lesion may disrupt the normal functioning of intact brain regions that may be functioning as a system with the damaged area. In this case, the function could not be attributed to the damaged

region alone, but rather to an impaired system of which the damaged region is a component. Similarly, focal brain damage may produce specific and general effects on cognitive function. If only one function is studied, conclusions cannot be drawn indicating that a direct association exists between the lesion and function studied.

The principle of double dissociation was developed as an experimental technique to address the problem of being able to differentiate between specific and general effects of focal brain damage (Teuber, 1975). Double dissociation involves comparison of subjects with lesions in one brain region to those with lesions in another brain region. If each lesion is associated with a unique functional deficit, each function is assumed to be implemented by a unique brain region.

Several other factors must be taken into account when trying to establish a valid correlation between a cognitive function and a focal lesion. Such factors include: 1) the nature of the pathological process; 2) the size of the lesion; 3) the timing of the anatomical and behavioral observations; 4) individual variations in neurological organization; and 5) the age, handedness, level of education, sex, and premorbid psychological and social factors of the individual being studied (Damazio & Geschwind, 1985). For example, lesions caused by cerebral vascular disease, brain tumor, CNS infection, cerebral anoxia, head injury, or surgery for epilepsy may have different behavioural effects due to the differing pathological processes producing the focal lesion. Surgery for epilepsy can provide good localization data, however one must consider the possibility of subjects also having premorbid learning disorders, drug toxicity due to epilepsy medication or psychological reactions to their disorder. Head injury, on the

other hand, provides poor localization data given that "contrecoup" injuries (i.e., the brain sustains a contusion in an area opposite the blow) are common (Roberts, 1976).

A second type of measure more recently employed to study localization of function involves brain imaging with techniques such as functional magnetic resonance imaging (fMRI), regional cerebral blood flow (rCBF), and positron emission tomography (PET). The theory underlying brain imaging studies is that regions involved in a cognitive function become more active and increase their rate of metabolism. In this way, healthy subjects can be studied under experimental conditions to assess localized changes in brain metabolism during specific cognitive tasks. The study of healthy subjects thus avoids possible confounding effects of brain lesions discussed above, such as compensatory reorganization of brain function.

As with focal lesion studies, conclusions regarding localization of function based on imaging studies must take into account the limitations of the techniques. These limitations include difficulties in the ability to determine the exact anatomical localization of the activity and in problems associated with translating experimental and clinical tasks used in focal lesion studies and clinical practice into similar tasks that can be conducted under the constraints (e.g., time limits) imposed by imaging technology (Haxby et al., 1991).

When selecting neuropsychological tests for use in this dissertation, the greatest importance was placed on research using the double dissociation technique whose examiners also considered factors such as age and handedness of their participants as well as factors such as the etiology of the lesion. Additionally, imaging studies corroborating

the focal lesion studies regarding localization of function were sought when available.

1.7 Processes Associated with Frontal, Temporal, and Posterior Brain Regions

To determine the processes especially associated with frontal, temporal, and posterior brain regions, focal lesion studies using the double dissociation technique and imaging studies were reviewed.

Tests Sensitive to Frontal Lobe Functioning

Impaired word fluency has been associated with frontal lobe damage (Benton, 1968; Butler, Rorsman, Hill and Tuma, 1993; Milner, 1964; Pendleton, Heaton, Lehman, & Hulihan, 1982; Perret, 1974; Ramier and Hecaen, 1970; Miceli, Caltagirone, Gainotti, Masullo, & Silveri, 1981). The first study demonstrating impaired word fluency in patients with frontal lobe lesions was reported by Milner (1964). She tested written word fluency in 7 patients with left frontal lobe lesions, 7 patients with left temporal lobe lesions and 4 patients with right frontal lobe lesions. Patients were given five minutes to write down as many words as possible beginning with the letter S. Another four minutes were given during which the patients were asked to write down as many words as possible beginning with the letter C. She found that patients with left frontal lobe lesions performed significantly more poorly (i.e., produced viewer words) on this task than the other two patient groups.

Following the initial report by Milner (1964), several studies were conducted to assess the relation existing between lesions of different parts of the brain and deficits

observed on verbal fluency tasks (Benton, 1968, Micelli et al., 1981; Perret, 1974). Benton (1968) studied 8 patients with lesions of the right frontal lobe, 10 patients with lesions of the left frontal lobe and 7 patients with bilateral frontal lobe lesions on the Controlled Oral Word Association (COWA) test. The COWA test requires an individual to verbalize as many words as he or she can beginning with a certain letter of the alphabet within three sequential one-minute time periods. Benton (1968) found greater verbal fluency deficits following left and bilateral frontal lobe lesions than right frontal lobe lesions.

Perret (1974) assessed verbal fluency in 118 patients with localized right and left frontal, right and left temporal, and right and left posterior cerebral lesions. The location of cerebral lesion was verified during each patient's neurosurgical procedure (i.e., brain surgery). The verbal fluency task was equivalent to the procedure used by Milner (1964) with the exception that the patients were required to speak the words rather than right them down. Results demonstrated that patients with left frontal lobe lesions performed significantly more poorly than all other groups on the verbal word fluency test. Patients with temporal lobe lesions did not significantly differ from posterior groups on level of performance on this task, but frontal groups did differ significantly from both temporal and posterior groups.

Miceli et al. (1981) assessed verbal word fluency using the COWA test in 82 right and 67 left focally brain-damaged patients. Lesions were localized to frontal, parietal, temporal or occipital areas according to neuroradiological examination, brain scan, or neurosurgeon report. Miceli et al. demonstrated that verbal word fluency was selectively

impaired by lesions involving the frontal lobes. Individuals with frontal lobe lesions performed more poorly on this task than the other subgroups (temporal, parietal, and occipital), independent of the side of lesion.

Recently, imaging techniques have been employed to assess areas of the brain selectively activated during verbal fluency tasks. These studies provide converging evidence to brain lesion studies (Cantor-Grae, Warkentin, Franzen, & Risberg, 1993; Cuenod, Bookheimer, Hertz-Pannier, Zeffiro, Theodore, & Le Bihan, 1995; Warkentin & Passant, 1993). Cantor-Grae et al. (1993) performed regional cerebral blood flow measurements on 22 (11 females) right-handed healthy volunteers during a modified version of the FAS (i.e., COWA) test. Individuals were instructed to produce aloud as many words as possible starting with a given letter (i.e., F, A, and S). The letters were changed every minute. Participants were instructed to keep their eyes closed during this word generation task. Imaging was also conducted under a resting condition during which time subjects were instructed to keep their eyes closed and to relax. The resting condition provided the procedural baseline for comparison with measurements during the FAS task. Their results showed significantly increased flow in the left dorsolateral prefrontal cortex during performance of the word fluency test. Cerebral blood flow was not significantly augmented in other brain regions, including superior frontal, frontotemporal, temporal, central, parietotemporal, and occipital, during the word fluency task.

Warkentin and Passant (1993) measured cerebral blood flow during the same word fluency task as that used by Cantor-Grae et al. (1993) in 49 (20 female) right-

handed healthy volunteers. Their results showed a significant increase in blood flow in the left anterior frontal and left inferior frontal areas. A significant reduction of flow in the upper central and anterior parietal areas was also seen during the word fluency task. This frontal lobe activation was seen in 85% of the subjects.

Cuenod et al. (1995) used the functional MRI technique to map cognitive function during a verbal fluency task. They studied nine (4 female) right-handed healthy volunteers during a modified version of the COWA test. Subjects were asked to silently generate words beginning with a certain letter while functional MRI images were acquired. Imaging during a rest period was also conducted to provide a baseline of brain activation. During both word generation and resting conditions, subjects were instructed not to physically generate sound or to move the tongue in order to limit motion artifacts. During rest, subjects were instructed to concentrate on their breathing. Results from this study indicated that the left hemisphere, and predominantly the frontal lobe, was most active during the word generation task.

Thus, studies assessing the relations among lesions of different parts of the brain and deficits observed on word fluency tasks, in conjunction with the results of imaging studies assessing healthy and brain damaged subjects, suggest that word fluency tasks, specifically the COWA test, provide localizing information with respect to the frontal lobes.

The Self-Ordered Pointing Test (Petrides & Milner, 1982) has also been associated with frontal lobe functioning, first in lesion patients and later on fMRI in normals. Petrides and Milner (1982) administered the self-ordered pointing test to 79 (31

female) patients with unilateral frontal or temporal brain lesions and 18 (9 female) right-handed normal control subjects. The self-ordered pointing tasks administered included the following stimuli: abstract designs, representational drawings, high-imagery words, and low-imagery words. Petrides and Milner (1982) demonstrated that patients with left and right frontal-lobe lesions were significantly impaired on the abstract designs and representational drawings subtests relative to normal controls. Patients with temporal-lobe lesions that did not include extensive damage to the hippocampal system were unimpaired on these tasks relative to controls. Comparisons between individuals with frontal lobe lesions and temporal lobe lesions were not reported. However, figures indicated that the right and left frontal-lobe lesion groups performed more poorly than the left and right temporal lobe lesion groups without extensive damage to the hippocampus on the abstract designs and representational drawings tasks (Petrides & Milner, 1982; Figures 6 and 8).

Wiegersma, van der Sheer, & Human (1990) tested three individuals with right frontal-lobe excisions, four individuals with left-frontal lobe excisions and seven healthy control individuals on a similar self-ordered pointing test to that developed by Petrides and Milner (1982). Patients and normal controls were matched in terms of age, sex, education and handedness. Individuals were required to randomly produce a sequence of numbers with the restrictions that numbers should not be spoken twice and that counting forwards or backwards was not permitted. Subjects were also required to sequentially point to one number of a set of numbers on consecutively presented sheets of paper while avoiding repetition and forward and backward counting orders. Performance of

individuals with frontal lobe lesions was significantly poorer than healthy controls on these self-ordered tasks.

Imaging studies have been conducted to examine cerebral activation during the Self-Ordered Pointing tasks (Petrides, Alivisatos, Evans and Meyer, 1993; Petrides, Alivisatos, Meyer and Evans, 1993). Petrides, Alivisatos, Evans and Meyer (1993) used positron emission tomography (PET) to examine regional cerebral blood flow in 9 right-handed male volunteer subjects. Subjects carried out a series of self-generated pointing responses to a set of 8 abstract designs (i.e., 8 item self-ordered pointing task). Significant increases in cerebral blood flow relative to a resting control condition were observed within the mid-dorsolateral frontal cortex. The regional cerebral blood flow increases were more pronounced within the right middorsolateral frontal cortex than in the left.

In a similar study, Petrides, Alivisatos, Meyer and Evans (1993) used PET to study regional cerebral blood flow in 10 right-handed male volunteers while they performed a verbal self-ordered task (i.e., subjects were required to randomly say aloud the numbers from 1 to 10 without repeating any one number). Significant increases in blood flow were observed bilaterally within the mid-dorsolateral frontal cortex relative to the control condition in which subjects were simply asked to count aloud. These results support Petrides, Alivasatos, Evans, and Meyer's (1993) findings that a self-ordered task increases blood flow to the frontal cortex. The results also establish that both verbal and visual self-ordered tasks activate the frontal cortex.

Thus, research assessing the relation existing between frontal lesions and

performance on the Self-Ordered Pointing test, in conjunction with PET studies conducted on healthy participants performing self-ordered tasks, provides evidence that performance on the self-ordered pointing task requires integrity of the frontal lobes. Damage to other brain regions (i.e., temporal lobes) does not significantly impair performance on this measure (Petrides & Milner, 1982).

Tests Sensitive to Temporal Lobe Functioning

Several studies have demonstrated that recall (immediate and delayed) of the WMS Logical Memory stories is impaired in individuals with lesions of the left temporal lobe (Barr et al., 1990; Chlopan, Hagen, & Russell, 1990 Frisk & Milner, 1990; Ivnik, Sharbrough, & Laws, 1987; Leonard, 1991; and Milner, 1958). For example, Milner (1958) reported that individuals with left-temporal lesions performed significantly more poorly on the immediate and delayed version of the Logical Memory subtest than individuals with right-temporal lobe lesions and individuals with frontal lobe lesions.

More recently, Frisk and Milner (1990) demonstrated that immediate recall of stories was impaired in individuals who had undergone left temporal lobectomy relative to individuals with right temporal lobectomy and normal controls. Individuals with frontal lobe lesions were not impaired on this task. Frisk and Milner (1990) also showed that individuals with left frontal lobe lesions were impaired on tasks assessing sentence comprehension and rapid naming ability while individuals with left temporal lobe lesions were not impaired on these tasks. Thus the results indicated a double dissociation of verbal deficits following left frontal and left temporal lobe excisions.

Recognition and memory of faces has been associated with functioning of the right hemisphere, and more specifically the right posterior and temporal regions, respectively. Warrington and James (1967a) studied right-handed patients with unilateral cerebral lesions of the right or left hemisphere on a recognition memory tests for faces. Twenty-seven (8 female) patients with left hemisphere lesions and 34 (18 female) patients with right-hemisphere lesions were tested on a recognition memory test involving retention of 8 male and 8 female faces. Left-hemisphere and right-hemisphere groups were further subdivided into temporal and parietal lesion location subgroups. Patients were shown a face for 10 seconds and then asked to identify that face from within a set of 8 male or female faces. Warrington and James (1967a) demonstrated that patients with right hemisphere lesions performed significantly more poorly than controls and individuals with left hemisphere lesions on this task. Individuals with right temporal lesions did not differ from individuals with right non-temporal (i.e., parietal) lobe lesions.

Warrington (1984) studied right-handed patients with right hemisphere lesions (N=134), right-handed patients with left-hemisphere lesions (N=145) and normal controls (N=310) on a similar memory test for faces to that used by Warrington and James (1967a). The test, called the Recognition Memory Test for Faces (RMF), consisted of presenting an individual with 50 photographs of unfamiliar male faces and then asking him or her to identify the faces previously seen from a set of 100 faces presented two at a time (i.e., a face previously seen is paired with a distracter face). The patient groups were further subdivided according to lesion localization within the hemisphere (frontal, temporal, parietal or occipital). Individuals with right hemisphere lesions were

significantly more impaired on the RMF task than normal controls and individuals with left-hemisphere lesions, replicating the findings of Warrington and James (1967a). A trend for the right temporal subgroup to perform worse on the RMF than the right non-temporal subgroups was found. However, a direct comparison between right temporal, right frontal, and right parietal lesion patients was not performed (Warrington, 1984).

Results from the studies conducted by Warrington and James (1967a) and Warrington (1984) suggest that performance on the RMF is impaired in individuals with right hemisphere lesions. The reason for the lack of dissociation within the right hemisphere (i.e., dissociation in performance between individuals with right temporal and right parietal lesions) could be due to the complexity of the task. Before a person can display accurate memory for a face, he or she must first perceive and identify the face. That is, the RMF confounds face memory with face perception/discrimination. The right parietal lobe is typically implicated as important for face discrimination (Lezak, 1995). Research on other face discrimination tasks that do not involve a memory component has shown that individuals with right parietal lesions perform more poorly on this task than do individuals with right temporal lobe lesions (Hamsher, Levin & Benton, 1979). Thus, the memory component of the RMF is likely the component which depends on integrity of the temporal lobe (Lezak, 1995). The deficits seen on this task in individuals with temporal lobe lesions are likely caused by deficient memory capacities. Conversely, deficits seen in individuals with parietal lobe lesions are likely caused by deficient discrimination capacities.

Tests Sensitive to Posterior Region Functioning

Three studies have assessed the ability of the Gollin Figures to discriminate between different brain lesion patient groups. Warrington and James (1967b) assessed 65 (27 female) right-handed patients with unilateral cortical lesions, including left temporal, right temporal, left parietal, and right parietal lesion groups. They reported a deficit in the right parietal group on the Gollin test relative to the right non-parietal group and relative to the left parietal group. Warrington and Rabin (1970) assessed 74 (34 female) right-handed patients with unilateral cortical lesions on the Gollin Figures test. The mean error scores for each patient group, including frontal, temporal, and parietal, did not differ significantly from one another. The results of the study by Warrington and Rabin (1970) thus failed to replicate the previous study by Warrington and James (1967b). Although performance on the Gollin did not differ significantly between lesion groups in the study by Warrington and Rabin (1970), the highest error score was found in the right parietal group.

Warrington and Taylor (1973) replicated the findings of Warrington and James (1967b). Warrington and Taylor (1973) assessed 74 right-handed patients with unilateral brain lesions categorized by a radiologist as anterior, temporal or posterior. Anterior patients included those individuals with frontal, fronto-parietal or fronto-temporal lesions. Temporal patients included those individuals with lesions restricted to the temporal lobe. Posterior patients included those individuals with occipital, parietal, temporo-parietal or occipito-parietal lesions. Warrington and Taylor (1973) demonstrated that individuals with right posterior lesions performed significantly more poorly on the Gollin Test than

controls and individuals with right anterior lesions. Thus, two of the three studies assessing performance on the Gollin test (Warrington & James, 1967b; Warrington & Taylor, 1973) suggest that performance on this measure is more likely impaired by posterior (i.e., occipital-parietal) than anterior (i.e., frontal-temporal) brain lesions. One study failed to support the notion that patients with right posterior lesions perform significantly more poorly than other lesion groups on the Gollin (Warrington & Rabin, 1970). However, a trend in support of this notion was evident in that the highest error score was found in the right parietal group.

Studies have been conducted to assess the relation between focal cerebral brain lesions and performance on face discrimination tasks. Three studies have found that individuals with lesions localized to the right hemisphere perform more poorly than controls and individuals with left hemisphere lesions on face discrimination tasks (Benton & Van Allen, 1968; De Renzi, Faglioni, and Spinnler, 1968; Warrington & James, 1967a). Two studies (Warrington & James, 1967a; Hamsher et al., 1979) have assessed different focal right hemisphere lesion groups to delineate areas within the right hemisphere which, when damaged, lead to significant impairment of face recognition tasks.

Hamsher et al. (1979) studied 196 control subjects and 145 patients with unilateral anterior or posterior focal cerebral lesions on the BFRT. They found that patients with right posterior lesions had the highest proportion of impaired scores relative to the other patient and control groups. Among patients with right hemisphere damage, those with posterior lesions showed a significantly higher frequency of defect than those with

anterior lesions. Individuals with left posterior lesions as well as aphasia and comprehension difficulties were also more likely than other focal lesion groups (i.e., left anterior lesions) to have impaired scores on this task.

As previously discussed (see Tests Sensitive to Temporal Lobe Functioning), Warrington and James (1967a) studied twenty-seven patients with left-hemisphere lesions, thirty-four patients with right-hemisphere lesions and ten control subjects on a face recognition test of sixteen photographs of unknown male and female faces. Left-hemisphere and right-hemisphere groups were further divided into temporal and parietal lesion location subgroups. Subjects were shown each photograph for 10 seconds and then asked to identify the face from memory from a set of photographs. Results indicated that individuals with right hemisphere lesions performed significantly more poorly than controls on this task. Individuals with right parietal lesions performed significantly more poorly than individuals with left parietal lesions. However, individuals with right parietal lesions did not perform significantly more poorly than individuals with right temporal lesions.

The studies by Hamsher et al. (1979) and Warrington and James (1967a) differed in the extent to which their tasks depended on memory processes. Hamsher et al. (1979) used a face discrimination task that required participants to match picutures of unknown faces. Warrington and James (1967a) required participants to identify faces previously seen from a set of photographs. As discussed previously (see Tests Sensitive to Temporal Lobe Lesions), the deficits seen on face matching tasks (e.g., Hamsher et al., 1979) likely reflect a deficit in discrimination (i.e., parietal lobe function). Conversely, the deficits

seen on face recognition tasks (e.g., Warrington & James, 1967a) reflect impaired memory and possibly discrimination processes (i.e., temporal and parietal lobe functions).

1.8 Hypotheses to be Tested

The purpose of this thesis was to test the Olfactory-Limbic Model of a disorder known as Multiple Chemical Sensitivity (MCS). The Olfactory-Limbic Model predicts specific cognitive deficits associated with the frontal and temporal lobes. Cognitive tests associated with frontal and temporal lobe functioning, as well as parietal and occipital lobe functioning were used to address the question: Do individual's with MCS have selective dysfunction of the frontal and temporal lobes?

Between-Group Hypotheses

It was hypothesized that if the Olfactory-Limbic Model is correct, individuals with MCS would perform more poorly on neuropsychological tests of frontal and temporal (i.e., anterior) lobe functioning than healthy or asthmatic controls matched for age, sex, race and education. Similarly, if the model is correct, individuals with MCS were not expected to perform more poorly than controls on neuropsychological tests of parietal or occipital (i.e., posterior) lobe functioning. A pattern of results indicating no impairment of individuals with MCS on any neuropsychological measures relative to controls would provide evidence contrary to the Olfactory-Limbic Model. Similarly, a pattern of results indicating that individuals with MCS are impaired on measures of parietal or occipital lobe functioning relative to controls would not support the Olfactory-Limbic Model.

Between-Test Hypotheses

It was also hypothesized that if the Olfactory-Limbic Model is correct, individuals with MCS would perform more poorly on neuropsychological tests of anterior (i.e., frontal and temporal lobe) functioning than tests of posterior (i.e., parietal and occipital lobe) functioning. A pattern of results indicating no difference between measures of frontal and temporal lobe functioning to posterior brain region functioning within the MCS group would not support the Olfactory-Limbic Model. A pattern of significantly poorer performance on frontal and temporal tasks than posterior tasks in either control group would not support the Olfactory-Limbic Model, as this model was developed specifically for MCS.

