

# A Behavior–Genetic Approach to Multiple Chemical Sensitivity

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This report emphasizes the application of behavior-genetic designs to the study of sensitivity to toxic chemicals, and features of multiple chemical sensitivity and substance abuse that are polar opposites. The implications of these issues for future research are discussed in relation to twin, adoption, and sibling pair studies, as well as in relation to the degree to which genetically selected lines of rodents that have been developed in the alcoholism field are applicable to multiple chemical sensitivity. — *Environ Health Perspect* 105(Suppl 2):505–508 (1997)

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## Introduction

Miller (1) presents an interesting model of multiple chemical sensitivity (MCS). It is similar in many ways to stress-diathesis models that are ubiquitous in clinical psychology (2). In these theories, a constitutional vulnerability (i.e., diathesis) is proposed that places an individual at heightened risk for developing a psychiatric disease such as alcoholism (3,4). This vulnerability may be genetic, environmental, or a genetic–environmental interaction. If vulnerable individuals are exposed to significant environmental stresses, they may manifest the disorder. However, if individuals at heightened risk are reared in nurturant, stress-buffering environments, or if they have other constitutional traits that protect against the effects of stress, the disorder may never be expressed clinically.

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Abbreviations used: CNS, central nervous system; HAD, high alcohol drinking; LAD, low alcohol drinking; MCS, multiple chemical sensitivities; NP, alcohol non-prefering; P, alcohol-prefering.

In Miller's (1) model, the diathesis for MCS could be a proneness for loss of tolerance when exposed to toxic chemicals. For example, an individual may have enhanced capacity for sensitization processes—both conditioned and unconditioned—that would amplify any preexisting aversion to toxic chemicals or to the odors of those substances. The stress component of the stress-diathesis model can be viewed either as an acute exposure to high levels of a toxic chemical, such as in an industrial accident, or as gradual, intermittent exposure to low-level chemicals, such as when a work building is remodeled.

## Behavior Genetics

Table 1 summarizes certain behavior-genetic designs that are often used to determine genetic and environmental factors in psychiatric disorders.

### Twins

Sophisticated methods have been developed to assess the genetic heritability of psychiatric vulnerabilities (5). If it were

found that MCS tended to run in families or to demonstrate intergenerational transmission, there would be a possibility that the disorder had a significant genetic component (6). However, this would not preclude the possibility of environmental transmission because pesticide use patterns, living or working locations with toxic pollutants, and similar factors could be common to different generations of the same families.

Twin studies may be used to assess the genetic heritability of MCS. In these studies, monozygotic and dizygotic twin pairs are assessed in terms of clinical manifestations of MCS or a subclinical aversion to chemicals. If the disorder has a genetic component, monozygotic twins—who have identical genes—would be expected to demonstrate greater concordance for the disorder or its subclinical manifestation(s) than dizygotic twins—who share half their genes on average.

The design is simple but the execution and statistical analyses are not. Twins pairs must be identified in which one or both of the twins has MCS or some heightened aversion to chemicals. The required number of twin pairs who meet these criteria to test the hypothesis of a significant genetic component is probably in the hundreds (5,7). This usually necessitates mass mailings of questionnaires to an established twin registry rather than structured clinical interviews. It can be expected that using self-report measures would tend to dilute the measured effect, so that even more twin pairs would be needed to provide a powerful test of the genetic hypothesis.

### Gene X Environment Interaction

Kendler (7) recently proposed at least two mechanisms for gene X environment interaction: genetic control of exposure to the environment and genetic control of sensitivity to the environment. In the first mechanism, an individual may have a genetic predisposition for exploratory

**Table 1.** Summary of selected experimental designs in behavior genetics.

Design	Genetic heritability estimates	Environmental transmission estimates	Interaction (gene X environment) estimates	Additional studies
Family	No	No	No	Intergenerational transmission
Twin	Yes	Yes	Yes	Discordant MZs; item loadings
Adoptee	Yes	Yes	Yes	Item loadings
Sibling pair	Yes	No	No	Molecular genetics
Genetically selected lines of rodents	Yes	Yes	Yes	Neurophysiology; highly toxic incitants

behavior or sensation-seeking that would make them more likely to be exposed to toxic chemicals. In the second mechanism, an individual may be more sensitive to environmental toxicity due to genetic predisposition. Kendler (7) discussed mathematical models for studying these potential mechanisms in psychiatric illness.

### Adoptees

A second design that has been used often to assess genetic effects is the study of adoptees (8,9). Adoptees who have a biological parent diagnosed with an MCS disorder but who have been placed in foster homes in which neither foster parent has an MCS disorder are compared to similar individuals whose biological parents do not have an MCS disorder. If the adoptees whose biological parent(s) have MCS are more likely to manifest the disorder than matched adoptees with no family history, MCS can be said to show a significant genetic component.

In both twin and adoption designs, many other hypotheses can be tested. These include genetic associations with other disorders (such as alcoholism), the degree to which MCS in the foster parents may elevate the adoptees' risk of manifesting the disorder due to environmental transmission, and the study of discordant monozygotic twins to isolate the environmental etiology or chronic effects of MCS. Moreover, these designs allow the researcher to separate those specific characteristics of MCS that have significant genetic loadings from those that do not (10).

### Molecular Genetics

If it could be firmly established that there were a significant genetic component to MCS, it would then be useful to proceed to behavioral/molecular family designs to determine the genetic locus of the vulnerability. This approach requires that candidate genes be available that may be expected to play a role in the disorder based on theoretical or empirical grounds. Other candidate genes would be those that control brain neurotransmitters such as dopamine, serotonin, or glutamate.