Chapter 2. Method

2.1 Participants

Twenty-one individuals with MCS, 21 with asthma, and 21 healthy controls participated in this study. An asthma group was included to serve as a control for the possible effects of chronic illness on the cognitive and emotional measures. Recruitment advertisements and telephone screening questionnaires are presented in Appendix B.

MCS Group Participants

Individuals with MCS were recruited through advertisements placed in local hospital newsletters, through brochures and posters placed in two environmental illness clinics, libraries, health food stores and Dalhousie University Campus. They self-reported the following four of five criteria derived from Cullen (1987) : 1) symptoms currently involve more than one organ system (e.g., respiratory and nervous system); 2) symptoms recur and abate in response to exposure to chemical/substances; 3) symptoms are elicited by exposures to very low levels of chemicals of diverse structural classes (e.g., solvents, pesticides); and 4) other medical conditions do not account for the symptoms. Cullen's criterion 1 (i.e., the disorder is acquired in relation to some documentable environmental exposure(s), insult(s), or illness(es) was not part of the screening. The decision not to exclude cases who did not meet this criterion was based on two factors. First, several researchers do not feel that self-report of a documentable environmental exposure is a necessary criterion for selecting MCS cases (Ashford & Miller, 1992; Staudenmayer, 1997). Second, this study was reviewed by the research

review committee of the Environmental Illness Clinic of Nova Scotia. Members of this committee recommended that Cullen's criterion 1 not be used to select MCS cases as, in their opinion, several individuals whom they felt had MCS would not meet this criterion.

During a seven month period, 47 individuals with MCS phoned the experimenter and were screened initially for eligibility into the study. The telephone interview assessed, via self-report, handedness, language spoken, sex, age, race, education, current medications, and history of neuropsychological assessments. Inclusionary criteria for entry into the MCS group (i.e., 4 of 5 Cullen's criteria) were also assessed via the telephone interview. Exclusionary criteria were assessed through a series of questions compiled by the examiner as well as through the use of the Brief Michigan Alcoholism Screening Test (Pokorny, Miller, & Kaplan, 1972) and the Drug Abuse Screening Test (Skinner, 1982). If an individual expressed any positive answers on the MAST or the DAST, with the exception of question 1 on the DAST, they were excluded from participating in this study. Stringent use of the MAST and DAST was employed because alcohol and drug use can have serious negative consequences on cognitive performance (Lezak, 1995). To summarize, individuals were excluded from participating in this study if they did not meet the selected Cullen's criteria for MCS or if they had experienced any of the following: 1) psychiatric hospitalization; 2) premorbid psychiatric conditions including psychoses or manic depression; 3) neurologic disease; 4) brain injury; 5) stroke; 6) cardiovascular disease; 7) kidney or liver disease; or a 8) pre-morbid learning disability. Individuals were also excluded from this study if they were not English speaking or if they were not right-handed.

Of the 47 individuals with MCS who called, 26 (55%) were excluded based on the following information: two due to prior head injuries, one due to prior coma, one due to potential alcohol use problems, one due to potential drug use problems, one because English was not her first language, seven because they did not meet our criteria for MCS, five because they were left-handed, two because of histories of psychiatric hospitalizations, and one because he reported having had a childhood learning disability. Five decided not to participate once they were made aware of the time commitment required.

Asthma Group Participants

Along with brochures, additional measures were necessary to recruit sufficient numbers of asthma participants. Advertisements were placed in local hospital newsletters and city newspapers, and on community cable television information channels. The researcher also recruited at meetings of a local asthma self-help group.

Over a seven month period, 32 individuals with asthma called the experimenter, and experienced a screening process similar to that used in selecting the MCS group. Individuals with asthma were asked to self-report handedness, language spoken, race, sex, education, history of neuropsychological testing and current medications used. Individuals with asthma also self-reported if a physician had diagnosed them with asthma. Only right-handed, English speaking individuals who matched a participant in the MCS group in terms of age (within 5 years), education (within 3 years), race, and sex who had also been diagnosed by a physician as asthmatic were selected for participation in the

asthma control group. Individuals were excluded if they had experienced any of the following: 1) psychiatric hospitalization; 2) premorbid psychiatric conditions including psychoses or manic depression; 3) neurologic disease; 4) brain injury; 5) stroke; 6) cardiovascular disease; 7) kidney or liver disease; 8) pre-morbid learning disability; 9) toxin exposure; or 10) MCS. Additionally, if an individual expressed any positive answers on the MAST or DAST, with the exception of question 1 on the DAST, he or she was excluded from participating in the study.

Four of the 32 individuals screened for participation in the asthma control group were excluded because they did not match an MCS case in age, education, race and sex, one due to a prior head injury, three because they were left-handed, and one had not received her diagnosis from a physician. Two individuals decided not to participate because of the time commitment required. Hence, 11 of the 32 individuals (34%) were excluded from participating in the asthma control group.

Healthy Control Group Participants

Recruitment of healthy controls occurred through all means described above for the asthma group. Over a seven month period 49 healthy individuals called the experimenter. A similar screening process as that used in the MCS and asthma control groups selected individuals for participation in the healthy control group. Individuals were excluded from participating in this group if they had MCS or asthma or if they met any of the following exclusionary criteria: 1) psychiatric hospitalization; 2) premorbid psychiatric conditions including psychoses or manic depression; 3) neurologic disease; 4)

brain injury; 5) stroke; 6) cardiovascular disease; 7) kidney or liver disease; 8) pre-morbid learning disability; or 9) toxin exposure. Additionally, if an individual expressed any positive answers on the MAST or DAST, with the exception of question 1 on the DAST, he or she was excluded from participating in the study.

Twenty-one of the 49 healthy individuals were excluded because they did not match an MCS case in sex, age, race and education, one due to a prior head injury, one due to a prior stoke, four because they were left-handed, and one due to a childhood learning disability. Hence, 28 of the 49 (57%) healthy individuals were excluded from participating in this study.

2.2 Power Analysis

An a priori power analysis established that a sample size of 63 subjects provided enough power (.80) to correctly reject the null hypothesis when the effect size was large (Cohen & Cohen, 1983). Additional testing of subjects to increase power was not indicated by the pattern of obtained results.

2.3 Materials

Ten neuropsychological tests, a test of motivation, and five questionnaires were used in this study (see Appendix C). The following section describes the measures and the rationale for their selection.

Screening Measures

Assessment of Handedness: Handedness Questionnaire

Only right-handed individuals were asked to participate in this study because neuropsychological localization research is less reliable for left- than right-handers (Milner, 1974). Hand preference was assessed through direct observational techniques by asking the participants to mime eight common actions (Kimura & Vanderwolf, 1970). Each participant was required to complete 6 of the 8 mimes, including hand writing, with their right hand in order to be considered right-handed (Kimura & Vanderwolf, 1970).

Assessment of Motivation: Abbreviated Hiscock Forced Choice Procedure

In order to assess motivation, an abbreviated version of the Hiscock Forced Choice Procedure (Guilmette, Hart, Giuliano, and Leininger's, 1994; Hiscock and Hiscock, 1984) was administered. This measure was employed to assess that a subject was performing to the best of his or her abilities on the neuropsychological tests. Guilmette et al. (1994) demonstrated that brain-damaged and psychiatric subjects performed well on the 36 item Hiscock Forced Choice Procedure. Each group obtained a mean of 98% correct. By contrast, normal individuals asked to simulate memory impairment obtained a mean of 56% correct. A cutoff of 90% was used in this study because Guilmette et al. (1994) recommended that an individual obtaining less than 90% correct should be suspected of producing less than optimal effort or malingering. Test results of individuals not obtaining at least 90% correct on this measure would have been excluded from further analysis.

The Hiscock Forced Choice Digit Memory Test consists of three sets of 12 card pairs. The first card in a pair has one 5-digit number printed on it. The second card in the pair has two 5-digit numbers printed on it, one above the other. One of the numbers matches that printed on the first card in the pair while the second number serves as a foil. In the first condition, subjects are told to read aloud the 5-digit number printed on card 1. The examiner then removes the card and waits 5 seconds. During this interval, subjects are not distracted. Following the delay, subjects are shown the next card on which the original 5-digit number and a foil are printed. The subject is told to point to the number initially presented. Subjects are provided with feedback as to whether their response is correct or incorrect. A total of 12 trials with a 5 second delay are administered.

After the first 12 trials with a 5 second delay are completed, subjects are told, regardless of actual performance, that because they performed so well, the delay interval will be increased to 10 seconds. A total of 12 trials with a 10 second delay are then administered.

After the second trial of presentations, the subject is told similarly that because he or she had done so well, the interval will be increased to 15 seconds. A total of 12 trials with a 15 second delay are administered. The total score was the number of correct recognitions out of 36. This score was then converted into a percentage correct.

Demographical Information and Health Characteristics

Tests of Pre-morbid Functioning: National Adult Reading Test - Revised (NART-R) and Barona and Chastain's (1986) Regression Equation

Estimates of pre-morbid Full Scale IQ were assessed with the NART-R (Blair & Spreen, 1989; Nelson, 1982) and Barona and Chastain's regression equation (1986). The NART-R has an advantage of actually using an individual's performance to estimate IQ. The regression has an advantage of not relying on current cognitive abilities, which may be impaired in the MCS group. Although the three groups were matched for age, education, race, and sex, these two estimates of premorbid intellectual functioning provided an additional check on estimated mean IQ's for each group.

The NART-R requires an individual to read aloud a series of single words. The total number of correctly pronounced words was used as an estimate of pre-morbid IQ in this study (maximum = 61). To estimate Full Scale IQ, the total number of errors the individual made is multiplied by .78 and then subtracted from 127.8. The maximum full scale IQ estimate is 127.8 and the minimum is 80.22. Performance on the NART-R is relatively resistant to neurological and psychiatric disorders (Crawford, Parker, & McKinlay, 1992; Vanderploeg, 1994). Blair and Spreen (1989) demonstrated that the standard error of estimate was 7.73 for estimated Full Scale IQ.

Certain demographic variables (e.g., education, occupational status) are strongly related to IQ (Barona, Reynolds & Chastain, 1984). Barona and Chastain (1986) developed a regression equation to estimate premorbid IQ based on demographic variables. Namely, knowledge of an individual's race, sex, occupation, region of residence, and whether they are from an urban or rural area is used to estimate premorbid Full Scale IQ.

Measure of MCS: The Substance Checklist

Kipen et al. (1995) developed a questionnaire to assess the presence or absence of chemical sensitivity. The questionnaire lists 122 substances for which an individual must indicate whether he or she is: currently symptomatic when exposed to that substance, formally symptomatic so now avoid that substance, no known symptoms when exposed to that substance, or never been exposed to that substance or don't know what the substance is. The total score was determined by summing the substances to which the individual reported current or former symptoms. Kipen et al. (1995) found that a score of 23 or more out of 122 provided adequate sensitivity (69%) to detect MCS and a specificity of 89%. Noteworthy, however, was the rate (53%) at which individuals with asthma reported scores higher than 23, suggesting that high scores on the substance checklist did not fully distinguish between individuals with asthma and individuals with MCS.

The purpose of administering this questionnaire to individuals with MCS was to ensure that all MCS participants scored at a level of at least 23 out of 122 (Kipen et al., 1995). Test results of MCS group participants who did not meet this cutoff would have been excluded from further analysis. A cutoff of at least 23 out of 122 was not used as an inclusionary or exclusionary criterion for the asthma and healthy control samples due to previous research findings suggesting an overlap in total scores for individuals with asthma and MCS (Kipen et al., 1995).

Health History Questionnaire: Type of MCS and Exposure History Questionnaire

According to Ashford and Miller (1991) MCS patients can be classified into one of 4 different groups: 1) heterogeneous work and home chemical exposures, generally at low levels; 2) tight building occupants, with offgassing from construction materials and office equipment, perfume, and tobacco smoke as major exposures; 3) industrial workers, with higher level acute and chronic industrial chemical exposures; 4) members of contaminated communities, with exposures from air and water contamination by toxic waste sites, pesticide spraying, or industrial dumping, at varying levels. A questionnaire developed by the experimenter was administered to determine to what factors individuals with MCS attributed their illness (see Appendix D). Estimated length of illness and exposure histories were assessed with this questionnaire.

Neuropsychological Measures

Tests Sensitive to Frontal Lobe Functioning: Controlled Oral Word Association Test (COWA) and Self-Ordered Pointing (SOP) Task

Frontal lobe functioning was assessed with the COWA Test, FAS oral version (Benton, 1968), and the SOP Task, Pictures and Designs 12 Item versions (Petrides & Milner, 1982). The COWA test is a commonly used clinical measure which consists of three word-generation trials, one trial for each of the letters F, A and S. The instructions for the test are as follows:

> "I will say a letter of the alphabet. Then I want you to give me as many words that begin with that letter as quickly as you can. For instance, if I

say 'B', you might give me 'bad', 'battle', 'bed'... I do not want you to use words that are proper names such as 'Boston', 'Bob', or 'Brylcreem'. Also, do not use the same word again with a different ending such as 'eat' and 'eating'. Any question?" (pause) "Begin when I say the letter. The first letter is 'F'. Go ahead."

The examiner then begins timing and allows one minute for each letter (F, A, and S). The examiner also says "Fine" or "Good" after each one-minute performance. If the individual discontinues before the end of the minute, the examiner encourages him or her to try to think of more words. If there is a silence of 15 seconds, the examiner repeats the basic instructions, and the letter. For scoring purposes, the examiner writes down the actual words in the order in which they are produced. All three letters (F, A, and S) are administered.

The score used in this study was the sum of all admissible words for the three letters. Inadmissible words (i.e., proper nouns, wrong words, variations, repetitions) were not counted as correct. There was no maximum total number of words that could be counted in the total score.

The Self-Ordered Pointing task is a task that requires an individual to organize a sequence of pointing responses to sets of pictures of abstract designs or objects presented to them on sheets of paper. The 12 item lists were used. Thus, two sets of stimuli were presented to each individual. The first set displayed 12 abstract designs on each sheet of paper. The second set displayed 12 objects on each sheet of paper. Each set consisted of three trials. Each trial consisted of a pile of 12 sheets of paper each displaying all 12

items to be presented. Each paper, however, displayed the items in different positions.

Instructions for this test were developed from descriptions published by Petrides and Milner (1982). The examiner presents the individual with a pile of papers consisting of the three trials in a set. Each trial is separated by a blank sheet of paper to indicate its end. Participants are told that they are to touch only one stimulus per sheet of paper and that after each response they are to turn to the next sheet, touch another stimulus, and to continue in this manner. The participants are then told that they are to touch all the stimuli, one at a time and in any order they wish, but without touching any given stimulus more than once. Using the first few sheets of paper from the first trial of the first set, the experimenter demonstrates the type of material to be presented and the fact that all designs are printed on each sheet of paper but that their positions vary from sheet to sheet. Testing begins only when it is clear that the subjects understand what they are expected to do. When the individuals encounter the first blank sheet indicating the end of the first trial, they are instructed to begin all over again. They are reminded that they are not to touch any stimulus more than once. It is again emphasized that they can touch the stimuli in any order they wish.

The examiner records the order in which the stimuli are touched and the time taken to complete each trial. Each participant is told that it is accuracy and not speed that is important for this test. He or she is told to maintain a comfortable pace and that the time is kept only to ensure that they do not proceed too quickly or too slowly through the test. It is pointed out to all subjects that if they proceed too quickly or too slowly, they will be asked to slow down or speed up. Emphasis is placed on the fact that if they hurry

through the test they might not have time to look at each item properly and that if they go too slowly the might forget items they had already touched.

The participant is not allowed to respond consistently to the same location on any given trial, because doing so merely requires him or her to recognize the recurrence of a given item in that location rather than to plan a sequence of responses. Subjects are not told that this approach is not permitted, unless they spontaneously attempt to use it.

The total combined error scores for abstract designs and objects were recorded and analysed. The maximum number of errors for each set was 33.

Tests Sensitive to Temporal Lobe Functioning: Logical Memory Subtest of the Wechsler Memory Scale (WMS); Recognition Memory Test for Faces (RMF)

The Logical Memory subtest (immediate and 60 minute delay) of the WMS Form II (Wechsler & Stone, 1973) and the RMF (Warrington, 1984) were chosen to assess temporal lobe functioning. The Logical Memories subtest is comprised of two memory passages of approximately 4 to 5 lines in length. Immediate and delayed versions of this test are designed to measure immediate and long-term recall of prose.

The instructions for this test are as follows:

"I am going to read to you a little selection of about 4 or 5 lines. Listen carefully because when I am through I want you to tell me everything I read to you. Are you ready?"

The examiner then reads a short passage out loud. At the end of the first story the examiner asks:

"Now what did I read to you? Tell me everything and begin at the beginning."

After the individual recalls as much of the story as he or she can, the examiner repeats the instructions for a second time. A second short passage is then read and the individual is asked to recall as much of the story as he or she can. A one hour delay then occurs during which time non-interfering tests were administered. The individual is not told that he or she will be asked to recall the stories at a later date. After the one hour delay, the subject is then asked to recall as much of each story as he or she can.

The examiner records verbatim what the individual recalled. The criteria outlined by Schwartz and Ivnik (1980) reported in Spreen & Strauss (1991) for gist scoring were used. The average number of items immediately recalled and average number of items recalled after a delay were recorded. The maximum number of items for each story was 24.

The RMF (Warrington, 1984) consists of 50 target photographs of unfamiliar male faces and 50 distracter male faces. The 50 target photographs are contained in one booklet, each face on a separate page. The pages of a second booklet present each target face paired with a foil. An individual is required to recognize which of the two faces he or she was presented earlier. The instructions for this task are as follows:

"This is a memory test for faces. I am going to show you this pack of faces one at a time and for each face I want you to say 'yes' if you think he looks pleasant and 'no' if you think he is not so pleasant. There is no right or wrong answer but I do want you to make a judgement about each face. Here is the first photograph. Does he look pleasant or not so pleasant?"

The examiner then displays the 50 faces to the individual at a rate of approximately 1 every 3 seconds. At the end, the examiner says:

"Now I am going to test your memory for the faces you have just seen in the pack. (Show first choice). Which of these faces have I just shown you? You are to guess if you are not sure."

The examiner records each response and the total number correct (maximum = 50).

Tests of Occipital-Parietal Lobe Functioning: Gollin Figures Test; Benton Facial Recognition Test (BFRT)

The Gollin Figures Test (Gollin, 1960) Form A (Mack, Patterson, Schnell, and Whitehouse, 1993) was used as a test of occipital-parietal lobe functioning. This test requires identification of incomplete drawings of objects and has been associated with functioning of posterior brain regions (Warrington & James, 1967b; Warrington & Rabin, 1970; Warrington & Taylor, 1973).

The Gollin Figures Test consists of 20 picture series of five line drawings of familiar objects (e.g., shoe, pig). The drawings range in completeness from suggestive sketches to complete drawings. The examiner records the number of incomplete drawings of the object the participant has to see before recognizing it.

Form A (Mack et al., 1993), which consists of 10 of the 20 picture series, was used. All 5 line drawings were presented for each of the 10 picture series. If the subject had already identified what the picture was, they were asked to simply keep repeating the

correct response each time the picture was presented. Each stimulus was presented until the subject gave a response or 30 seconds elapsed, whichever came first. The best possible score on this test was 10 and the worst possible score was 50.

The BFRT (Benton, Hamsher, Varney & Spreen, 1983) was also employed as a measure of posterior (i.e., occipital-parietal lobe) brain functioning. The BFRT is a face-matching task in which an individual is required to find a target face from among a set of six faces presented simultaneously. This test was developed as a measure of face recognition ability without a memory component (Lezak, 1995).

The BFRT short form (Benton et al., 1983) consists of 16 stimulus cards requiring 27 separate matches. The participant is presented with a booklet containing the stimulus faces on the upper page and the 6 faces to choose a match from on the bottom page. Three sets are presented to the individual: a. Identical front views; b. front with side views; and c. front views taken under different lighting conditions. Six of the items involve only single responses (i.e., only one of the six pictures on the stimulus card is of the same person as the sample), and the remaining items require three matches to the sample stimulus. It has been determined that the short form correlates highly with the long form (.88 to .93) (Levin, Hamsher, & Benton, 1975). The short form of this test was used to limit administration time. Conversions of short form scores into long form scores is possible using a table published on the BFRT response form.

The examiner records correct responses and errors made on a response sheet. The long form converted total number of correct responses was analysed. The maximum number of correct responses was 54.

The BFRT was included in this study as a measure of posterior region functioning. Thus, it was possible to compare performance of subjects on both a facial recognition test involving memory (RMF) and a facial discrimination test not involving memory (BFRT).

Questionnaires Assessing Subjective Mood and Memory Complaints

Measures Assessing Dysphoric and Anxious Mood: Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI)

Simon et. al (1993) demonstrated that once emotional distress had been covaried from memory scores, differences between MCS and chronic illness controls in memory scores disappeared. Accordingly, it is important in subsequent studies that compare MCS groups with controls to investigate if emotional variables may account for any cognitive differences. Dysphoric symptoms were measured with the BDI (Beck, 1978) and anxiety symptoms with the BAI (Beck & Steer, 1990).

The BDI is a 21-item self-report questionnaire designed to assess the severity of depression in adolescents and adults. The instructions for this instrument are as follows:

"This questionnaire consists of 21 groups of statements. After reading each group of statements carefully, circle the number (0, 1, 2, or 3) next to the one statement in each group which best describes the way you have been feeling the past week, including today. If several statements within a group seem to apply equally well, circle each one. Be sure to read all the statements in each group before making your choice."

The total score, cognitive-affective subscale score, and the somatic-performance

complaints subscale score were coded. The Cognitive Affective Subscale of the BDI (Beck & Steer, 1993) was used in all statistical analyses because it minimizes the effect of somatic disturbances on estimates of depression (Beck & Steer, 1993; Brown-DeGagne, McGlone, & Santor, unpublished manuscript; Nyenhuis, Rae, Zajecka, Luchetta, Bernardin, & Garron, 1995). The maximum possible score on the Cognitive Affective Subscale was 39.

The BAI (Beck & Steer, 1990) is a 21-item self-report questionnaire that measures symptoms of anxiety. The instructions for this questionnaire are as follows:

"Below is a list of common symptoms of anxiety. Please carefully read each item in the list. Indicate how much you have been bothered by each symptom during the PAST WEEK, INCLUDING TODAY, by placing an X in the corresponding space in the column next to each symptom."

To each of the 21 items, the individual responds "not at all", "mildly (it did not bother me much)", "moderately" (it was very unpleasant, but I could stand it), or "severely (I could barely stand it). The maximum possible score for this test was 63.

Measure of Subjective Memory Complaints: Memory Observation Questionnaire - 2 (MOQ-2)

Individuals may perceive their memory problems to be either less severe or more severe than their test scores suggest. For example, McGlone (1994) assessed subjective memory complaints and actual memory performance before and after temporal lobectomy. Post-surgery memory complaints remained similar to those pre-surgery or

they diminished. Memory performance, however, declined after surgery. Regression analyses showed that self-reported depression post-operatively was a predictor of postoperative memory complaints. Additionally, factor analysis indicated that dementia patients' memory complaints correlated with depression but not with objective memory performance (McGlone, Gupta, Humphrey, Oppenheimer, Mirsen & Evans, 1990). Together, these results suggest that memory complaints may be influenced by mood.

Subjective memory complaints were assessed with the Memory Observation Questionnaire 2 (MOQ-2) (McGlone, Gupta, & Humphrey, 1987). The MOQ-2 is a self-report questionnaire that asks an individual to answer questions regarding his or her memory. Part A of this questionnaire asks the individual to respond true or false to a series of 32 questions. Part B of this questionnaire asks an individual to rate his or her memory change over the past several months (i.e., much worse, worse, the same, better, much better). There are 23 questions in Part B. The instructions for this questionnaire are as follows:

"Please answer this Questionnaire on your own without consulting anyone. Find a quiet place to do this where there are no distractions (e.g., telephone ringing, conversations, radio or T.V., etc.), so that you can concentrate. There are 2 parts to this Questionnaire. Begin with Part A, and then do Part B. Part A: Read each statement carefully. If you agree with the statement, circle TRUE, if you disagree with it, circle FALSE. Please try to give an accurate appraisal of yourself. Remember to answer questions on both sides of the page. Part B: In this part, you should indicate whether your memory for things has changed or stayed the same. Examine the 5 column headings

("Much Worse", "Worse", etc.) On the right side of the page. These headings represent degree of memory change over the past several months. Read each statement and then select one level of memory change that applies to you. CIRCLE the X that is on the line directly under the memory change you have selected. If you believe there has been no change, circle the X in "The Same" column. Please respond to items on both sides of the page. REMEMBER, answer the questions by yourself without consulting anyone."

The total scores for MOQ-2 Parts A and B were recorded to provide measures of individuals' subjective memory complaints and changes in memory over the past several months. The maximum score for Part A was 20. Low scores on the MOQ-2A indicate greater memory complaints. The maximum score for Part B was + or - 46 as items were scored as follows: "Much Worse" = -2; "Worse" = -1; "The Same" = 0; "Better" = 1; "Much Better" = 2.

2.4 Procedure

This study was approved by the Ethics Review Board of the Queen Elizabeth II Health Sciences Centre, the Human Ethics Committee of Dalhousie University's Graduate Studies Program, and the Research Review Committee of the Environmental Illness Clinic, Nova Scotia. All participants gave informed consent prior to completing the tests and questionnaires (see Appendix E). All neuropsychological tests and the questionnaires were completed in the same order (see Appendix F) in approximately 2 1/2 consecutive hours. Participants were not provided with information regarding the hypotheses of the study. The examiner was not blinded to group membership. Each

participant was paid $10.00 to help cover the costs of travel.

2.5 Statistical Analyses

Univariate Analyses of Variance (ANOVAs)

Univariate ANOVAs were conducted in order to examine between group performance on the seven neuropsychological measures sensitive to frontal, temporal, and posterior lobe functioning. Huberty and Morris (1989) recommend the use of univariate ANOVAs when no multivariate predictions or hypotheses are proposed and when the questions formulated by the researcher are univariate questions. In addition to analysing the 7 neuropsychological tests separately, composite scores for each of the 3 proposed brain regions (frontal, temporal, and posterior) were identified and analysed. Scores for each subject on all 7 measures were transformed into Z scores using the healthy control group means and standard deviations as norms on each of the relative 7 measures. Z scores were used in order to facilitate aggregation of test scores. Aggregation of test scores into region scores would not have been possible without the use of standard scores given the variable measurement scales for each test (Toothaker, 1986).

For tests assigned to a brain region, the Z scores were averaged to yield a region score. In order to combine scores where low values indicated better performance (i.e., a negative z score indicated better performance) with scores where high values indicated better performance, negative z scores were first reverse scored and then aggregated with the positive z scores. For labelling purposes, the terms "frontal, temporal and posterior" are used. However, it is understood that labels reflect the measures' sensitivity to a brain

region's functioning rather than circumscribed frontal, temporal, and posterior regions, per se. A frontal region score was devised by averaging Z scores on the COWA and SOP tests for each individual. A temporal region score was devised by averaging Z scores on Logical Memory (immediate and delayed) and the RMF. In addition, an anterior region score was devised by averaging frontal and temporal region Z scores. A posterior region score was devised by averaging Z scores on the Gollin Figures Test and the BFRT. Univariate ANOVAs were then carried out on the 3 region scores (i.e., frontal, temporal, and posterior). Post-hoc testing of any significant overall F values on each ANOVA was accomplished with the use of Bonferroni tests.

Univariate analyses of variance (ANOVAs) were conducted to examine between group differences on premorbid estimates of IQ (NART-R Full Scale IQ, regression equation Full Scale IQ) and current estimates of anxiety (BAI) and depression (BDI).

Analyses of Covariance (ANCOVAs)

In order to control for the influence of premorbid IQ estimates on current estimates of cognitive performance, a univariate analysis of covariance (ANCOVA) using the composite premorbid IQ scores as a covariate was performed. In order to control for the influence of depression and anxiety on cognitive measures, a second ANCOVA using the BDI cognitive affective subscale score and the BAI total score as covariates was performed.

Between-Test Analyses

In order to assess between-test differences on localizing cognitive measures, a repeated measures analysis of variance was conducted. To further understand significant between-test findings, dependent sample t-tests were performed on composite region scores for the MCS and asthma control groups. Dependent sample t-tests were not performed on composite region scores for the healthy control group because this group was the benchmark against which standard scores for the other two groups were calculated.

Medication Analyses

Because medication can affect cognitive performance (Lezak, 1995), analyses were performed to assess relations between medication use and cognitive functioning. The number and types of medications taken were recorded. The mean number of medications currently taken for each individual across groups was compared using ANOVA. Any significant findings were followed up with post hoc comparisons using the Bonferroni correction.

To assess the relation between region scores and the number of medications taken, frontal, temporal, and posterior region z scores and number of medications were correlated.

To observe group differences in the absence of medication as a potential confounding factor, subgroups were created consisting of only those individuals currently not taking medication. Univariate ANOVA's comparing MCS, asthma and healthy

control groups on frontal, temporal and posterior region scores were then calculated. Within the subsamples not on medication, dependent sample t-tests were calculated to compare frontal, temporal and posterior region z scores.

Substance Checklist Scores and Asthma Group Findings

Individuals in the asthma group varied in their Substance Checklist total scores. It was hypothesized that high scores on the Substance Checklist indicated overlap between MCS and asthma. Only those individuals in the asthma group who scored high on this measure would score significantly more poorly on frontal and temporal lobe tasks than posterior tasks. To assess the effect of high and low Substance Checklist scores on cognitive test scores in the asthma group, the asthma group was split into two groups using the Substance Checklist scores. Individuals with high scores were separated from those with low scores, using the median (52) as a midpoint. ANOVAs assessed between group differences on the frontal, temporal and posterior regions z scores. Dependent sample t-tests assessed frontal, temporal and posterior region score differences within the two asthma groups.

Correlational Analyses

In order to assess the relation between memory performance and subjective memory complaints, Pearson correlation coefficients were computed between the composite memory scores and the MOQ-2A scores within each of the three groups. No correction was necessary to control for type one error increase as only single pairwise

comparisons were computed.

In order to assess the relation between subjective memory complaints and anxiety and depression, correlation coefficients were computed between the BDI and BAI, and the MOQ-2A scores within each of the three groups. Because several pairwise comparisons were made, an adjusted Bonferroni alpha level was used.

In order to assess the relation between anxiety and depression and the cognitive measures, correlation coefficients were computed between the BDI and BAI, and the frontal, temporal and posterior region scores. Due to the large number of comparisons, an adjusted Bonferroni alpha was computed and used to determine significance of correlation coefficients.

Finally, in order to assess the relation between anxiety and depression and scores on the Substance Checklist, correlation coefficients were computed between the BAI and BDI and the substance checklist total scores. An adjusted Bonferroni alpha was calculated to determine significance of the correlation coefficients.

Chapter 3. Results

3.1 Screening

Handedness

All 63 participants screened for right-handedness via the telephone interview also demonstrated a right hand preference on the Handedness Questionnaire. All participants met the 6 out of 8 mime criterion on this measure.

Motivation

All participants in the MCS and asthma control groups obtained a score of 100% on the Abbreviated Hiscock Forced Choice Procedure. One individual in the healthy control group made an error on this measure, obtaining a total score of 97.2%. No person was excluded based on the Abbreviated Hiscock Forced Choice Procedure.

Substance Checklist

Table 1 contains the means and standard deviations on the Substance Checklist for all three groups.

Insert Table 1 about here.

All individuals in the MCS sample scored above the cutoff of 23 out of 122 on the Substance Checklist. No MCS participants were excluded due to a low score on this

measure. Seventy-one percent of the asthma group scored above 23 on the Substance Checklist. No individuals in the healthy control group scored above 23 on the Substance Checklist. A significant between group difference was found on the substance checklist scores ($F_{(2,60)} = 88.08$; $p<.05$). Post-hoc analyses using the Bonferroni correction indicated that individuals with MCS had significantly higher substance checklist scores than individuals with asthma ($t_{(1,40)} = 6.12$, $p<.05$) and healthy controls ($t_{(1,40)} = 13.26$, $p<.05$). The number of substances endorsed by asthmatics was significantly higher than healthy controls ($t_{(1,40)} = 7.14$, $p<.05$).

3.2 Demographics and Health Characteristics

Sex, Age, and Education

Ninety-five percent of the sample was female. Means and standard deviations for each group on age and years of education are presented in Table 1. Age ($F_{(2,60)} = 1.68$, $p>.05$) and years of education ($F_{(2,60)} = .98$, $p>.05$) did not differ significantly among groups.

Estimated Premorbid IQ

Means and standard deviations for each group on the two measures of estimated premorbid Full Scale IQ are presented in Table 1. Results of ANOVAs comparing the three groups on the estimates of premorbid IQ revealed no significant between group differences on the regression equation IQ estimates ($F_{(2,60)} = 1.69$; $p>.05$). However, a significant between group difference was found on the NART-R IQ estimate ($F_{(2,60)} =$

4.34; $p<.05$). Post-hoc analyses using the Bonferroni correction indicated that individuals in the asthma control group had significantly lower NART-R IQ estimates than the healthy control group ($t_{(1,40)} = 2.78$, $p<.05$). No other significant group differences were found.

A composite premorbid IQ estimate score was derived by averaging the two premorbid estimate scores (NART-IQ and regression equation IQ). A significant between group difference was found on this composite IQ estimate ($F_{(2,60)} = 3.51$; $p<.05$). Post-hoc comparisons using the Bonferroni correction indicated that individuals with asthma had significantly lower composite IQ estimates than the healthy control group ($t_{(1,40)} = 2.46$, $p<.05$). All other comparisons between groups were not significantly different. Premorbid IQ weighted means and standard deviations for region scores are contained in Table 2. Because of the significant between-group difference on premorbid estimates of IQ, premorbid IQ scores were entered as a covariate in a subsequent analysis of covariance (ANCOVA) assessing frontal, temporal, and posterior region scores (see Neuropsychological Measures, Between-Group Analyses).

Insert Table 2 about here.

MCS Questionnaire

Responses on the MCS Questionnaire revealed that 7 of the 21 (33.3%) individuals with MCS felt that they belonged to a diverse group in which chemicals in the

home or at work had caused their illness. Thirteen (61.9%) individuals felt their symptoms began in the workplace; that they had worked in a tight building (i.e., sick building) where they had been exposed to offgassing from construction materials, perfumes, tobacco smoke or other substances. One (1.6%) individual reported that she was a member of a contaminated community; exposures from air and water contamination by toxic waste sites, pesticide spraying, or industrial dumping caused the illness. No individuals in the MCS group reported being an industrial worker having experienced higher level acute and chronic industrial chemical exposure.

The average number of months that individuals with MCS reporting being ill was 84.9 (SD = 71.41; range = 18 - 276). On a scale from 1 to 10, where 1 indicated the least severe and 10 indicated the most severe, the MCS group reported an average severity rating of 6.31 (SD = 2.26; range = 2 - 10). Six (28.6%) individuals reported their symptoms had worsened greatly since their onset. Two (9.5%) individuals reported that their symptoms had worsened slightly since their onset. One (4.8%) individual reported that symptoms had remained the same since their onset. Six (28.6%) individuals reported that their symptoms had improved slightly. Finally, six (28.6%) individuals reported that their symptoms had improved greatly since their onset.

Nine (42.9%) of the 21 MCS participants reported that they had received compensation for MCS. Of these nine individuals, three received Worker's Compensation, four received a Canada Pension Plan, and two received compensation through private insurance.

Several different treatments were reported by the MCS group. An average of 5

treatments (SD = 3, range = 0 - 13) had been used by each individual in the MCS group. Twenty (95%) individuals reported taking vitamins, ten (48%) reported dietary changes, nine (43%) reported practising avoidance, eight (38%) used antigens, seven (33%) used massage therapy, and six (29%) used exercise. Acupuncture, homeopathy, and sauna were each used by five (24%) individuals. Four (19%) individuals reported using Enzyme Potentiated Desensitization and three (14%) used physiotherapy. Colonics (bowel cleansing), vitamin B12 injections, magnesium, and relaxation therapy were each used by two (10%) individuals. Finally, air filters, Chinese herbs, chiropractic treatments, fasting, hydrotherapy, oxygen, magnesium sulfate baths, therapeutic touch, and yoga were each reported by one (5%) individual. One (5%) individual reported using no form of treatment for her disorder.

3.3 Neuropsychological Measures

Between-Group Analyses

Means and standard deviations for each group on the neuropsychological tests are presented in Table 3.

Insert Table 3 about here.

Results from separate univariate ANOVA's indicated a significant between group difference on the RMF ($F_{(2,60)} = 3.37$, $p < .05$). Post hoc analyses using the Bonferroni

correction indicated that the asthma group had significantly lower scores than the MCS group on this test ($t_{(1,40)}$ = , $p<.05$). No other significant group differences were found. However, when an ANCOVA was performed to control for the influence of premorbid IQ on the RMF, the between group difference was no longer significant ($F_{(2,60)} = 2.92$, $p>.05$).

The transformed z score means and standard deviations for the three groups on each of the neuropsychological tests are presented in Table 4.

Insert Table 4 about here.

Means and standard deviations for the frontal, temporal, anterior, and posterior composite z scores are presented in Table 5.

Insert Table 5 about here.

Results from univariate ANOVAs revealed no significant group differences on frontal ($F_{(2,60)} = 1.76$, $p>.05$), temporal ($F_{(2,60)} = 3.02$, $p>.05$), or posterior ($F_{(2,60)} = .59$, $p>.05$) region scores. A significant group difference was found on the composite anterior region score ($F_{(2,60)} = 3.16$, $p<.05$). Post hoc comparisons revealed that the asthma group had significantly lower anterior scores than the healthy control group ($t_{(1,40)} = 2.48$, $p<.05$).

When an ANCOVA was performed to control for the influence of premorbid IQ estimates on region scores, no significant between-group differences were found on

frontal ($F_{(2,59)} = .54$, $p>.05$), temporal ($F_{(2,59)} = .39$, $p>.05$), anterior ($F_{(2,59)} = 1.07$, $p>.05$), or posterior ($F_{(2,59)} = .19$, $p>.05$) region scores.

Between-Test Analyses

The repeated measures ANOVA revealed a significant between-test effect for the region scores ($F_{(2,60)} = 6.19$; $p<.05$) (see Figure 1). Subsequent dependent sample t-tests revealed that within the MCS group, the mean frontal and temporal region scores were significantly lower than the mean posterior region score in the MCS group ($t_{(20)} = 2.05$ and 2.92 respectively; $p<.05$). Additionally, the mean composite anterior score was significantly lower than the mean composite posterior score ($t_{(20)} = 2.86$; $p<.05$). Frontal and temporal region scores did not differ significantly from each other ($t_{(20)} = 1.12$, $p>.05$) in the MCS sample.

Insert Figure 1 about here.

The asthma group showed the same pattern of results. Frontal and temporal means were both significantly lower than the posterior mean ($t_{(20)} = 3.25$ and 4.03 respectively; $p<.05$). Their mean composite anterior score was significantly lower than the posterior mean ($t_{(20)} = 4.18$; $p <.05$). Frontal and temporal means did not differ significantly from each other ($t_{(20)} = 1.07$, $p<.05$) (see Figure 1).

3.4 Measures of Anxious and Dysphoric Mood

Means and standard deviations for each group on measures of anxious and dysphoric mood are reported in Table 6.

Insert Table 6 about here.

Significant group differences on levels of anxiety ($F_{(2,60)} = 5.72$; $p < .05$) and depression ($F_{(2,60)} = 4.62$; $p < .05$) were found on the BAI and the BDI cognitive-affective subscale scores, respectively. Post-hoc comparisons using the Bonferroni correction indicated that individuals with MCS reported significantly more anxiety ($t_{(1,40)} = 3.35$, $p < .05$) and depression ($t_{(1,40)} = 2.99$, $p < .05$) than healthy controls. The asthma group did not differ from MCS in anxiety ($t_{(1,40)} = 1.25$, $p > .05$) and depression ($t_{(1,40)} = 1.94$, $p > .05$). Nor did the asthma group report significantly more anxiety ($t_{(1,40)} = 2.09$, $p > .05$) and depression ($t_{(1,40)} = 1.05$, $p > .05$) than healthy controls.

Because significant group differences were found on anxiety and depression, the BAI and BDI cognitive-affective subscale scores were also entered as covariates into an ANCOVA assessing frontal, temporal, anterior, and posterior region scores. Anxiety and depression weighted means are contained in Table 7. No significant between group differences were found on the adjusted frontal ($F_{(2,58)} = 1.89$, $p > .05$), temporal ($F_{(2,58)} = 2.91$, $p > .05$), or posterior ($F_{(2,58)} = .93$, $p > .05$) region scores. Anterior region z scores remained significantly different ($F_{(2,58)} = 3.23$, $p < .05$).

Insert Table 7 about here.

3.5 Memory Complaints

Means and standard deviations for each group on the MOQ-2A and MOQ-2B are reported in Table 6. Significant group differences were found on reported memory complaints (MOQ-2A) ($F_{(2,60)} = 23.43$, $p<.05$). Post-hoc comparisons using the Bonferroni correction indicated that individuals with MCS reported significantly more memory complaints than individuals with asthma ($t_{(1,40)} = 5.59$, $p <.05$) and healthy controls ($t_{(1,40)} = 6.21$, $p <.05$). Individuals with asthma did not report significantly more memory complaints than individuals in the healthy control group ($t_{(1,40)} = .62$, $p >.05$).

Groups did not differ significantly on the MOQ-2B ($F_{(2,60)} = 1.27$, $p>.05$). As is evident from the large standard deviation presented in Table 6, individuals in the MCS group varied in their response to Part B of this questionnaire.

3.6 Medication Analyses

Table 8 contains a list of the different types of medication taken by individuals in the MCS, asthma and healthy control groups.

Insert Table 8 about here.

Groups differed significantly in the number of medications taken ($F_{(2,60)} = 11.99$, $p<.05$). Post hoc analyses using the Bonferroni correction indicated that individuals with asthma ($\underline{M} = 2.67$; $SD = 2.76$) took significantly more medications than individuals with MCS ($\underline{M} = .86$; $SD = 1.06$; $t_{(1,40)} = 3.41$, $p <.05$) and healthy controls ($\underline{M} = .14$; $SD = .36$; $t_{(1,40)} = 4.75$, $p <.05$). The mean number of medications taken did not differ significantly between healthy and MCS groups ($t_{(1,40)} = 1.35$, $p >.05$).

Correlation analyses found no relation between the number of medications taken and the frontal ($r_{(19)} = -.24$, $p >.05$), temporal ($r_{(19)} = -.12$, $p >.05$), anterior ($r_{(19)} = .21$, $p>.05$), and posterior ($r_{(19)} = .03$, $p >.05$) region scores.

Ten individuals with MCS, four individuals with asthma, and eighteen healthy individuals were not taking medication. The means and standard deviations on region scores are presented in Table 9.

Insert Table 9 about here

No significant between group differences were found on frontal ($F_{(2,29)} = .35$, $p>.05$), temporal ($F_{(2,29)} = 1.46$, $p>.05$), anterior ($F_{(2,29)} = 1.08$, $p>.05$), and posterior ($F_{(2,29)} = .65$, $p>.05$) region scores for the non-medicated subsamples.

Further analyses were conducted to see if the anterior-posterior differences reported for the entire MCS and asthma groups remained in the non-medicated subsamples. Within the MCS no-medication subsample, no significant differences were found on frontal and temporal ($t_{(9)} =1.03$, $p>.05$), frontal and posterior ($t_{(9)} = .55$, $p>.05$),

temporal and posterior ($t_{(9)} = 1.39$, $p>.05$), or anterior and posterior ($t_{(9)} = 1.22$, $p>.05$) region scores.

Within the asthma no-medication subsample, frontal region scores remained significantly lower than posterior region scores, despite the small sample size ($t_{(3)} = 3.22$, $p < .05$). Temporal region scores did not differ from posterior region ($t_{(3)} = 2.32$, $p>.05$) scores. Anterior region scores did not differ from posterior region scores ($t_{(3)} = 3.02$, $p>.05$).

3.7 Substance Checklist and Asthma

Region score means and standard deviations for high and low Substance Checklist asthma groups are contained in Table 10.

Insert Table 10 about here.

High and low Substance Checklist asthma groups did not differ on frontal ($t_{(1,19)} = .45$, $p>.05$), temporal ($t_{(1,19)} = .94$, $p>.05$), anterior ($t_{(1,19)} = .78$, $p>.05$), or posterior ($t_{(1,19)} = .21$, $p>.05$) region scores. Dependent sample t-tests found that asthmatic individuals with high Substance Checklist scores had significantly lower temporal region scores than posterior region scores ($t_{(9)} = 2.68$, $p<.05$). Frontal region scores did not differ significantly from posterior region scores ($t_{(9)} = 1.96$, $p>.05$). The composite anterior region scores were significantly lower than the posterior region scores ($t_{(9)} = 2.63$, $p<.05$) Asthmatic individuals with low Substance Checklist scores had significantly lower

frontal, temporal, and anterior region scores than posterior region scores ($t_{(9)} = 2.52$, $p<.05$; $t_{(9)} = 2.99$, $p<.05$, $t_{(9)} = 3.17$, $p<.05$, respectively).

3.8 Correlational Analyses

Table 11 contains the correlation coefficients within each group between anxiety, depression, memory complaint scores, and memory change scores and notes whether they are significant at the conventional .05 alpha level and the adjusted .01 Bonferroni alpha.

Insert Table 11 about here.

Anxiety and depression scores were positively correlated for all three of the MCS, asthma and healthy control groups of participants. Anxiety and depression negatively correlated with memory complaints scores (i.e., low scores indicate more memory complaints) for individuals in the MCS group only prior to application of the Bonferroni correction. Anxiety and depression negatively correlated with memory change scores (i.e., low scores indicate negative changes) for individuals in the MCS group regardless of whether the Bonferroni correction was applied. Anxiety and depression did not significantly correlate with memory complaints or memory change scores in the asthma or healthy control groups.

Pearson correlation coefficients within each group between anxiety, depression and region scores are presented in Table 12. Posterior region scores negatively correlated with depression scores in the asthma sample. Neither anxiety nor depression significantly

correlated with the region scores in the MCS and healthy groups.

Insert Table 12 about here.

Pearson correlation coefficients within each group between memory complaints and memory performance (i.e., temporal region z score) are presented in Table 13. Memory complaints did not significantly correlate with temporal region scores in any of the groups.

Insert Table 13 about here.

Anxiety and depression did not significantly correlate with total Substance Checklist scores for the MCS ($r_{(20)} = .06$, $p>.05$), asthma ($r_{(20)} = -.07$, $p>.05$), or healthy control ($r_{(20)} = .19$, $p>.05$) groups. Severity ratings (i.e., the ratings individuals with MCS gave when asked to indicate how severe their symptoms of MCS were), however, correlated negatively with memory complaints ($r_{(20)} = -.72$, $p<.05$) and memory change scores ($r_{(20)} = -.55$, $p<.05$) in the MCS group.

Chapter 4. Discussion

4.1 Review of the Neuropsychological Test Findings

The Olfactory-Limbic Model of MCS (Bell, 1992) predicted that cognitive weaknesses would be associated more with limbic (i.e., frontal and/or temporal) regions of the brain than with non-limbic regions (i.e., posterior cortex). Between-group comparisons showed that the MCS group performed as well as controls on all cognitive tasks. These findings are consistent with the results of three prior studies of cognitive functioning in individuals with MCS (Fiedler et al., 1992; 1996; Simon et al., 1993). Although somewhat different case definitions and cognitive measures were used, none of the studies found cognitive deficits to substantiate the complaints reported symptomatically in MCS. A list of the cognitive measures administered in each study, including this thesis, is presented in Table 14.

Insert Table 14 about here.

Like the present study, Fiedler et al. (1992) used Cullen's (1987) criteria to select MCS cases and found no cognitive abnormalities relative to norms with the exception of one test of verbal memory (i.e., CVLT). As discussed previously, however, the poor performance on the CVLT relative to norms may have been in part due to the fact that the CVLT was normed on a highly educated sample. Simon et al. (1993) used unique criteria to select MCS cases and found that, once emotional factors had been covaried from the results, no case-control differences on cognitive measures were evident. Fiedler et al.

(1996) again used Cullen's (1987) criteria to select cases and found no cognitive abnormalities with the exception of a complex test of visual memory (CVMT). Multiple regression revealed that achievement test (WRAT-R) scores and age accounted for a significant amount of variance in the CVMT total score. Together, the results do not support the idea that persons identified with MCS perform more poorly on cognitive tests than controls.

Unexpectedly, between-test comparisons showed that both the MCS and asthma groups performed significantly more poorly on tasks sensitive to frontal and temporal regions than to posterior regions. To the author's knowledge, no prior study had assessed cognitive strengths and weaknesses within MCS samples. The MCS between-test findings provided support for the Olfactory-Limbic Model. However, the findings required further analysis given that relative weakness on anterior tasks compared to posterior tasks was not predicted for the asthma control group.

4.2 How Do We Explain the Discrepant Between-Group and Between-Test Findings?

The fact that between-test results were not restricted to the MCS group was an important issue to consider while examining the discrepant between- and between-test findings. Between-test analyses revealed that individuals with asthma scored significantly lower on measures of frontal and temporal region functioning than measures of posterior region functioning. Hypotheses based on the Olfactory-Limbic Model, which were described specifically for MCS (Bell, 1992) did not predict this pattern of

functioning in groups other than those with MCS.

In order to clarify the significance of the between- and between-test findings, several issues needed to be addressed:

1. Does unusually poor performance by healthy individuals on posterior tasks account for the pattern of results in the MCS and asthma groups given that z scores were derived from the healthy group's test means and standard deviations? Similarly, does unusually good performance by MCS and asthma groups on posterior tasks account for the pattern of results?
2. Are the observed cognitive strengths and weaknesses in the asthma group due to asthma related cognitive deficits?
3. Are the findings indicative of similarity between MCS and asthma?
4. Does chronic illness produce this pattern of results?
5. Is there something about the frontal and temporal tasks, other than localizing ability, that makes them different from the posterior tasks that could help explain the findings?
6. Considering individuals with asthma take the greatest amount of medication, is medication a factor in the findings?
7. Do high scores on the Substance Checklist account for the asthma group findings?

1. Does Unusually Good or Poor Performance by Any One Group Account for the Between-Test Findings?

Unusually poor performance by healthy individuals on posterior tasks could have produced the pattern of results seen in the asthma and MCS groups. Poorer performance by healthy individuals would lead to relatively higher z scores in other groups because the z scores were derived from the healthy control group mean and standard deviation. If the mean was unusually low, z scores derived from this mean would be unusually high.

In order to assess whether unusually poor performance by healthy individuals on posterior tasks accounted for the pattern of results in the MCS and asthma groups, performance by healthy individuals on these tasks was compared to published norms (see Table 3). The posterior region scores were derived from combining z scores on the Benton Facial Recognition Test and the Gollin Incomplete Figures Test. According to Benton et al. (1983) norms for the BFRT are as follows: <37 = severely defective; 37-38 = defective; 39-40 = borderline; 41-42 = low average; 43-46 = average; 47-49 = high average; 50-52 = superior; 53-54 = very superior. The mean score for healthy controls in this study was 48.52 (SD = 3.79) suggesting high average performance. Therefore, poor performance on the BFRT by healthy controls cannot explain the finding of significantly better performance on posterior tasks than frontal and temporal lobe tasks by individuals in the MCS and asthma control groups.

Warrington and James (1967b) reported that a sample of controls needed approximately 20.2 incomplete pictures to correctly identify 10 figures on the Gollin Figures Test. In the present study, healthy controls needed only an average of 16.14 (SD

= 2.97) incomplete pictures to correctly identify 10 figures. As with the BFRT, unusually poor performance on the Gollin Incomplete Pictures Test cannot explain the significantly better performance on posterior tasks than frontal and temporal lobe tasks by individuals in the MCS and asthma control groups. Interesting, however, was how well individuals with MCS and asthma performed on the Gollin Figures Test relative to norms (Warrington & James, 1967b). Although they did not perform significantly better than healthy controls, the possibility remained that unusually good performance on the Gollin Figures Test accounted for the present findings. Unfortunately, Warrington and James (1967b) did not publish the mean age and education of their normative sample and more recent normative studies using the Gollin Figure have not been published. However, Dr. James Mack (personal communication, July 28, 1997) is currently conducting normative studies on the Gollin Figures Test. He found that well educated ($\underline{M}$ = 15 years) healthy controls below the age of 50 years (N=26) require, on average, 14.9 (SD = 3.5) incomplete drawings to identify 10 pictures. Healthy controls between the ages of 58 and 69 years (N=72) require, on average, 15.3 (SD = 3.2) incomplete drawings to identify 10 pictures. Thus, the MCS, asthma and healthy control groups in this study did not perform outside the range of what would have been expected given the normative results obtained by Dr. James Mack. Unusually poor performance by healthy controls, or unusually good performance by MCS and asthma groups, did not account for the between-test differences on the region tasks.

Control groups were included in this study to provide a comparison on which to interpret results. Normative studies provide useful information regarding average

performance on a test. However, they do not control for differences in test administration or sample characteristics as control groups can. Thus, more emphasis should be placed on control comparisons rather than norm-based comparisons in this study.

2. Are the Observed Cognitive Strengths and Weaknesses in the Asthma Group Due to Asthma Related Cognitive Deficits?

Possible mechanisms by which asthma could have caused cognitive deficits include anoxia related brain impairments and medication related effects on cognitive abilities. Literature searches (i.e., Medline, Psyclit) conducted to determine if cognitive deficits were associated with asthma found that meta-analyses of studies assessing neuropsychological dysfunction in children with asthma found no deficits due to asthma or asthma medication (Annett & Bender, 1994; Stein, Krasowski, Leventhal, Phillips, & Bender, 1996). Moreover, no reports of asthma related cognitive deficits in adulthood were found through Medline and Psyclit searchers. Thus, the published research on childhood asthma and the lack of published studies relating to cognitive deficits in adult asthma, suggested that cognitive deficits would not have been predicted for the asthma group. The pattern of between-test findings could not be explained by past studies on asthma and cognitive functions. However, this finding does not rule out the possibility of between-test differences in asthma as no published studies assessing between-test differences on cognitive measures could be found.

3. Are the Findings Indicative of Similarity Between MCS and Asthma?

MCS differs from asthma in its nonspecific and multiple symptom pattern (Miller & Mitzel, 1995). The third issue to consider, however, was the possibility that the similar between-test findings for individuals with MCS and asthma indicated overlap in the disorders either in terms of subject selection or illness mechanism. Symptoms of MCS are, by definition, attributed to the environment. For example, individuals with MCS report that substances such as perfume, gasoline, and cigarette smoke provoke reactions (Kipen et al., 1995). Similarly, symptoms of asthma are also often linked to environmental exposures. For example, individuals with asthma may attribute the onset of their disorder to environmental conditions, such as in occupation induced asthma, or they may report increased symptomatology when exposed to specific environmental substances (Hyland, 1990; Rees, 1964). Kipen et al. (1995) noted that many individuals with asthma (53% of their sample) scored in the high range on their Substance Checklist (a checklist designed to measure MCS) suggesting overlap in the substances that provoke symptoms in the two disorders. In the present study, 71% of the asthma sample scored in the high range on the Substance Checklist.

Measures were taken to ensure that participants in this study's asthma group were not in fact individuals with MCS. First, all recruitment advertisements indicated that only those individuals with asthma who did not have MCS were invited to participate in the study. Second, individuals were excluded from participating in this study if they reported a belief that they had, or may have had, MCS. Third, all participants were asked to complete the MCS and Exposure History Questionnaire. All asthma group participants

indicated that none of the questions applied to them.

Although several measures were taken to ensure that individuals in the asthma group did not report MCS, the question remains whether the mechanism of MCS and asthma are similar enough to create analogous patterns of cognitive strengths and weaknesses. Neither research nor theory has been developed to explain these findings. The Olfactory-Limbic Model did not predict these results.

4. Does Chronic Illness Produce the Observed Pattern of Cognitive Strengths and Weaknesses?

The fourth issue to consider related to the possibility that chronic illness, per se, produces a pattern of results indicating poorer performance on frontal and temporal region tasks than posterior region tasks. Literature searches (i.e., Medline, Psyclit) on this issue failed to find studies that report certain brain regions are impaired by chronic illness in general. Chronic illness is typically not studied as a unitary factor, but rather is separated into various specific illness groups. Asthma was selected as the chronic illness comparison group in this study because of past research conclusions indicating no cognitive impairment in asthma and its similarity to MCS in terms of symptom production and avoidance of substances in the environment. Comparing performance by individuals with MCS to individuals with asthma was done to control for the possibility that simply being ill could affect cognitive performance. Therefore, because no group differences were found on frontal and temporal lobe tasks, the possibility remains that the pattern of relative strengths and weaknesses seen in the asthma and in the MCS groups is

attributable to chronic illness, per se.

5. Does Task Difficulty Account for the Pattern of Obtained Results?

The fifth issue was the possibility that there was something about the anterior tasks, other than localizing ability, that made them different from the posterior tasks that could help explain the relative poorer performance on these tests. This issue essentially relates to task difficulty regardless of the reasons for why the tasks may be different. The question as to whether the frontal and temporal tasks were more difficult than the posterior tasks can be answered in two ways. First, tests were selected to ensure that neither ceiling nor floor effects would impact on test performance. Studies of measures demonstrating that healthy individuals often obtained perfect scores on that measure were excluded from use in this study (e.g., Visual Object and Space Perception Battery; Warrington & James, 1991). The posterior tasks were selected to ensure that task difficulty was high enough to provide ranges of observed performance (see Table 2). Similarly, the frontal and temporal tasks were easy enough that individuals could perform adequately on the tests. Second, z scores were derived from the healthy control group means and standard deviations, indicating that level of difficulty was accounted for. Even if the frontal and temporal tasks were more difficult, the manner in which tests were equated according to the healthy sample's scores on these measures eliminated the potential confounding effect of task difficulty.

6. Can Medication Use Explain the Findings?

Medication use can affect cognitive ability (e.g., benzodiazepine effects on memory; Lister, 1985), but do they account for the pattern of results in this study? Analysis of the numbers of medications taken revealed no significant relation between number of medications taken and frontal, temporal or posterior region functioning in any of the groups. However, when between-test analyses were performed on the no-medication subgroups, the significant between-test finding for the MCS sample were no longer apparent. Individuals with MCS did not perform significantly more poorly on frontal and temporal tasks than posterior tasks. The difference between frontal and posterior tasks for individuals with asthma remained significant, but temporal-posterior differences no longer were apparent.

Thus, the medication analyses suggested that medication may have played a part in the between-test findings for the MCS and asthma groups. However, this interpretation should be made cautiously. First, sample size was greatly reduced when creating subsamples not on medication. A lack of power may have accounted for the nonsignificant findings. Moreover, results from these small samples may not generalize to other groups of individuals with MCS or asthma. Second, the type and dosage of medication was not considered in the analyses. An analysis which considered type and dosage of medication was not possible given that groups were taking different types of medication. Not all medications are expected to affect cognitive performance. However, all individuals taking medication in this study were excluded when medication analyses were completed. Thus, the potential for factors such as illness severity (i.e., individuals

taking medication might be more ill than individuals not taking medication) rather than medication use, per se, may be accounting for the discrepant findings between individuals taking and not-taking medication.

7. Do High Scores on the Substance Checklist Account for the Asthma Group Findings?

The question of whether high scores on the Substance Checklist could account for the asthma between-test findings was also addressed with additional analyses. It was hypothesized that high scores on the Substance Checklist indicated overlap between MCS and asthma. Only those individuals in the asthma group who scored high on this measure would score significantly more poorly on frontal and temporal lobe tasks than posterior tasks.

Results of these analyses suggest that the number of substances an individual reacted to did not account for the asthma between-test findings. Individuals with asthma, regardless of whether they reported a high or a low number of substances that provoked symptoms, performed significantly more poorly on temporal than posterior region tasks. Individuals reporting a lower number of reactive substances also performed significantly more poorly on frontal than posterior region tasks. The findings are not consistent with the hypothesis that reports of high environmental stimulus reactivity accounted for the pattern of between-test results.

4.3 Do the Results Support the Olfactory-Limbic Model?

Several issues were considered to clarify the significance of the apparently discrepant between- and between-test findings in terms of the Olfactory-Limbic Model's predictions for cognitive performance in MCS. Four of the issues considered were determined to be unlikely explanations for the results. First, unusually poor performance by healthy individuals on posterior tasks did not account for the pattern of results in the MCS and asthma groups. Similarly, unusually good performance on the Gollin Figures Test by individuals with MCS and asthma did not account for the findings. Second, literature reviews would not have predicted the observed cognitive strengths and weaknesses in the asthma group. Third, task difficulty was believed to be accounted for through careful task selection and the z score transformations. Finally, additional analyses indicated that high scores on the Substance Checklist did not account for the asthma group findings.

Three possible explanations for the pattern of results obtained within the MCS and asthma groups remain. First, the pattern of strengths and weaknesses in the MCS and asthma samples may have been due to effects of chronic illness. Second, medication use may have affected cognitive performance. When only those individuals who were not on medication were considered, between-test differences on frontal, temporal and posterior tasks disappeared for individuals with MCS. For individuals with asthma, only frontal and posterior scores remained significantly different. The caveat to this finding, however, was the limited sample size that remained once individuals on medication were eliminated from analysis. A trend of decreased frontal and temporal performance relative

to posterior performance remained in both the MCS and asthma groups.

One possible explanation remains that suggests the between-test findings indicate support for the Olfactory-Limbic Model. It is possible that the findings indicate similarity between mechanisms of MCS and asthma. Although measures were taken to ensure minimal overlap in the disorders during subject selection, the possibility remains that the nature of the two disorders (i.e., reactivity to and avoidance of environmental substances) provides adequate overlap to account for the findings. Factors that make this interpretation unlikely, however, include: 1) individuals with asthma did not report memory complaints; 2) a theoretical explanation for the findings is lacking; 3) self-reported reactivity, as measured by the Substance Checklist, was not related to cognitive ability in the asthma sample.

4.4 Memory Complaints and MCS

The MCS group reported significantly more memory complaints than the asthma and healthy control groups. Despite this increase in memory complaints, individuals with MCS performed as well as controls on all cognitive measures. Moreover, memory complaints did not correlate with objective memory tests. Results from this study suggested that the focal brain dysfunction hypothesis proposed by Bell (1992) could not explain the memory complaint behaviours observed in MCS. Factors such as depression, anxiety, Somatization Disorder and malingering, as well as factors related to the heterogeneous nature of MCS samples, may have related to the discrepant findings regarding subjective and objective memory abilities. The likelihood of each of these

factors contributing to memory complaint behaviours in the MCS group is addressed below.

Depression and Anxiety

Results of this study indicated that individuals with MCS reported significantly more anxiety and depression than healthy controls. The trend for the MCS group to report more anxiety and depression than asthmatic controls was not statistically significant. The increase in anxiety and depressive symptomatology in the MCS group was consistent with case-series reports (Stewart & Raskin, 1985) and case-control studies (Black et al., 1990; Fiedler et al., 1996; Simon et al., 1990; 1993).

Depression and anxiety have been associated with memory complaint behaviours (Gass & Apple, 1997; McGlone et al., 1990). In the current study, memory complaints were significantly correlated with depression and anxiety in the MCS sample prior to application of a Bonferroni correction to control for increases in Type 1 error. Memory complaints were not significantly correlated with anxiety and depression in the asthma and healthy control groups. The correlations between anxiety and memory complaints and depression and memory complaints in the MCS group were high (i.e., $r = -.51$ and $-.50$, respectively). Because it can be argued that an a priori rationale for predicting these significant correlations was evident (i.e., depression and anxiety have been associated with memory complaint behaviours in past research) it can be concluded that the high correlations between anxiety and depression and memory complaints indicate a relation between increased anxious and dysphoric mood and increased memory complaints in the

MCS sample.

Somatoform Disorder

Brodsky (1983; 1987) concluded that MCS is a manifestation of psychiatric conditions known as somatoform disorders. According to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; 1994):

> The common feature of the Somatoform Disorders is the presence of physical symptoms that suggest a general medical condition (hence, the term somatoform) and are not fully explained by a general medical condition, by the direct effects of a substance, or by another mental disorder (e.g., Panic Disorder). The symptoms must cause clinically significant distress or impairment in social, occupational, or other areas of functioning. In contrast to Factitious Disorders and Malingering, the physical symptoms are not intentional (i.e., under voluntary control). (Page 445)

Somatoform disorders include such disorders as Somatization Disorder, Conversion Disorder and Hypochondriasis. Somatization Disorder has been defined as a "polysymptomatic disorder that begins before age 30 years, extends over a period of years, and is characterized by a combination of pain, gastrointestinal, sexual, and pseudoneurological symptoms." (Page 445; DSM-IV, 1994) Several of the diagnostic criteria for Somatization Disorder apply to the features of MCS. For example, according to the DSM-IV (1994):

> The essential feature of Somatization Disorder is a pattern of recurring, multiple, clinically significant somatic complaints. A somatic complaint is considered to be clinically significant if it results in medical treatment (e.g., the taking of medication) or causes significant impairment in social, occupational, or other important areas of functioning...The multiple somatic complaints cannot be fully explained by any known general medical condition or the direct effects of a substance...Most individuals with the disorder describe the presence of nausea and abdominal bloating...There must also be a history of at least one symptom, other than pain, that suggests a neurological condition...Finally, the unexplained symptoms in Somatization Disorder are not intentionally feigned or produced. (Page 446)

Several of the diagnostic features for this disorder, however, do not match the features of MCS. For example, according to the DSM-IV (1994):

> The somatic complaints must begin before the age 30 years and occur over a period of several years...Vomiting, diarrhea, and food intolerance are less common...Individuals with Somatization Disorder usually describe their complaints in colorful, exaggerated terms, but specific factual information is often lacking." (Page 446)

Thus, the symptomatology and features of MCS, most notably the lack of a medical explanation to support subjective complaints, are similar to what has been described in the psychiatric literature as Somatization Disorder. However, several

features of MCS, notably the very detailed medical histories that are provided to examiners and the onset of symptoms often after the age of 30 years (Cullen, 1994), do not match the DSM-IV description of Somatization Disorder.

Somatization Disorder is a descriptive label applied to individuals experiencing multiple somatic symptoms for which no medial explanation has been derived. The label implies a psychiatric component to the symptomatology. MCS is a descriptive label applied to individuals experiencing multiple somatic complaints for which they attribute environmental causes. No medical explanations have yet been provided to fully explain the MCS phenomenon. Labelling MCS as thus a variant of Somatization Disorder provides little additional information and may imply psychogenic causes for the disorder where none have been demonstrated scientifically. In fact, any condition for which a medical explanation is lacking could be considered a variant of Somatization Disorder if multiple somatic complaints are experienced. A lack of understanding for the mechanisms involved in a disorder should not be used to imply psychogenic origins.

Malingering

Individuals with MCS complain of memory impairment but are not found to be significantly impaired relative to controls on objective neuropsychological tests. One might assume that complaints reflect desire to mislead others into believing impairments exist where none are experienced. Moreover, nine of the twenty-one individuals in the MCS group reported receiving compensation for MCS. In order to assess whether participants in this study were motivated to perform their best on the neuropsychological

measures, the Abbreviated Hiscock Forced Choice Procedure (Guilmette et al., 1988) was administered. All individuals with MCS achieved a score of 100% on this measure suggesting that complaints did not reflect a tendency to malinger brain impairment.

4.5 Are the Results of This Study Related to the Heterogeneity of the MCS Sample?

Diagnosis of MCS and Memory Impairments

The lack of agreement on an operational definition for MCS has proved a hindrance to scientific analysis of the disorder and a limited understanding of the problem. To distinguish individuals with MCS from other individuals experiencing similar symptoms (e.g., fatigue, headache, dizziness, lack of concentration, memory loss) but labelled with other diagnoses such as chronic fatigue, an attempt has been made to define MCS in terms of attribution to environmental exposures. Cullen's definition (1987) was used in this study to help select a relatively homogeneous sample of individuals with MCS. However, due to the nature in which participants were selected (i.e., self-report) the question remains as to whether the sample was in fact homogeneous. It is possible that some individuals in the sample attributed their symptoms to MCS whose symptoms were produced by some other illness (e.g., chronic fatigue syndrome, psychiatric disturbance). Moreover, Cullen's criterion 1 (i.e., the disorder is acquired in relation to some documentable environmental exposure(s), insult(s), or illnness(es)) was not used in this study as an inclusionary factor. Some individuals (i.e., 15 /21) met all of Cullen's (1987) criteria, while others (i.e., 6/21) met all but criterion 1.

Researchers such as Bell et al. (1992) and Fiedler et al. (1996) have raised the

issue of possible differences between subgroups of individuals with MCS. Bell et al. (1992) hypothesized that the Olfactory-Limbic Model of MCS would likely best apply to individuals with a clear onset of the disorder. Although it was hypothesized that the model would apply to all cases of MCS, the pathophysiology of a kindling like mechanism (i.e., sensitization model) might best apply to cases in whom a major chemical exposure event preceded the marked decrement in health.

Fiedler et al. (1996) actually compared different samples with symptoms of MCS on psychiatric and neuropsychological measures. They separated those individuals with chemical sensitivities who did not experience a clear onset of their symptoms (CS) from those who did (MCS) and found that although the majority of the findings indicated that both individuals with MCS and CS performed as well as controls on cognitive tasks, only individuals who reported a clear onset of their symptoms performed significantly more poorly than controls on a measure of visual memory. Moreover, individuals with CS had a higher rate of psychiatric morbidity (69%) than individuals with MCS (43%).

To further understand the present study's findings, the MCS sample was subdivided into two groups. The first group (MCS-Clear Onset) consisted of 15 (71% of MCS group) individuals who reported a clear onset of symptoms (Cullen's criterion 1). The second group (MCS- No Clear Onset) consisted of 6 (29% of MCS sample) individuals who could not recall a clear onset of symptoms. ANOVA's were then computed to compare MCS-Clear Onset, MCS- No Clear Onset, asthma and healthy control groups on frontal, temporal, and posterior region scores. ANOVAs were also computed to compare MCS-Clear Onset, MCS- No Clear Onset, asthma and healthy

control groups on BDI, BAI, MOQ-2 and Substance Checklist scores. Dependent sample t-tests compared region scores in the MCS- Clear Onset and MCS- No Clear Onset samples. Results of these analyses are presented in Appendix G.

The MCS- Clear Onset group reported significantly more depression and anxiety than healthy controls. The MCS-No Clear Onset group did not report significantly more depression and anxiety than healthy controls. Both the MCS-Clear Onset and MCS-No Clear Onset groups reported more memory complaints than the asthma and healthy control groups. Both MCS groups also had significantly higher Substance Checklist scores than the asthma or healthy control groups. Substance Checklist scores did not differ for the MCS-Clear Onset and MCS-No Clear Onset groups.

The only significant between-group difference found was for temporal region scores. Individuals with asthma performed significantly more poorly on temporal tasks than individuals in the MCS-No Clear Onset group. No other significant between-group differences were found.

Dependent sample t-tests comparing frontal, temporal, posterior and anterior region scores indicated that individuals with MCS- Clear Onset scored significantly lower on temporal and anterior (but not frontal) scores than posterior scores. No significant between-test differences were found for individuals with MCS- No Clear Onset.

The results indicated few differences between individuals classified as MCS-Clear Onset and those classified as MCS- No Clear Onset. Both groups reported significantly more memory complaints than asthma or healthy controls. Analysis of group differences on region scores failed to support the notion that only individuals with

MCS-Clear Onset perform significantly more poorly than controls on cognitive tasks. However, only the MCS-Clear Onset group had elevated scores on mood measures relative to controls.

The results of the between-test analyses indicated differences for individuals with MCS-Clear Onset and those with MCS-No Clear Onset. Like asthmatics, only individuals with MCS-Clear Onset performed significantly more poorly on temporal and anterior region scores than posterior region scores. Individuals with MCS-No Clear onset showed no relative between-test strengths and weaknesses on the cognitive tasks.

Within samples of individuals with MCS, cognitive profiles may differ depending on whether symptom onset can be identified. Only those individuals with MCS-Clear Onset had cognitive profiles in support of the Olfactory-Limbic Model. This interpretation should be made cautiously, however, given that the sample size for MCS-No Clear Onset group was very small (N=6). The pattern of obtained results suggested that the lack of significant between-test findings for the no clear onset group was not due to lack of power. However, the small sample size may not be representative of individuals with no clear onset of MCS in general. To better understand the generalizability of these findings, this same study could be run with larger samples of each of these two subgroups of MCS.

Severity of MCS and Memory Impairments

An additional potential explanation for this study's discrepant findings regarding subjective and objective memory abilities in MCS relates to severity of the disorder. The

participants in this study ranged in reported severity of symptomatology. Symptom severity was rated on a ten point scale. Some reported that their symptoms were severe while others reported that symptoms were relatively mild. In order to better understand the relation between memory complaints, memory ability, and severity of illness, correlational analyses were performed between these factors for individuals in the MCS sample.

Severity ratings did not significantly correlate with any region scores for individuals with MCS. Severity ratings, however, significantly correlated with memory complaints. Results from these analyses suggest that severity ratings of MCS were not related to objective cognitive impairment but were related to subjective memory complaints. The notion that only those individuals with MCS who report severe symptomatology are cognitively impaired thus seems unlikely. However, those individuals with severe MCS were more likely to perceive cognitive deficits.

4.6 What Are the Limitations of the Present Study?

The findings of this study are potentially limited by the following factors: 1) the examiner was not blind to group membership; 2) neuropsychological tests were used to perform a localizing function; and 3) criterion 1 of Cullen's definition of MCS was not used as an inclusionary criterion.

Testing not Blind

The examiner in this study was not blind to group membership. The potential for

confounding results due to experimenter bias (e.g., unintentional changes in protocol across groups) existed. To minimize the potential for the examiner to influence test performance, all participants were administered the tests in the same order. Additionally, standardized instructions were given to all subjects. Scoring of all test material was completed by the examiner as well. Again standardized scoring techniques were used to minimize use of subjective impressions of performance to derive test scores.

Use of Neuropsychological Tests to Localize Function

In this study, neuropsychological tests were used to assess whether cognitive deficits in MCS could be localized to the frontal and temporal lobes. Localizing tests were selected based on available data documenting deficits associated with specific localized lesions. Additionally, corroborating evidence from imaging studies was sought to help substantiate the localization claims. Thus, rather than directly assessing brain regions through the use of imaging or autopsy techniques, brain regions were assessed via functions associated with those regions. Inferences were drawn from function to anatomy. The results are potentially limited because of the less than perfect relationship between function and anatomy.

Few double dissociation studies (i.e., Frisk & Milner, 1990; Logical Memory) were available to provide good localization data. Moreover, single dissociations are often provided for tests of right vs. left temporal lobe functions (Ellis, Hillam, Gardno, & Kay, 1991; Morris & Abrahams, 1995), but are lacking with respect to other regions and within-hemisphere comparisons. Imaging studies were reviewed when available to

substantiate results from the dissociation studies. However, not all measures used in this study have been analysed with imaging technology. Thus, although steps were taken to select cognitive measures with the best localizing ability, the results of this study are limited by the extent to which the neuropsychological tests selected can in fact localize function.

Cullen's Definition of MCS

Cullen's definition of MCS (1987) requires that: 1) the disorder is acquired in relation to some documentable environmental exposure(s), insult(s) or illness(es); 2) symptoms involve more than one organ system; 3) symptoms recur and abate in response to predictable stimuli; 4) symptoms are elicited by exposures to chemicals of diverse structural classes and toxicological modes of action; 5) symptoms are elicited by exposures that are demonstrable. In this study, the criteria outlined by Cullen (1987) were assessed via self-report. Any conclusions, therefore, must be considered in light of the limitations associated with self-report studies such as the possibility of intentional or unintentional untruthful responses and the desire to respond in a manner in which it is believed he or she should.

Moreover, failure to meet criterion 1 (i.e., the disorder is acquired in relation to some documentable environmental exposure(s), insult(s), or illness(es)) was not used as an exclusionary measure in this study. The decision to include individuals in the MCS group who failed to meet Cullen's (1987) first criterion was based on two factors. First, researchers such as Ashford and Miller (1991) reported that they did not believe that

documentable environmental exposures should be used to identify individuals with MCS. Second, research reviewers of a local environmental clinic suggested that criterion 1 not be used to exclude individuals because, based on their experience, several individuals whom they felt had MCS did not meet this criterion.

In the present study, 15 of the 21 individuals with MCS met Cullen's criterion 1. Analyses assessing group differences on localizing tasks revealed that neither individuals meeting all of Cullen's criteria nor individuals meeting all but criterion 1, performed significantly more poorly than asthmatic or healthy controls on the localizing tasks. These results suggest that although the present group of MCS participants differs from past studies which have used all of Cullen's criteria to select subjects (Fiedler et al., 1992; 1996), individuals who met all of Cullen's criteria did not differ in terms of ability to perform cognitive tasks from those individuals who did not.

4.7 Can the Results of This Study Generalize to Exposure Conditions?

The results of this study may not generalize to conditions in which an individual is exposed to substances believed to create symptoms. The findings of this study suggested that under conditions in which an individual is not exposed to substances believed to cause symptoms, individuals with MCS perform as well as asthmatic and healthy controls. Controlled exposure studies are needed to test the hypothesis that individuals with MCS experience cognitive deficits relative to controls under exposure conditions.

4.8 What Future Studies Should Be Done?

Future studies assessing cognitive deficits in MCS are not needed to provide additional evidence that MCS groups perform as well as controls on neuropsychological tests. Research is needed, however, to: 1) clarify the between-test findings in this study; 2) test the hypothesis that individuals with MCS experience cognitive deficits under exposure conditions; and 3) test competing hypotheses regarding the nature of psychiatric disturbances seen in individuals with MCS.

Clarifying Between-Test Findings

The results of this study indicated that individuals with MCS performed more poorly on tests of anterior than posterior region functioning. This finding supports the Olfactory-Limbic Model predictions. However, individuals with asthma showed this discrepancy even more strongly than the MCS group. This finding was not predicted by the Olfactory-Limbic Model because participants with asthma were included as a chronic illness control group. Similar between-test analyses could not be conducted on healthy controls as the findings from this group of subjects were used to create region z scores (i.e., region scores for the healthy control group had a mean of 0).

The between-test findings may be due to several factors. As noted, deficits due to chronic illness, medication use, Cullen's criterion 1, or some factor common to both MCS and asthma (e.g., environmental triggers of symptoms) may be accounting for the findings. Future studies are needed to clarify these possibilities. For example, the present study could be run with the addition of other illness control groups and with the inclusion

of an additional exclusionary factor for all groups, namely medication use. Individuals infected with the influenza virus might serve as an illness control group. Their symptomatology in part resembles MCS. However, their symptoms are not attributable to chronic, ongoing environmental exposures but rather are attributed to viral infection. Additionally, participants with musculoskeletal injuries might serve as a second illness control group. Cognitive findings within this group would be attributable to factors associated with chronic musculoskeletal injury such as pain or restricted activity.

Assessing additional illness control groups would help clarify the nature of this study's between-test findings. If additional illness control groups perform significantly more poorly on anterior than posterior tasks, the conclusion that factors related to being ill are likely producing the findings is substantiated. If, however, other illness control groups do not perform significantly more poorly on anterior than posterior tasks, the hypothesis that environmental exposures and/or factors similar between MCS and asthma are producing the between-test findings needs further assessment.

Testing Under Exposure Conditions

Individuals with MCS report that memory difficulties are exacerbated by exposure to substances that provoke symptoms related to their disorder. At present, no study has been conducted to assess the possibility that cognitive impairments associated with MCS are evident during exposure conditions.

Several issues need to be addressed prior to conducting research to assess cognitive abilities during exposure conditions. First, access to adequate testing chambers

is necessary. Second, several factors associated with testing chambers and the constraints of performing neuropsychological tests under restricted conditions need to be considered.

Difficulties associated with testing chambers include producing adequately "clean" chambers (Jewett et al., 1990; Staudenmayer et al., 1993) to ensure that study participants are not reacting to residual levels of environmental substances during placebo and test trials, and creating chambers in which neuropsychological tests could be completed without interfering with exposures. Difficulties associated with administration of neuropsychological tests during exposure conditions include ensuring that tests are robust to practice effects, or using tests that have reliable alternate forms, given that testing is conducted under test and placebo conditions and potentially to several different test substances. Also altering tests to limit administration time is necessary as the duration of an effect from a test substance may be too short to complete traditional neuropsychological measures such as those assessing short and long-term memory. Staudenmayer et al. (1993) varied length of chamber exposure from 15 minutes to two hours depending on each participant's history of the exposure time necessary for induction of symptoms. Future provocation studies including a neuropsychological test battery would need to consider if testing should occur as soon as exposure is initiated or after symptom production is induced. At present, no study has been conducted to examine the relation between length of exposure and symptom production nor between onset of symptom and symptom duration. Results of such studies would clarify the constraints of neuropsychological testing under exposure conditions.

Imaging techniques may provide useful ways to assess brain functioning under

exposure conditions. Functional MRI (fMRI) is an online measure of brain metabolism. Past studies have been conducted to assess brain changes during cognitive tasks (e.g., Petrides et al., 1993; Warkintin & Passant, 1993). Exposing individuals with MCS to substances believed to create symptoms could be superimposed on this technique to observe brain related changes associated with exposures. The difficulties associated with observing potentially short-lived changes with neuropsychological tests may be circumvented with such techniques. The difficulties associated with creating "clean" environments would, however, remain.

Competing Hypotheses Regarding Psychiatric Disturbances in MCS

The majority of the research conducted on MCS has focussed on determining whether MCS is an organic or psychiatric disturbance. Evidence of current psychiatric disturbance has been perceived as indicative of psychogenic origins of MCS. Little attention has been payed to the nature of these psychiatric disturbances (e.g., proportions of MCS samples with similar vs. heterogeneous psychiatric disturbance), the timing of the onset of these disturbances (e.g., pre- vs. post-exposure), the chronicity of psychiatric disturbances, or the percentage of individuals with MCS who do not experience psychiatric disturbances.

Davidoff and Fogarty (1994) stated that, "studies of psychiatric profiles observed in MCS syndrome need to be designed to differentiate between competing psychogenic and biogenic hypotheses." (Page 316). Assessing the transient or chronic nature of the psychiatric disturbances, the timing of the onset of psychiatric disturbances, the

consistency of psychiatric disturbances across a sample of individuals with MCS, and the ability of psychosocial interventions to cure MCS would help to clarify the nature of the psychiatric disturbances measured in individuals with this disorder.

Prospective research designs could be used to test several of the competing psychiatric and biogenic hypotheses. For example, a large number of individuals in a community or workplace setting could be tested on cognitive, psychiatric and medical measures. Individuals could then be followed over a period of time with the expectation that a portion would develop MCS. Meggs et al. (1996) found that 33% of a rural population reported symptoms of MCS. However, this estimate is likely higher than what would be expected if Cullen's (1987) criteria were used to select cases. The only defining characteristic for MCS used in the Meggs et al. study (1996) was feeling sick after smelling chemical odors. At a future date, individuals could again be tested on the cognitive, psychiatric and medical measures and group comparisons could be made regarding premorbid and current states. This type of design would provide information regarding the possibility that certain premorbid psychiatric profiles predispose individuals to developing MCS. It would also provide premorbid measures of cognitive functioning to which current abilities could be compared without the need for matched samples and inferences regarding variables associated with cognitive abilities. Moreover, if immune measures were also taken prior to developing the disorder, similar changes from baseline in terms of immune functioning could be assessed. Prospective research designs would allow powerful comparisons to be made between an individual's current medical/cognitive/psychiatric condition and their previous state. The feasibility of these

studies, however, depends on a research centre's ability to recruit and follow large samples.

4.9 Conclusions

Despite an increased number of memory complaints, the MCS group's cognitive scores did not differ from controls. These findings are not consistent with predictions based on the Olfactory-Limbic Model. These findings, however, are consistent with three prior MCS studies that reported results from standardized neuropsychological tests did not substantiate the cognitive impairments reported symptomatically (Fiedler et al, 1992; 1996; Simon et al., 1993). Together, the results do not support the idea that cognitive complaints in MCS represent impairments that are secondary to brain dysfunction or brain damage, per se.

Partial support for the Olfactory-Limbic Model using between-test analysis was found, but the findings were tentative given that several other factors may have accounted for the results. First, the asthma group, who were included to provide a chronic illness control, also performed significantly more poorly on anterior tasks than posterior tasks. Second, when between-test analyses were performed on the MCS subgroups not on medication, the significant between-test findings were no longer apparent. Thus, factors other than the Olfactory-Limbic Model (i.e., chronic illness, medication use, or environmental reactivity in general) may have accounted for the between-test findings.

Researchers have noted that memory complaints are a common symptom of MCS (Cullen, 1994; Miller & Mitzel, 1995). Memory complaints have most often been

interpreted to indicate Central Nervous System (CNS) involvement in this disorder (Bell et al., 1992). To the author's knowledge, the relation between memory complaints and memory functioning had not been directly assessed in prior MCS studies. In this study, memory complaints were related to measures of depression, anxiety, and illness severity, but not to objective memory abilities. Thus, although the lack of a relation between memory complaints and memory functioning does not preclude CNS involvement, it does suggest that memory complaints vary in relation to severity of anxiety and depression.

In conclusion, there is no evidence that the MCS sample experienced brain damage consistent with the Olfactory-Limbic Model's predictions. Further research is necessary before it can be concluded that the between-test findings support the notion that the Olfactory-Limbic Model adequately describes the cognitive strengths and weaknesses of MCS. The possibility that the between-test findings are due to test selection, medication use or chronic illness, or to some factor related to environmental reactivity in general, remains to be tested. Memory complaints in this MCS sample related to anxiety and depression, but not to objective memory functioning. Because the Olfactory-Limbic Model does not partial cognitive and affective processes, this finding cannot be used to diminish its heuristic value.

Table 1. Demographics and Health Characteristics

This table reports the means (and standard deviations) for each group on demographic variables and the Substance Checklist.

	MCS (N=21)	Asthma (N=21)	Healthy (N=21)
# Female	20	20	20
Age (years)	44 (6)	40 (11)	43 (9)
Education (years)	16 (2)	16 (3)	17 (2)
NART- R Estimated Premorbid IQ	111 (6)	109 (8)	115 (6)
Regression Estimated Premorbid IQ	113 (7)	111 (10)	116 (7)
Substance Checklist (Total Scores)	81 (18)	45 (28)	2 (3)

Table 2. Weighted Frontal, Temporal, Anterior and Posterior Region Scores using Premorbid IQ Estimates for MCS, Asthma, and Healthy Groups

This table reports the IQ adjusted means for each group on the 3 brain region scores. Scores have been adjusted using ANCOVA to remove the influence of estimated premorbid IQ.

	MCS (N=21)	Asthma (N=21)	Healthy (N=21)
Frontal Region	-0.07	-0.32	-0.13
Temporal Region	-0.26	-0.49	-0.16
Anterior Region	-0.17	-0.41	-0.15
Posterior Region	0.29	0.28	-0.12

Table 3. Neuropsychological Test Scores for MCS, Asthma, and Healthy Groups

This table reports the means (and standard deviations) for each group on each of the cognitive tests. For comparison, published norms are contained in this table as well.

	MCS	Asthma	Healthy	Source Study Data
Frontal Region				
COWA	41.00 (10.55)	43.76 (14.19)	48.95 (14.51)	49.53 (5.61)[1]
*SOP	5.19 (2.98)	7.62 (4.27)	6.24 (2.79)	Approx 4[2]
Temporal Region				
Logical Stories Immediate	12.02 (3.55)	11.5 (3.20)	13.74 (2.91)	11.72 (2.51)[3]
Logical Stories Delayed	9.95 (3.51)	9.73 (3.17)	11.76 (3.04)	10.53 (2.95)[3]
RMF	45.86 (2.83)	43.19 (3.68)	44.71 (3.45)	44.30 (3.5)[4]
Posterior Region				
*Gollin Figures	14.52 (2.27)	14.81 (2.93)	16.14 (2.97)	20.25[5]
BFRT	48.52 (4.09)	48.14 (3.62)	48.52 (3.79)	43 to 46 = average[6]

* Numbers indicate errors; low scores indicate better performance. COWA = Controlled Oral Word Association; SOP = Self-Ordered Pointing; RMF = Recognition Memory Test for Faces; BFRT = Benton Facial Recognition Test.

1. Yendall et al. (1986) reported on Page 222, Table 7-4 in Spreen and Strauss (1991).
2. Petrides and Milner (1982), Figures 7 and 9. Value is approximate because means and standard deviations are not reported for total number of errors.
3. Spreen and Strauss (1991), Page 197, Table 6-31. Note scores have been divided by 2 to enable comparison with this study.
4. Warrington (1984), Table 4.
5. Warrington and James (1967), Table 4.
6. Benton et al. (1983). Norms are reported in ranges rather than means and standard deviations.

Table 4. Neuropsychological Test Scores Transformed into Z scores for MCS, Asthma, and Healthy Groups

This table reports the z score means (and standard deviations) for each group on each of the cognitive tests.

	MCS	Asthma	Healthy
Frontal			
COWA	-.55 (.72)	-.36 (.98)	.00 (1.00)
*Self-Ordered Pointing	.38 (1.07)	-.49 (1.53)	.00 (1.00)
Temporal			
Logical Memory Immediate	-.59 (1.22)	-.77 (1.09)	.00 (1.00)
Logical Memory Delayed	-.59 (1.16)	-.67 (1.04)	.00 (1.00)
RMF	.33 (.82)	-.44 (1.06)	.00 (1.00)
Posterior			
*Gollin Figures	.54 (.77)	.45 (.99)	.00 (1.00)
BFRT	.00 (1.08)	-.10 (.96)	.00 (1.00)

* Z scores have been reverse scored to provide consistency across measures. Positive scores now indicate better performance.

Table 5. Frontal, Temporal, Anterior and Posterior Region Scores for MCS, Asthma, and Healthy Groups

This table reports the means (and standard deviations) of the transformed z scores for each group by brain region.

	MCS	Asthma	Healthy
Frontal Region	-.09 (.62)	-.43 (.94)	.00 (.74)
Temporal Region	-.28 (.87)	-.63 (.88)	.00 (.72)
Anterior Region	-.18 (.64)	-.53 (.80)	.00 (.60)
Posterior Region	.27 (.77)	.17 (.83)	.00 (.88)

Table 6. Measures of Anxious and Dysphoric Mood and Memory Complaints

This table reports the means (and standard deviations) for each group on the measures of mood and the memory complaints questionnaire.

	MCS	Asthma	Healthy
BAI	11.86 (12.56)	8.38 (8.68)	2.52 (3.47)
BDI CA Subscale	5.48 (4.26)	3.29 (3.29)	2.10 (3.33)
***MOQ-2 A**	7.67 (4.07)	13.71 (3.26)	14.38 (3.11)
***MOQ-2 B**	-7.62 (18.32)	-3.71 (7.80)	-2.00 (3.74)

BDI CA Subscale = Beck Depression Inventory - Cognitive Affective Subscale

BAI = Beck Anxiety Inventory

MOQ-2A = Memory Observation Questionnaire - 2 Part A

MOQ-2B = Memory Observation Questionnaire - 2 Part B

*** Low scores on the MOQ-2A indicate greater subjective memory complaints.**

Negative scores on the MOQ-2B indicate negative changes in memory.

Table 7. Weighted Frontal, Temporal, Anterior, and Posterior Region Scores using BAI and BDI Scores for MCS, Asthma, and Healthy Groups

This table reports the BAI and BDI adjusted means for each group on the 3 brain region scores. Scores have been adjusted using ANCOVA to remove the influence of anxious and dysphoric mood.

	MCS	Asthma	Healthy
Frontal Region	-0.10	-0.44	0.03
Temporal Region	-0.25	-0.64	-0.01
Anterior Region	-0.17	-0.54	0.01
Posterior Region	0.34	0.15	-0.04

Table 8. Medication Taken by MCS, Asthma and Healthy Control Groups

MCS	N	Asthma	N	Healthy	N
Ventolin	2	Ventolin	8	Estraderm	3
Aldacton	1	Palmacorte	5		
Baclofort	1	Seravent	4		
Elavil	1	Bricanyl	3		
Estraderm	1	Flovent	3		
Flonase	1	Zantac	3		
Flovent	1	Norvasc	2		
Inderal	1	Tilade	2		
Norvasc	1	Baclofort	1		
Rheumatrex	1	birth control	1		
Sinoff	1	Didronel	1		
		Elavil	1		
		Estraderm	1		
		Flonase	1		
		Losec	1		
		Micro K	1		
		Moduret	1		
		Paxil	1		
		Prepulsid	1		
		Proventil	1		
		Reactine	1		
		Synthroid	1		

Table 9. Frontal, Temporal, Anterior and Posterior Region Scores for MCS, Asthma, and Healthy Subgroups Not Taking Medication

This table reports the means (and standard deviations) of the region scores for each subgroup not on medication.

	MCS (N=10)	Asthma (N=4)	Healthy (N=18)
Frontal Region	.08 (.56)	-.24 (.51)	-.03 (.77)
Temporal Region	-.20 (.97)	-.72 (.77)	.01 (.66)
Anterior Region	-.06 (.66)	-.48 (.44)	-.01 (.57)
Posterior Region	.21 (.70)	.48 (.29)	.03 (.83)

Table 10. Frontal, Temporal, Anterior and Posterior Region Scores for High and Low Substance Checklist Asthma Groups

This table reports the means (and standard deviations) of the region scores for high and low Substance Checklist subgroups.

	High Substance Checklist Scores (N=10)	**Low Substance Checklist Scores (N=11)**
Frontal Region	**-.33 (1.17)**	**-.52 (.73)**
Temporal Region	**-.44 (.90)**	**-.80 (.86)**
Anterior Region	**-.38 (.96)**	**-.66 (.65)**
Posterior Region	**.26 (1.12)**	**.13 (.49)**

Table 11. Correlations Between Anxiety, Depression, Memory Complaints, and Memory Change Scores for MCS, Asthma and Healthy Control Groups

This table represents the obtained Pearson Correlation Coefficients between anxiety, depression, memory complaints, and memory change scores for each of the groups studied.

		BAI	BDI-CA	MOQ-2A	MOQ-2B
MCS					
	BAI	-			
	BDI-CA	.69**	-		
	MOQ-2A	-.51*	-.50*	-	
	MOQ-2B	-.69**	-.64**	.43	-
Asthma					
	BAI	-			
	BDI-CA	.63**	-		
	MOQ-2A	-.09	.05	-	
	MOQ-2B	-.37	-.04	.60*	-
Healthy					
	BAI	-			
	BDI-2	.75**	-		
	MOQ-2A	-.05	.15	-	
	MOQ-2B	-.41	-.41	.15	-

* Correlations are significant at the .05 level.

** Correlations are significant at the Bonferroni adjusted alpha level of .01.

Table 12. Correlations Between Anxiety, Depression and Region Scores for MCS, Asthma and Healthy Groups

This table represents the obtained Pearson Correlation Coefficients between anxiety, depression, and region scores for each of the groups studied.

		BAI	BDI-CA	Frontal	Temporal	Posterior
MCS						
	BAI	-				
	BDI-CA	.69**	-			
	Frontal	-.01	-.01	-		
	Temporal	-.03	-.22	.45*	-	
	Posterior	.09	.10	.35	.43*	-
Asthma						
	BAI	-				
	BDI-CA	.63**	-			
	Frontal	.06	-.19	-		
	Temporal	-.13	-.26	.56*	-	
	Posterior	-.31	-.66**	.55*	.44*	-
Healthy						
	BAI	-				
	BDI-CA	.75**	-			
	Frontal	.42	.26	-		
	Temporal	.47*	.30	.36	-	
	Posterior	-.03	-.07	.33	.24	-

* Correlations are significant at the .05 level.

** Correlations are significant at the Bonferroni adjusted alpha level of .005.

Table 13. Correlations Between Memory Complaints and Memory Scores for MCS, Asthma and Healthy Groups

This table represents the obtained Pearson Correlation Coefficients between memory complaints and memory scores for each of the groups studied.

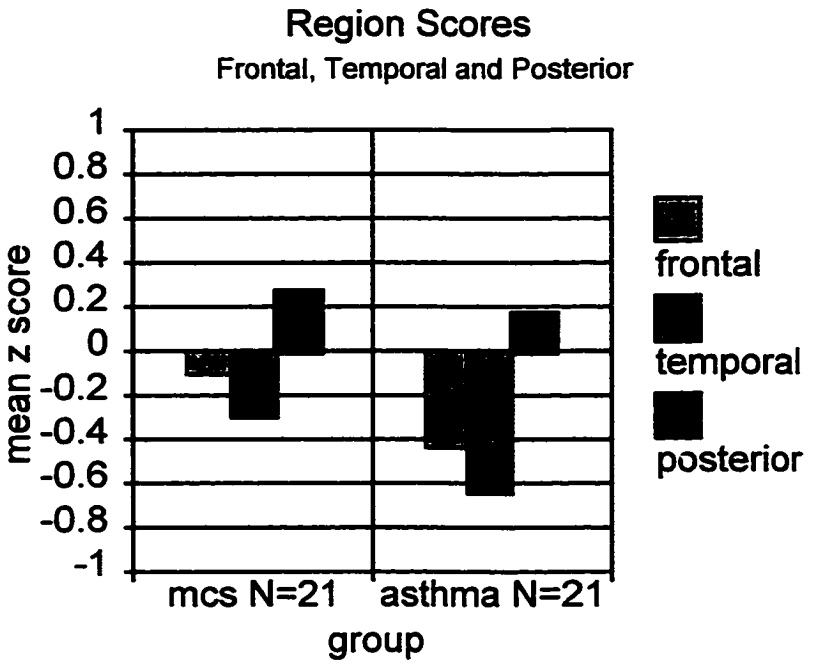
		MOQ-2 A	Temporal Region Z Score
MCS			
	MOQ-2 A	-	
	Temporal Scores	0.27	-
Asthma			
	MOQ-2 A	-	
	Temporal Scores	0.18	-
Healthy			
	MOQ-2	-	
	Temporal Scores	0.06	-

* Note: None of the correlations are significant at the .05 level.

Table 14. Neuropsychological Tests Given to MCS Samples in Three Past Studies and the Present Study

Author/Year	Tests Administered
Fiedler et al. 1992	WAIS-R Digit Span WAIS-R Digit Symbol Stroop Test California Verbal Learning Test WMS-R Visual Reproduction
Simon et al. 1993	WMS-R Logical Memory WMS-R Visual Reproduction Trails A and B Rey Auditory-Verbal Learning Test WAIS-R Digit Span WAIS-R Digit Symbol
Fiedler et al. 1996	Computerized Reaction Time Computerized Continuous Performance Test WAIS-R Digit Span Stroop Test WAIS-R Digit Symbol Computerized Hand-Eye Coordination Grooved Pegboard California Verbal Learning Test Continuous Visual Memory Test WMS-R Visual Reproduction
The Present Study	Controlled Oral Word Association Test Petrides Self-Ordered Pointing Test WMS Logical Memory Recognition Memory Test for Faces Benton Facial Recognition Test Gollin Figures Test

Figure 1. Region Scores for MCS and Asthma Control Group Participants.



Appendix A.

Cullen's Definition of Multiple Chemical Sensitivity

1. The disorder is acquired in relation to some documentable environmental exposure(s), insult(s) or illness(es).

*2. Symptoms involve more than one organ system.

*3. Symptoms recur and abate in response to predictable stimuli.

*4. Symptoms are elicited by exposures to chemicals of diverse structural classes and toxicological modes of action.

*5. Symptoms are elicited by exposures that are demonstrable.

*6. Exposures that elicit symptoms must be very low, by which we mean many standard deviations below "average" exposures known to cause adverse human exposure.

*7. No single widely available test of organ system function can explain symptoms.

* Criteria used in this study.

Appendix B.

Recruitment Advertisement and Telephone Screening Measures for MCS, Asthma and Healthy Control Groups.

You Are Invited to Participate in a Research Study on the Psychological Effects of Multiple Chemical Sensitivity

Who Can Participate?

Men and Women with Multiple Chemical Sensitivity
Men and Women with Asthma who DO NOT have Multiple Chemical Sensitivity
Men and Women who are Healthy and DO NOT have Multiple Chemical Sensitivity and DO NOT have Asthma

What Will I Have to Do?

Answer some questions about your health over the telephone
Come to Dalhousie University one time to do some paper and pencil type tests and questionnaires

What are the Risks?

There are no physical risks or hazards involved in this study
Some people find it tiring to do the paper and pencil type tests

What are the Benefits?

You will be given $10.00 for coming to Dalhousie University
You will be helping to increase scientific knowledge about Multiple Chemical Sensitivity

For More Information Contact:
Anne-Marie Brown-DeGagne
Clinical Neuropsychology Research Lab
Dalhousie University
494-5179
ambrown@is2.dal.ca (e-mail)

Subject Demographics Sheet - Telephone Interview

Group: MCS _____ Asthma Control _____ Healthy Control _____

Name: _____

Subject Number: _____

Age of Subject (yrs): _____ Date of Birth: _____

Highest Level of Education:
Years: _____
Circle one: 1 = some public school
2 = finished grade 8
3 = some high school
4 = finished grade 12 or 13
5 = some college
6 = some university
7 = college graduate
8 = university graduate
9 = graduate school

Sex: _____

Race: _____

Home
Address:_____

_____

Phone Number: _____

What is your first language? _____ Do you speak any other languages? _____

Do you currently take any medications?
_____

Are you right-handed? _____ Left-handed? _____ Ambidextrous? _____

Have you seen a psychologist or a neuropsychologist for psychological testing before? _____

If yes, when were you tested? _____ How many times were you tested? _____

Does this individual meet the inclusionary criteria outlined for their group? _____

Does this individual fail to meet the exclusionary criteria outlined for their group? _____

Inclusionary and Exclusionary Criteria for MCS Group Participants
Telephone Interview

Name: _____ Date: _____

Inclusionary Criteria
Each participant in the MCS group must answer yes to the following questions:

(1) Were your symptoms of MCS acquired in relation to some identifiable environmental exposure(s), insult(s) or illness(es)? (note: this question will be asked, but individuals will not be excluded if they cannot identify an initial environmental exposure). _____
(Note: this question was asked but not used as an inclusionary criterion)

(2) Do your symptoms currently involve more than one organ system (e.g., respiratory and nervous system)? _____

(3) Do your symptoms recur and abate in response to exposure to predictable stimuli (e.g., certain chemicals or substances)? _____

(4) Are your symptoms elicited by exposure to very low levels of chemicals of diverse structural classes (e.g., pesticides, solvents)? _____

(5) Do no other medical conditions account for your symptoms? _____

Exclusionary Criteria
Each participant in the MCS group must answer no to the following questions:

(1) Have you ever been hospitalized for a psychiatric illness (e.g., schizophrenia, manic depression, depression)? _____

(2) Have you ever been diagnosed with any serious psychiatric conditions such as manic depression, schizophrenia? _____

(3) Are you currently seeking or contesting compensation for disability due to MCS (e.g., Worker's Compensation Board, Canada Pension, private insurance)? (note: this question will be asked, but individuals involved in litigation will not be excluded from participating in this study) _____
(Note: this question was asked but not used as an exclusionary criterion)

(4) Have you ever had a neurological disease or a disease that affects your nervous system (e.g., epilepsy, cerebral palsy, multiple sclerosis)? _____

(5) Have you ever had a serious accident or injury that involved your head? Did this

injury require medical attention? (e.g., concussion, car accident)? _____

(6) Have you ever had a stroke? _____

(7) Do you have any form of cardiovascular disease? _____

(8) Do you have any type of kidney or liver disease? _____

(9) Did anyone ever tell you that you had a childhood learning disability? _____

(10) Have you undergone neuro-cognitive retraining? _____

In addition to answering no to the above questions, individuals will be administered the brief MAST and the DAST. Any answers indicating that the individual may have a drinking or drug use problem will exclude the participant from the study.

Inclusionary and Exclusionary Criteria for Asthma Control Participants
Telephone Interview

Name: _____ Date: _____

Inclusionary Criteria
Each participant in the asthma control group must answer yes to the following question:

(1) Has a physician diagnosed you with asthma?

Exclusionary Criteria
Each participant in the asthma control group must answer no to the following questions:

(1) Do you have Multiple Chemical Sensitivities? _____

(2) Have you ever been hospitalized for a psychiatric illness (e.g., schizophrenia, manic depression, depression)? _____

(3) Have you ever been diagnosed with any serious psychiatric conditions such as manic depression, schizophrenia? _____

(4) Have you ever had a neurological disease or a disease that affects your nervous system (e.g., epilepsy, cerebral palsy, multiple sclerosis)? _____

(5) Have you ever had a serious accident or injury that involved your head? Did this injury require medical attention? (e.g., concussion, car accident)? _____

(6) Have you ever had a stroke? _____

(7) Do you have any form of cardiovascular disease? _____

(8) Do you have any type of kidney or liver disease? _____

(9) Has anyone ever told you that you had a childhood learning disability? _____

(10) Have you ever been exposed to large amounts of toxins (e.g., at work, history of a peak exposure)? _____

In addition to answering no to the above questions, individuals will be administered the brief MAST and the DAST. Any answers indicating that the individual may have a drinking or drug use problem will exclude the participant from the study.

Exclusionary Criteria for Healthy Controls
Telephone Interview

Name: _____ Date: _____

Exclusionary Criteria
Each participant in the healthy control group must answer no to the following questions:

(1) Do you have Multiple Chemical Sensitivities? _____

(2) Do you have asthma? _____

(3) Have you ever been hospitalized for a psychiatric illness (e.g., schizophrenia, manic depression, depression)? _____

(4) Have you ever been diagnosed with any serious psychiatric conditions such as manic depression, schizophrenia? _____

(5) Have you ever had a neurological disease or a disease that affects your nervous system (e.g., epilepsy, cerebral palsy, multiple sclerosis)? _____

(6) Have you ever had a serious accident or injury that involved your head? Did this injury require medical attention? (e.g., concussion, car accident)? _____

(7) Have you ever had a stroke? _____

(8) Do you have any form of cardiovascular disease? _____

(9) Do you have any type of kidney or liver disease? _____

(10) Has anyone ever told you that you had a childhood learning disability? _____

(11) Have you ever been exposed to large amounts of toxins (e.g., at work, history of a peak exposure)? _____

In addition to answering no to the above questions, individuals will be administered the brief MAST and the DAST. Any answers indicating that the individual may have a drinking or drug use problem will exclude the participant from the study.

Brief MAST
Telephone Interview

Name:_____ Date:_____

1. Do you feel you are a normal drinker?	Yes	No
2. Do friends or relatives think you are a normal drinker?	Yes	No
3. Have you ever attended a meeting of Alcoholics Anonymous (AA)?	Yes	No
4. Have you ever lost friends or girlfriends/boyfriends because of drinking?	Yes	No
5. Have you ever gotten into trouble at work because of drinking?	Yes	No
6. Have you ever neglected your obligations your family, or your work for two or more days in a row because you were drinking?	Yes	No
7. Have you ever had the delirium tremens (DT's), severe shaking, heard voices, or seen things that were not there after heavy drinking?	Yes	No
8. Have you ever gone to anyone for help about you drinking?	Yes	No
9. Have you ever been hospitalized because of drinking?	Yes	No
10. Have you ever been arrested for drunk driving or driving after drinking?	Yes	No

DAST
Telephone Interview

Name: _____ Date:_____

The following questions concern information about your involvement and abuse of drugs. Drug abuse refers to (1) the use of prescribed or "over-the-counter" drugs in excess of the directions, and (2) any non-medical use of drugs. Please listen to each statement carefully, and decide whether your answer is Yes, No, or not applicable.

1. Have you used drugs other than those required for medical reasons? _____

2. Have you abused prescription drugs? _____

3. Do you abuse more than one drug at a time? _____

4. Can you get through the week without using drugs (other than those required for medical reasons)?
_____

5. Are you always able to stop using drugs when you want to? _____

6. Do you abuse drugs on a continuous basis? _____

7. Do you try to limit your drug use to certain situations? _____

8. Have you had "blackouts" or "flashbacks" as a result of drug use? _____

9. Do you ever feel bad about your drug abuse? _____

10. Does your spouse (or parents) ever complain about your involvement with drugs?
_____

11. Do your friends or relatives know or suspect that you abuse drugs? _____

12. Has drug abuse ever created problems between you and your spouse (boyfriend/girlfriend)? _____

13. Has any family member ever sought help for problems related to your drug use?
_____

14. Have you ever lost friends because of your use of drugs? _____

15. Have you ever neglected your family or missed work/school because of your drug use? _____

16. Have you ever been in trouble at work because of drug abuse? _____

17. Have you ever lost a job because of drug abuse? _____

18. Have you gotten into fights when under the influence of drugs? _____

19. Have you ever been arrested for unusual behaviour while under the influence of drugs? _____

20. Have you ever been arrested for driving while under the influence of drugs? _____

21. Have you engaged in illegal activities in order to obtain drugs? _____

22. Have you ever been arrested for possession of illegal drugs? _____

23. Have you ever experienced withdrawal symptoms as a result of heavy drug intake? _____

24. Have you medical problems as a result of your drug use (e.g., memory loss, hepatitis, convulsions, bleeding, etc.)? _____

25. Have you ever gone to anyone for help for a drug-related problem? _____

26. Have you ever been to a hospital for medical problems related to your drug use? _____

27. Have you ever been involved in a treatment programme specifically related to drug use? _____

28. Have you been treated as an out-patient for problems related to drug abuse? _____

Appendix C. Psychological Measures and Questionnaires

Screening Measures

Hand Preference Questionnaire

Abbreviated Hiscock Forced Choice Procedure

Demographics and Subject Characteristics

National Adult Reading Test - Revised

Barona and Chastain's Regression Equation

Substance Checklist

Type of MCS and Exposure History Questionnaire

Neuropsychological Measures

Controlled Oral Word Association Test

Self-Ordered Pointing Test

WMS Logical Memories

Recognition Memory Test For Faces

Gollin Figures Test

Benton Facial Recognition Test

Questionnaires Assessing Subjective Mood and Memory Complaints

Beck Depression Inventory

Beck Anxiety Inventory

Memory Observation Questionnaire - 2

Appendix D. Type of MCS and Exposure History Questionnaire

Type of MCS and Exposure History Questionnaire

Name: _____ Date: _____

It may be possible to divide individuals with Multiple Chemical Sensitivity into different types of groups based on their experiences with how they developed the disorder. To better understand your type of illness, please state to which group you feel you most belong by circling the number of the statement to which you feel you most belong.

1 A diverse group in which work and home chemicals, experienced at generally low levels have caused your illness.

2 You worked in a tight building (i.e., sick building) where you may have been exposed to offgassing from construction materials, perfumes, tobacco smoke or other substances. Your symptoms began in the workplace.

3 You are an industrial worker. You may have experienced higher level acute and chronic industrial chemical exposures.

4 You are a member of a contaminated community. Exposures from air and water contamination by toxic waste sites, pesticide spraying, or industrial dumping may have caused your illness.

Please answer the following as accurately as you can:

1. For how many months have you had Multiple Chemical Sensitivity? _____

2. What do you feel caused your illness?

_____
_____
_____
_____

3. On a scale from 1 to 10, where 1 is the least severe and 10 is the most severe, how severe would you rate your symptoms? _____

4. Do you feel your symptoms have (please circle the letter of the response that most applies to you):

a. worsened greatly since their onset
b. worsened slightly since their onset
c. remained the same since their onset
d. improved slightly since their onset
e. improved greatly since their onset

5. Have you received any treatments for MCS? _____

If yes, what types of treatments have you received in the past?

_____
_____
_____
_____
_____

If yes, what types of treatments are you receiving now?

_____
_____
_____
_____
_____

6. Have you received any type of compensation for MCS (e.g., Worker's Compensation Board, private insurance, Canada Pension)? _____

If yes, please specify the type of compensation received._____

Appendix E. Informed Consent Form

Consent Form

Study Title: Multiple Chemical Sensitivity and Memory

Investigators: Principle Investigator: Anne-Marie Brown-DeGagne, B.A.
Associate Investigator: Jeannette McGlone, Ph.D.

Contact Person: Anne-Marie Brown-DeGagne, Department of Psychology, Dalhousie University, Telephone: 494-5179

Introduction

We invite you to partake in a research study at Dalhousie University. Taking part in this study is voluntary. The quality of your medical care will not be affected whether you participate or not. Participating in this study will not benefit you, but we might learn things that will benefit others. You may withdraw from the study at any time without affecting your care. The study is described below. This description tells you about the risks, inconvenience, or discomfort you might experience. You should discuss any questions you have about this study with Anne-Marie Brown-DeGagne.

Purpose of the Study

The purpose of this study is to look at how people with Multiple Chemical Sensitivity do on certain paper and pencil tests. We want to understand the problems some people with Multiple Chemical Sensitivity have with remembering things. We need people with Multiple Chemical Sensitivity to join our study. We also need people without Multiple Chemical Sensitivity to join our study so that we can compare how they do on our tests to how people with Multiple Chemical Sensitivity do on these same tests.

Who Can Participate in this Study?

We are inviting three different groups of people to join this study. The first group will be people who have Multiple Chemical Sensitivity. The second group will be people who have asthma. The third group will be people who are healthy and do not have Multiple Chemical Sensitivity and do not have asthma. All people who are now being invited to join our study were already asked many questions about their health over the telephone. We needed to ask these questions because certain health problems and certain lifestyles (e.g., heavy drinking) can sometimes affect how people do on paper and pencil type tests. We wanted to make sure that everyone who joined our study did not experience things in their past that could affect how they do on our paper and pencil tests.

Procedures of the study

If you decide to join the study you will meet one-on-one with Anne-Marie Brown-DeGagne at Dalhousie University in a well-ventilated room. She will ask you to do some

paper and pencil tests. You will also be asked to fill in some questionnaires that ask about your mood, about problems you may be having with remembering things, and about Multiple Chemical Sensitivity. Part of the assessment will look at your motivation. The total time you will need to spend at Dalhousie University will be about 2.5 hours.

Risks and Discomforts

There are no physical risks or hazards involved in this study. However, some people feel uncomfortable answering some of the questions on the questionnaires. Some people also find it tiring to do the paper and pencil tests.

Compensation

You will be given $10.00 to help cover the cost of travelling to and from Dalhousie University and to pay for parking.

Confidentiality

If you decide to join our study, any information learned about you will be confidential and your privacy will be protected at all times. Files will be kept in a locked cabinet. Your name will never be entered into a computer data base. Instead, we will use number codes to protect your identity. Your name or other identifying information about yourself will never be written in any paper or scientific publication.

Questions or Problems

If you have any questions about this study please feel free to ask Anne-Marie Brown-DeGagne about them. You may ask questions at anytime when you meet with her at Dalhousie University. You may also telephone her at 494-5179.

Other Information

Thank-you very much for taking the time to learn about our study. Specific test results will not be given to you. However, a summary of the findings from this study will be sent to you when the study has been completed. You may keep this page of information for your records. If you would like to join our study, and feel that your questions have been answered to your satisfaction, please sign your name on the next page.

Signatures

I have read the explanation about this study. I have been given the opportunity to discuss it and my questions have been answered to my satisfaction. I hereby consent to take part in this study.

_____ _____

Signature Date Signed

_____ _____

Witness Date Signed

Appendix F. Order of Tests Administered

1. WMS Logical Memory Stories - Immediate
2. Abbreviated Hiscock Forced Choice Procedure
3. Hand Preference Questionnaire
4. Regression Equation
5. NART-R
6. RMF
7. COWA Test
8. Gollin Figures Test
9. Self-ordered Pointing Test
10. BFRT
11. WMS Logical Memory Stories - Delayed
12. Type of MCS and Exposure History Questionnaire
13. BDI
14. BAI
15. MOQ-2 Self Form
16. Substance Checklist

Appendix G. MCS Clear Onset (MCS) vs. No Clear Onset (CS) Results

Analyses Completed

1. ANOVAs comparing MCS, CS, asthmatics, and healthy controls on frontal, temporal, and posterior region scores.
2. ANOVAs comparing MCS, CS, asthmatics, and healthy controls on BDI, BAI, MOQ-2, Substance Checklist, severity ratings, and ratings of improvement.
3. Dependent sample t-tests comparing region scores in MCS and CS samples.

Results

1. The means and standard deviations for each group on the region scores are presented in Table 1A. Results from univariate ANOVAs revealed a significant group difference for temporal region scores ($F_{(2,60)} = 4.18$, $p<.05$). Post hoc comparisons using the Bonferroni correction revealed that individuals with asthma performed significantly more poorly on temporal tasks than individuals in the CS group ($p<.05$). No other group differences were noted.

2. The means and standard deviations for each group on the BDI, BAI, MOQ-2A, Substance Checklist, severity ratings and ratings of improvement are presented in Table 2A. Results from univariate ANOVAs revealed significant group differences on the BDI ($F_{(2,60)} = 3.56$, $p<.05$), BAI ($F_{(2,60)} = 4.47$, $p<.05$), MOQ-2A ($F_{(2,60)} = 15.37$, $p<.05$), and Substance Checklist ($F_{(2,60)} = 58.07$, $p<.05$). Post hoc comparisons using the Bonferroni correction revealed that individuals with MCS scored significantly higher on the BDI cognitive-affective subscale than healthy individuals ($p<.05$). Individuals with MCS also scored significantly higher on the BAI than healthy individuals ($p<.05$). Individuals with MCS scored significantly lower on the MOQ-2A than individuals with asthma and healthy individuals ($p<.05$). Individuals with CS also scored significantly lower on the MOQ-2A than asthmatic and healthy controls ($p<.05$). Finally, individuals with MCS scored significantly higher on the Substance Checklist than asthmatic and healthy controls ($p<.05$). Individuals with CS scored significantly higher on the substance checklist than asthmatic and healthy controls ($p<.05$). Neither ratings of severity nor improvement differed significantly between the MCS and CS samples.

3. Dependent sample t-tests comparing frontal, temporal, posterior and anterior region scores indicated that individuals with MCS scored significantly lower on temporal tasks than posterior tasks ($t_{(14)} = 3.15$, $p<.05$) as well as significantly lower on anterior tasks than posterior tasks ($t_{(14)} = 2.65$, $p<.05$). No significant between-test findings were found for individuals with CS.

Table 1A. Frontal, Temporal, Anterior and Posterior Region Scores for MCS, CS, Asthma and Healthy Control Groups

	MCS (N=15)	CS (N=6)	Asthma (N=21)	Healthy (N=21)
Frontal Region	-.14 (.69)	.05 (.94)	-.24 (.51)	-.03 (.77)
Temporal Region	-.55 (.87)	.39 (.33)	-.72 (.77)	.01 (.66)
Anterior Region	-.35 (.66)	.22 (.33)	-.48 (.44)	-.01 (.57)
Posterior Region	.22 (.90)	.41 (.25)	.48 (.29)	.03 (.83)

Table 2A. BDI, BAI, MOQ-2A, Substance Checklist, Severity Ratings and Improvement Scores for MCS, CS, Asthma and Healthy Control Groups

	MCS (N=15)	CS (N=6)	Asthma (N=21)	Healthy (N=21)
BDI CA Subscale	6.07 (4.65)	4.00 (2.90)	3.29 (3.29)	2.10 (3.33)
BAI	13.53 (14.28)	7.67 (5.54)	8.38 (8.68)	2.52 (3.47)
MOQ-2 A	7.73 (4.22)	7.50 (4.04)	13.71 (3.26)	14.38 (3.11)
Substance Checklist	79.93 (16.94)	84.67 (22.13)	44.62 (28.18)	1.81 (3.12)
Severity Rating	6.37 (2.30)	6.42 (2.40)	NA	NA
Improvement Score	3.53 (1.55)	2.33 (1.75)	NA	NA

References

Adamec, R. (1994). Modelling anxiety disorders following chemical exposures. Toxicology and Industrial Health, 10, 391-420.

American Psychiatric Association (1987). Diagnostic and Statistical Manual of Mental Disorders - Revised 3rd Edition. Washington D.C.: APA.

American Psychiatric Association (1994). Diagnostic and Statistical Manual of Mental Disorders IV. Washington D.C.: APA.

Annett, R. D., & Bender, B. G. (1994). Neuropsychological dysfunction in asthmatic children. Neuropsychology Review, 4, 91-115.

Ashford, N. A., & Miller, C. S. (1991). Case definitions for multiple chemical sensitivity. In N.A. Ashford and C.S. Miller Chemical Exposures: Low Levels and High Stakes. New York: Van Nostrand Reinhold.

Barona, A, & Chastain, R. L. (1986). An improved estimate of premorbid IQ for blacks and whites on the WAIS-R. International Journal of Clinical Neuropsychology, 8, 169-173.

Barona, A., Reynolds, C. R., & Chastain (1984). A demographically based index of premorbid intelligence for the WAIS-R. Journal of Consulting and Clinical Psychology, 52, 885-887.

Barr, W. B., Goldberg, E., Wasserstein, J., & Novelly, R. A. (1990). Retrograde amnesia following unilateral temporal lobectomy. Neuropsychologia, 28, 243-255.

Beck, A. T. (1978). Beck Depression Inventory. San Antonia, TX: The Psychological Corporation.

Beck, A. T., & Steer, R. A. (1990). Beck Anxiety Inventory. San Antonia, TX: The Psychological Corporation.

Beck, A. T., & Steer, R. A. (1993). The Beck Depression Inventory Manual. New York: The Psychological Corporation.

Bell, I.R. (1982). Possible mechanisms in environmental illness. In: Clinical Ecology A New Medical Approach to Environmental Illness. Bolinas: Common Knowledge Press.

Bell, I. R. (1992). Neuropsychiatric and biopsychosocial mechanisms in multiple chemical sensitivity: An olfactory-limbic system model. In National Research Council Report: Multiple Chemical Sensitivities. Addendum to Biologic Markers in Immunotoxicology. Washington: National Academy Press.

Bell, I. R., Miller C. S., & Schwartz, G. E. (1992). An olfactory-limbic model of Multiple Chemical Sensitivity Syndrome: Possible relationships to kindling and affective spectrum disorders. Biological Psychiatry, 32, 218-242.

Benton, A. L. (1968). Differential behavioral effects in frontal lobe disease. Neuropsychologia, 6, 53-60.

Benton, A. L., Hamsher, K., Varney, N. R., & Spreen, O. (1983). Facial Recognition Test. In Contributions to Neuropsychological Assessment. Oxford University Press, Inc.

Benton, A. L., & Van Allen, M. W. (1968). Impairment in facial recognition in patients with cerebral disease. Cortex, 4, 344-358.

Black, D. W., Rathe, A., & Goldstein, R. B. (1990). Environmental illness: A controlled study of 26 subjects with "20th Century Disease." Journal of the American Medical Association, 264, 3166-3170.

Blair, J. R., & Spreen, O. (1989). Predicting premorbid IQ: A revision of the National Adult Reading Test. The Clinical Neuropsychologist, 3, 129-136.

Bolla-Wilson, K., Wilson, R. J., & Bleecker, M. L. (1988). Conditioning of physical symptoms after neurotoxic exposure. Journal of Occupational Medicine, 30, 684-686.

Brodsky, C. M. (1983). Psychological factors contributing to somatoform diseases attributed to the workplace. Journal of Occupational Medicine, 27, 459-464.

Brodsky, C. M. (1987). Multiple Chemical Sensitivities and other "environmental illness": A psychiatrist's view. Occupational Medicine: State of the Art Reviews, 2, 695-704.

Brown-DeGagne, A. M., McGlone, J., & Santor, D. (Unpublished). Somatic complaints disproportionately contribute to BDI estimates of depression severity in individuals with multiple chemical sensitivity. Paper submitted to the Journal of Psychosomatic Research.

Butler, R. W., Rorsman, I., Hill, J. M., & Tuma, R. (1993). The effects of frontal brain impairment on fluency: Simple and complex paradigms. Neuropsychology, 7, 519-529.

Cantor-Grae, E., Warkentin, S., Franzen, G., & Risberg, J. (1993). Frontal lobe challenge: A comparison of activation procedures during rCBF measurements in normal subjects. Neuropsychiatry, Neuropsychology, and Behavioral Neurology, 6, 83-92.

Chlopan, B. E., Hagen, R. L., & Russell, E. W. (1990). Lateralized anterior and posterior lesions and performance on digit span and Russell's revision of the Wechsler Memory Scale. Journal of Consulting and Clinical Psychology, 58, 855-861.

Cohen, J., & Cohen, P. (1983). Applied Multiple Regression/Correlation Analysis for the Behavioral Sciences, Second Edition. Hillside, New Jersey: Lawrence Erlbaum Associates, Publishers.

Crawford, J. R., Parker, D. M., & McKinlay (Eds.) (1992). A Handbook of Neuropsychological Assessment. Hillsdale: Lawrence Erlbaum Associates, Publishers.

Cuenod, C. A., Bookhiemer, S. Y., Hertz-Panneir, L., Zeffiro, T. A., Theodore, W. H., & Le Bihan, D. (1995). Functional MRI during word generation, using conventional equipment: A potential tool for language localization in the clinical environment. Neurology, 45, 1821-1827.

Cullen, M. R. (1987). The worker with multiple chemical sensitivities: An overview. Occupational Medicine: State of the Art Reviews, 2, 655-661.

Cullen, M. R. (1994). Multiple chemical sensitivities. Is there evidence of extreme vulnerability of the brain to environmental chemicals? In R. L. Isaacson and K. F. Jensen (Eds.). The Vulnerable Brain and Environmental Risks. Volume 3 Toxins in Air and Water. New York: Plenum Press.

Damazio, A. R., & Geschwind, N. (1985). Anatomical localization in clinical neuropsychology. In J.A.M. Frederiks (Ed.) Handbook of Clinical Neurology, Vol. 1: Clinical Neuropsychology. Elsevier Science Publishers.

Davidoff, A. L., & Fogarty, L. (1994). Psychogenic origins of Multiple Chemical Sensitivity Syndrome: A critical review of the research literature. Archives of Environmental Health, 49, 316-325.

Delis, D. C., Kramer, J. H., Kaplan, E., & Ober, B. A. (1987). California Verbal Learning Test. New York: Psychological Corporation.

De Renzi, E., Faglioni, P, & Spinnler, H. (1968). The performance of patients with unilateral brain damage on face recognition tasks. Cortex, 4, 17-34.

Doty, R. L., Deems, D. A., Frye, R. E., Pelberg, R., & Shapiro, A. (1988). Olfactory sensitivity, nasal resistance, and autonomic function in patients with multiple chemical sensitivities. Archives of Otolaryngol Head and Neck Surgery, 114, 1422-1427.

Ellis, A. W., Hillam, J. C., Cardno, A., & Kay, J. (1991). Processing of words and faces by patients with left and right temporal lobe epilepsy. Behavioural Neurology, 4, 121-128.

Fiedler, N., Kipen, H., DeLuca, J., Kelly-McNeil, K., & Natelson, B. (1996). A controlled comparison of multiple chemical sensitivities and chronic fatigue syndrome. Psychosomatic Medicine, 58, 38-49.

Fiedler, N., Kipen, H., & Kelly-McNeil, K. (1992). Neuropsychological and psychiatric profile of patients with multiple chemical sensitivities. Paper presented at the Annual Conference of the American Psychological Association, August, 1992.

Fiedler, N., Maccia, C., Kipen, H. (1992). Evaluation of chemically sensitive patients. Journal of Occupational Medicine, 34, 529-538.

Frisk, V., & Milner, B. (1990). The role of the left hippocampal region in the acquisition and retention of story content. Neuropsychologia, 28, 349-359.

Frisk, V., & Milner, B. (1991). Does left temporal lobectomy adversely affect the rate at which verbal material can be processed? Neuropsychologia, 29, 113-123.

Gass, C. S., & Apple, C. (1997). Cognitive complaints in closed-head injury: Relationship to memory test performance and emotional disturbance. Journal of Clinical and Experimental Neuropsychology, 19, 290-299.

Gass, C. S., & Daniel, S. K. (1990). Emotional impact on trail making test performance. Psychological Reports, 67, 435-438.

Gilbert, M. E. (1992). Neurotoxicants and limbic kindling. In R.L. Isaacson and K. F. Jensen (Eds.). The Vulnerable Brain and Environmental Risks. Volume 1: Malnutrition and Hazard Assessment. New York: Plenum Press.

Gollin, E. S. (1960). Developmental studies of visual recognition of incomplete objects. Perceptual Motor Skills, 11, 289-298.

Guernsey, J. R. (1993). Multiple chemical sensitivity and sick building syndrome:

A literature review. Paper presented to the Department of Health & Epidemiology, Dalhousie University.

Guilmette, T. J., Hart, K. J., Giuliano, A. J., & Leininger, B. E. (1994). Detecting simulated memory impairment: Comparison of the Rey Fifteen-Item Test and the Hiscock Forced-Choice Procedure. The Clinical Neuropsychologist, 8, 283-294.

Hamsher, K., Levin, H. S., & Benton, A. L. (1979). Facial recognition in patients with focal brain lesions. Archives of Neurology, 36, 837-839.

Harrison, P. J., & Pearson, R. C. A. (1989). Olfaction and psychiatry. British Journal of Psychiatry, 155, 822-828.

Hartman, D. E. (1992). Neuropsychological toxicology. In A. E. Puente and R. J. McCaffrey (Eds.). Handbook of Neuropsychological Assessment: A Biopsychosocial Perspective. New York: Plenum Press.

Hartman, D. E. (1995). Neuropsychological Toxicology: Identification and Assessment of Human Neurotoxic Syndromes, Second Edition. New York: Plenum Press.

Haxby, J. V., Grady, C. L., Horwitz, B., Ungerleider, L. G., Mishkin, M., Carson, R. E., Herscovitch, P., Schapiro, M. B., & Rapoport, S. I. (1991). Dissociation of object and spatial visual processing pathways in human extrastriate cortex. Proceedings of the National Academy of Science, United States of America, 88, 1621-1625.

Haxby, J. V., Grady, C. L., Ungerleider, L. G., & Horwitz, B. (1991). Mapping the functional neuroanatomy of the intact human brain with brain work imaging. Neuropsychologia, 29, 539-555.

Hermann, B. P., & Wyler, A. R. (1988). Neuropsychological outcome of anterior temporal lobectomy. Journal of Epilepsy, 1, 35-45.

Hermann, B. P., Wyler, A. R., Bush, A. J., & Tabatabai, F. R. (1992). Differential effects of left and right anterior temporal lobectomy on verbal learning and memory performance. Epilepsia, 33, 289-297.

Hiscock, M., & Hiscock, C. K. (1989). Refining the forced-choice method for the detection of malingering. Journal of Clinical and Experimental Neuropsychology, 11, 967-974.

Huberty, C. J., & Morris, J. D. (1989). Multivariate analysis versus multiple univariate analyses. Psychological Bulletin, 105, 302-308.

Hyland, M. E. (1990). The mood peak-flow relationship in adult asthmatics: A pilot study of individual differences and direction of causality. British Journal of Medical Psychiatry, 63, 379-384.

Ivnik, R. J., Sharbrough, F. W., & Laws, E. R. (1987). Effects of anterior temporal lobectomy on cognitive function. Journal of Clinical Psychology, 43, 128-137.

Jewett, D. L., Fein, G., & Greenberg, M. H. (1990). A double-blind study of symptom provocation to determine food sensitivity. The New England Journal of Medicine, 323, 429-433.

Kertesz, A. (1983). Issues in localization. In A. Kertesz (Ed.) Localization in Neuropsychology. Academic Press, Inc.

Kiernan, R. (1981). Localization of function: The mind-body problem revisited. Journal of Clinical Neuropsychology, 3, 345-352.

Kimura, D., & Vanderwolf, C. H. (1970). The relation between hand preference and the performance of individual finger movements by left and right hands. Brain, 93, 769-774.

Kipen, H., Hallman, W., Kelly-McNeil, K., & Fiedler, N. (1995). Measuring chemical sensitivity: A questionnaire for population studies. American Journal of Public Health, 85, 574-577.

Leonard, G. (1991). Temporal lobe surgery for epilepsy: Neuropsychological variables related to surgical outcome. Canadian Journal of Neurological Sciences, 18, 593-597.

Levin, H. S., Hamsher, K. S., & Benton, A. L. (1975). A short-form of the test of facial recognition for clinical use. The Journal of Psychology, 91, 223-228.

Lezak, M. D. (1995). Neuropsychological Assessment, Third Edition. New York: Oxford University Press.

Lister, R. G. (1985). The amnesic action of benzodiazepines in man. Neuroscience and Biobehavioral Review, 9, 87-94.

Lorig, T. S. (1989). Human EEG and odour response. Progressive Neurobiology, 33, 387-398.

Mack, J. L., Patterson, M. B., Schnell, A. H., Whitehouse, P. J. (1993). Performance of subjects with probable Alzheimer's Disease and normal elderly controls

on the Gollin Incomplete Pictures Test. Perceptual & Motor Skills, 77, 951-969.

McGlone, J. (1994). Memory complaints before and after temporal lobectomy: Do they predict memory performance or lesion laterality? Epilepsia, 35, 529-539.

McGlone, J., Gupta, S., & Humphrey, D. (1987). Memory Observation Questionnaire - 2. London, Ontario.

McGlone, J., Gupta, S., Humphrey, D., Oppenheimer, S., Mirsen, T., & Evans, D. R. (1990). Screening for early dementia using memory complaints from patients and relatives. Archives of Neurology, 47, 1189-1193.

Meggs, W. J., & Cleveland, C. H. (1993). Rhinolaryngoscopic examination of patients with the Multiple Chemical Sensitivity Syndrome. Archives of Environmental Health, 48, 14-18.

Meggs, W. J., Dunn, K. A., Bloch, R. M., Goodman, P. E., & Davidoff, A. L. (1996). Prevalence and nature of allergy and chemical sensitivity in a general population. Archives of Environmental Health, 51, 275-282.

Miceli, G., Caltagirone, C., Gainotti, G., Masullo, C., & Silveri, M. C. (1981). Neuropsychological correlates of localized cerebral lesions in non-aphasic brain-damaged patients. Journal of Clinical Neuropsychology, 3, 53-63.

Miller, C. S., & Mitzel, H. C. (1995). Chemical sensitivity attributed to pesticide exposure versus remodeling. Archives of Environmental Health, 50, 119-129.

Milner, B. (1958). Psychological defects produced by temporal lobe excision. The Brain and Human Behavior (Chapter VIII, 244-257) (get reference for the text).

Milner, B. (1964). Some effects of frontal lobectomy in man. In J. M. Warren & K. Akert (Eds.), The frontal granular cortex and behavior. New York: McGraw Hill.

Milner, B. (1972). Disorders of learning and memory after temporal lobe lesions in man. Clinical Neurosurgery, 19, 421-446.

Milner, B. (1974). Hemispheric specialization: Scope and limits. In F.O. Schmitt & F.G. Worden (Eds.), The Neuroscience Third Study Program. Cambridge, MA: MIT Press.

Milner, B. (1982). Some cognitive effects of frontal-lobe lesions in man. Phil. Trans. R. Soc. Lond., 298, 211-226.

Milner, B., & Petrides, M. (1984). Behavioural effects of frontal-lobe lesions in man. Trends in Neuroscience, .

Morris, R. G., & Abrahams, S. (1995). Recognition memory for words and faces following unilateral temporal lobectomy. British Journal of Clinical Psychology, 34, 571-576.

Morrow, L. A., Callender, T. J., Lottenberg, S., Buchsbaum, M. S., Hodgson, M. J., & Robin, N. (1991). PET and neurobehavioral evidence of tetrabromine encephalopathy. Journal of Neuropsychiatry and Clinical Neuroscience, 2, 431-435.

Morrow, L. A., Robin, N., Hodgson, M. J., & Kamis, H. (1992). Assessment of attention and memory efficiency in persons with solvent neurotoxicity. Neuropsychologia, 30, 911-922.

Morrow, L. A., Ryan, C. M., Goldstein, G., & Hodgson, M. J. (1989). A distinct pattern of personality disturbance following exposure to mixtures of organic solvents. Journal of Occupational Medicine, 31, 743-746.

Morrow, L. A., Ryan, C. M., Hodgson, M., & Robin, N. (1990). Alterations in cognitive and psychological functioning after organic solvent exposure. Journal of Occupational Medicine, 32, 444-450.

Nelson, H. E. (1982). National Adult Reading Test (NART): Test Manual. Windsor: NFER-Nelson.

Nethercott, J. R., Davidoff, L. L., & Curbow, B. (1993). Multiple chemical sensitivities syndrome: Toward a working case definition. Archives of Environmental Health, 48, 19-26.

Nyenhuis, D. L., Rae, S. M., Zajecka, J. M., Luchetta, T., Bernardin, L., & Garron, D. C. (1995). Mood disturbance versus other symptoms of depression in multiple sclerosis. Journal of the International Neuropsychological Society, 1, 291-296.

Otto, D., Molhave, L., Rose, G., Hudnell, H. K., & House, D. (1990). Neurobehavioural and sensory irritant effects of controlled exposure to a complex mixture of volatile organic compounds. Neurotoxicology and Teratology, 12, 649-652.

Pendleton, M. G., Heaton, R. K., Lehman, R. A. W., & Hulihan, D. (1982). Diagnostic utility of the Thurstone Word Fluency Test in neuropsychological evaluations. Journal of Clinical Neuropsychology, 4, 307-317.

Perret, E. (1974). The left frontal lobe of man and the suppression of habitual

responses in verbal categorical behaviour. Neuropsychologia, 12, 323-330.

Petrides, M., Alivisatos, B., Evans, A. C., & Meyer, E. (1993). Dissociation of human mid-dorsolateral from posterior dorsolateral frontal cortex in memory processing. Proceedings of the National Academy of Scieces, USA, 90, 873-877.

Petrides, M., Alivisatos, B., Meyer, E., & Evans, A. C. (1993). Functional activation of the human frontal cortex during the performance of verbal working memory tasks. Proceedings of the National Academy of Scieces, USA, 90, 878-882.

Petrides, M., & Milner, B. (1982). Deficits on subject-ordered tasks after frontal- and temporal-lobe lesions in man. Neuropsychologia, 20, 249-262.

Phillips, C. G., Zeki, S., & Barlow, H. B. (1984). Localization of function in the cerebral cortex: Past, present and future. Brain, 107, 328-361.

Pokorny, A. D., Miller, B. A., & Kaplan, H. B. (1972). The Brief MAST: A shortened version of the Michigan Alcoholism Screening Test. American Journal of Psychiatry, 129, 342-345.

Ramier, A. M., & Hecaen, H. (1970). Role respectif des atteintes frontales et de la lateralisation lesionelle dans les deficits de la "fluence verbale." Revue Neurologique, Paris, 123, 17-22.

Randolph, T. G. (1978). Specific adaptation. Annals of Allergy, 40, 333-345.

Rausch, R., Henry, T. R., Ary, C. M., Engel, J., & Mazziotta, J. (1994). Asymmetric interictal glucose hypometabolism and cognitive performance in epileptic patients. Archives of Neurology, 51, 139-144.

Rea, W. J. (1978). Environmentally triggered cardiac disease. Annals of Allergy, 40, 243-251.

Rees, L. (1964). The importance of psychological, allergic and infective factors in childhood asthma. Journal of Psychosomatic Research, 7, 253-262.

Roberts, A. H. (1976). Long-term prognosis of severe accidental head injury. Proceeding of the Royal Society of Medicine, 69, 137-140.

Rossi, J. (1996). Sensitization induced by kindling and kindling-related phenomena as a model for multiple chemical sensitivity. Toxicology, 111, 87-100.

Ryan, C. M., Morrow, L. A., Bromet, E. J., & Parkinson, D. K. (1987).

Assessment of neuropsychological dysfunction in the workplace: Normative data from the Pittsburg Occupational Exposures Test Battery. Journal of Clinical and Experimental Neuropsychology, 9, 665-679.

Ryan, C. M., Morrow, L. A., & Hodgson, M. (1988). Cacosmia and neurobehavioral dysfunction associated with occupational exposure to mixtures of organic solvents. American Journal of Psychiatry, 145, 1442-1445.

Savage, E. P., Keefe, T. J., Mounce, L. M., Heaton, R. K., Lewis, J. A., & Burcar, P. J. (1988). Chronic neurological sequelae of acute organophosphate pesticide poisoning. Archives of Environmental Health, 43, 38-45.

Schottenfeld, R. S., & Cullen, M. R. (1985). Occupation-induced post-traumatic stress disorders. American Journal of Psychiatry, 142, 198-202.

Simon, G. E., 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, 97-103.

Simon, G. E., Katon, W. J., & Sparks, P. J. (1990). Allergic to life: Psychological factors in environmental illness. American Journal of Psychiatry, 147, 901-906.

Skinner, H. A. (1982). The Drug Abuse Screening Test. Addictive Behaviours, 7, 363-371.

Sparks, P. J., Daniell, W., Black, D. W., Kipen, H. M., Altman, L. C., Simon, G. E., & Terr, A. I. (1994). Multiple chemical sensitivity syndrome: A clinical perspective. Journal of Occupational Medicine, 36, 718-730.

Spreen, O., & Strauss, E. (1991). A Compendium of Neuropsychological Tests. New York: Oxford University Press.

Staudenmayer, H. (1997). Multiple chemical sensitivity or idiopathic environmental intolerances: Psychophysiologic foundation of knowledge for a psychogenic explanation. Journal of Allergy and Clinical Immunology, 99, 434-437.

Staudenmayer, H., Selner, J. C., & Buhr, M. P. (1993). Double-blind provocation chamber challenges in 20 patients presenting with "multiple chemical sensitivity". Regulatory Toxicology and Pharmacology, 18, 44-53.

Staudenmayer, H., Selner, M. E., & Selner, J. C. (1993). Adult sequelae of childhood abuse presenting as environmental illness. Annals of Allergy, 71, 538-546.

Stein, M. A., Krasowski, M., Leventhal, B. L., Phillips, W., & Bender, B. G. (1996). Behavioral and cognitive effects of methylxanthines: A meta-analysis of theophylline and caffeine. Archives of Pediatric and Adolescent Medicine, 150, 284-288.

Stewart, D. E., & Raskin, J. (1985). Psychiatric assessment of patients with "20th century disease" ("total allergy syndrome"). Canadian Medical Association Journal, 133, 1001-1006.

Terr, A. I. (1986). Enviromental illness: A clinical review of 50 cases. Archives of Internal Medicine, 146, 145-149.

Terr, A. I. (1987). "Multiple chemical sensitivities:" Immunologic critique of clinical ecology theories and practice. Occupational Medicine: State of the Art Reviews, 2, 683-694.

Terr, A. I. (1993). Immunological issues in "Multiple chemical sensitivities." Regulatory Toxicology, 18, 54-60.

Teuber, H. L. (1975). Effects of focal brain injury on human behavior. In D.B. Tower (Ed.), The Nervous System (Vol.2). The Clinical Sciences. New York: Raven Press.

Toothaker, L. E. (1986). Introductory Statistics for the Behavioral Sciences. New York: McGraw-Hill.

Trenerry, M. R., Crosson, B., DeBoe, J., et al. (1989). Stroop Neuropsychological Screening Test Manual. Odessa: Psychological Assessment Resources, Inc.

Vanderploeg, R. D. (1994). Estimating premorbid level of functioning. In R. D. Vanderploeg (Ed.), Clinician's guide to neuropsychological assessment. New Jersey: Lawrence Erlbaum Associates, Publishers.

Warkintin, S., & Passant, U. (1993). Functional activation of the frontal lobes: Regional cerebral blood flow findings in normals and in patients with frontal lobe dementia performing a word fluency test. Dementia, 4, 188-191.

Warrington, E. K. (1984). Recognition Memory Test Manual. Windsor: NFER-Nelson.

Warrington, E. K., & James, M. (1967a). An experimental investigation of facial recognition in patients with unilateral cerebral lesions. Cortex, 3, 317-326.

Warrington, E. K., & James, M. (1967b). Disorders of visual perceptions in

patients with localised cerebral lesions. Neuropsychologia, 5, 253-266.

Warrington, E. K., & James, M. (1991). The Visual Object and Space Perception Battery. Bury: Thames Valley Test Company.

Warrington, E. K., & Rabin, P. (1970). Perceptual matching in patients with cerebral lesions. Neuropsychologia, 8, 475-487.

Warrington, E. K., & Taylor, A. M. (1973). The contribution of the right parietal lobe to object recognition. Cortex, 9, 152-164.

Wechsler, D., & Stone, C. (1945). Wechsler Memory Scale Manual. New York: New York Psychological Corporation.

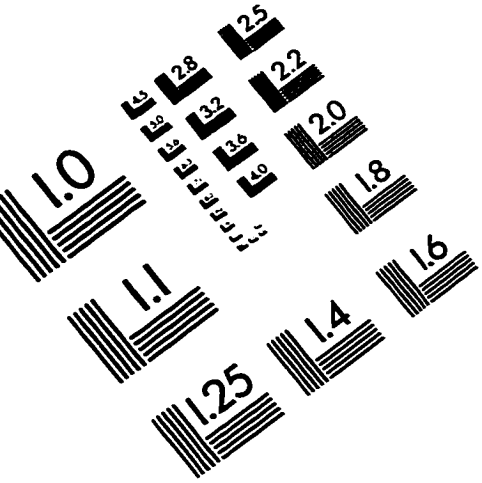
White, R. F., Feldman, R. G., & Travers, P. H. (1990). Neurobehavioral effects of toxicity due to metals, solvents, and insecticides. Clinical Neuropharmacology, 13, 392-412.

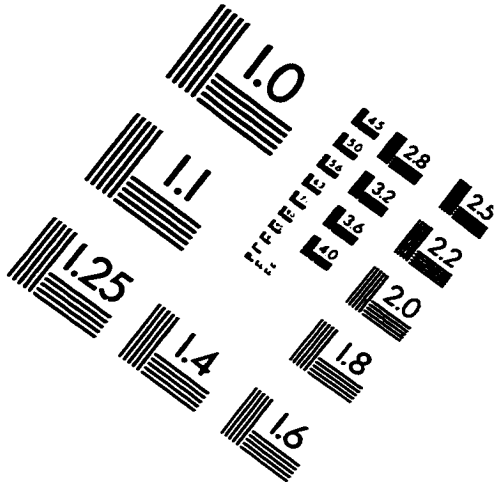
White, R. F., & Proctor, S. P. (1992). Research and clinical criteria for development of neurobehavioural test batteries. Journal of Occupational Medicine, 34, 140-148.

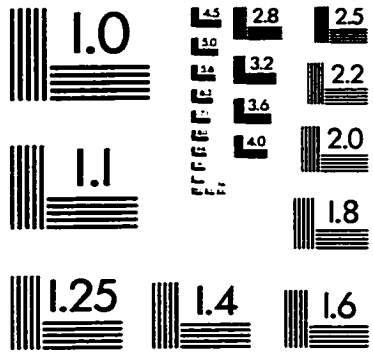
Wiegersma, S., van der Sheer, E., & Hijman, R. (1990). Subjective ordering, shor-term memory, and the frontal lobes. Neuropsychologia, 28, 95-98.

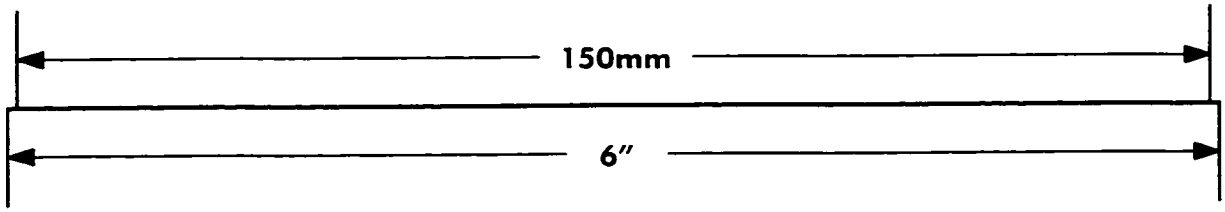
Yeo, R. A., Turkheimer, E., & Bigler, E. D. (1990). Neuropsychological methods of localizing brain dysfunction: Clinical versus empirical approaches. Neuropsychiatry, Neuropsychology, and Behavioral Neurology, 3, 290-303.

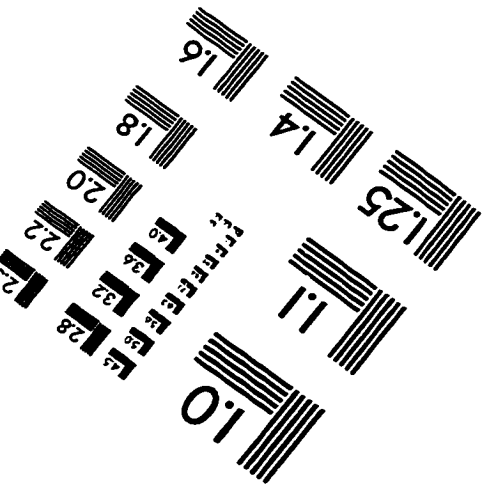
IMAGE EVALUATION
TEST TARGET (QA-3)

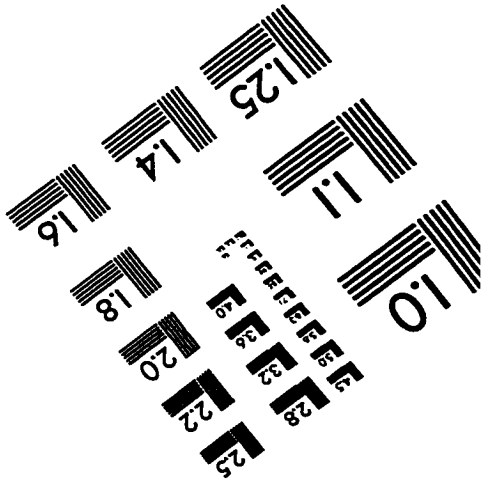












APPLIED IMAGE, Inc
1653 East Main Street
Rochester, NY 14609 USA
Phone: 716/482-0300
Fax: 716/288-5989

© 1993, Applied Image, Inc., All Rights Reserved