The simplest behavioral/molecular family design (11) involves studying sibling pairs—at least one of whom has an MCS disorder—as well as serum collected from both parents. Assays of DNA from white blood cells from both siblings and both parents are used to identify polymorphisms that can be localized on the human genome and that have known associations with

relevant physiological functions. The sibling pairs (but not the parents) must be evaluated clinically for the presence or absence of an MCS disorder. The presence or absence of relevant gene polymorphisms is then related to the presence or absence of MCS in the siblings. If both siblings have an MCS disorder, they would both be expected to possess a relevant polymorphism. If only one sibling is diagnosed as having an MCS disorder, only the affected individual would be expected to have the relevant polymorphism. The DNA of the parents is used to further specify the descent of the relevant gene(s) (12,13).

This is a potentially powerful design, but it is absolutely necessary to replicate the "hit" with a different sample of families if a gene locus is identified. The design is prone to false positives, so independent replication prior to publication is needed to verify the results (14). In the replication study, only the gene polymorphism that had a hit in the first study needs to be assayed—a major saving in effort and expense. Sibling pairs are more easily recruited than twins, and a number of potential candidate genes have been identified. However, if the true candidate gene is not among those assayed, the study has little or no hope of discovering it.

### MCS and Substance Abuse as Polar Opposites

Miller (1) introduces the term "abdiction" in MCS patients to denote extreme aversion to chemicals, as opposed to "addiction" to them. There are at least two possible ways in which addiction (to drugs) and abdiction (from chemicals) may be related. First, MCS and substance abuse may represent polar opposites in the sense that they have some clinical features that are diametrically opposed to each other. A second possibility is that MCS and substance abuse have the same diathesis that is expressed alternatively as abdiction or

addiction. The null hypothesis is that they are entirely orthogonal disorders.

Table 2 lists characteristics that differ between the two disorders and methodologies to study them. Several clinical features that are opposite in MCS and substance abuse follow.

### Orientation toward Chemicals

Substance abusers move toward chemical stimuli (i.e., drugs) while MCS patients move away from them (15). This basic orientation toward affective stimuli is a fundamental dimension of human and mammalian functioning. Moreover, in animals this moving toward versus moving away from stimuli can be measured readily using autoshaping/sign-tracking procedures. In these paradigms, the animals literally move toward or away from conditioned stimuli that are correlated in time—positively or negatively—with some biologically relevant unconditioned stimulus—appetitive or aversive. This is Pavlovian rather than operant conditioning (16).

### Demographics

The relative demographics appear opposite in MCS and substance abuse. Substance abusers are approximately twice as likely to be men than women (3), and the prevalence is moderately inversely correlated with socioeconomic status. For example, over the last decade cigarette smoking has become primarily a poor and working class phenomenon in the United States (17). In contrast, the typical MCS patient is a middle class or professional woman (18). The age of onset of substance abuse is typically the teens or early twenties (19), while that of MCS is often later. Although the demographics of substance abuse and addiction have been well studied in the community, it is possible that the apparent demographics of MCS are due to clinical bias. Middle-aged, educated women may simply be more likely to seek treatment and to volunteer for clinical research.

**Table 2.** Summary of opposing features of multiple chemical sensitivity and substance abuse.

Dimension	MCS	Substance abuse	Methodology
Orientation toward chemicals	Abdiction; moving away; avoidant	Addiction; moving toward; sensation-seeking	Structured interview; autoshaping/sign tracking; genetic rodent model
Demographics	Educated, middle-aged women	Poorly educated young men	Epidemiology; community samples
Sensitization	To aversive properties	To rewarding properties	Locomotor activity; brain microdialysis
Temperament	Shyness	Antisociality	Self report; behavioral measures

## Sensitization

Current research on substance abuse proposes that the addictive process can be represented at least in part by sensitization to the rewarding effects of abused drugs (19). In contrast, theorists studying MCS have proposed that the development of the disorder is due to sensitization to the aversive properties of chemicals. Therefore, it may be profitable to study the cortico-mesolimbic dopamine system and its interaction with other neurotransmitter systems in rodents that are particularly sensitive to low-level toxic chemicals.

## Temperament

Substance abuse is strongly related to antisocial behavior. For example, individuals in the community meeting criteria for antisocial personality disorder are 27 times more likely to be substance abusers than those without this diagnosis (20). In contrast, there is evidence (21) that MCS patients tend toward shyness. These personality differences reflect temperamental trait differences that could potentially reflect underlying genetic diatheses that differ between substance abuse and MCS.

## Naltrexone

These differences between addiction and abstinence are not exhaustive, nor are they all well established in empirical studies. However, the reasoning may be useful in the development of future research questions and experimental designs to study MCS (and substance abuse). For example, recent evidence (21,22) indicates that the broad-band opiate antagonist naltrexone (Revia) is moderately effective in the treatment of alcoholism. One implication of the argument above is that naltrexone is a candidate medication for MCS. Although clinical evidence indicates that MCS patients often have medication intolerance, it is possible that an normally inactive antagonist such as naltrexone may be better tolerated than active agonists.

Following the argument that MCS and substance abuse may be polar opposites, an opiate agonist such as methadone or a

partial agonist/antagonist such as buprenorphine may be a candidate medication for MCS as well. However, many MCS patients may not tolerate these drugs, so homeopathic doses may be necessary.

## Animal Models

### Miller's Postulates

If we assume for the moment that there is a genetic or environmental association between MCS and substance abuse, this association has important implications for how to develop an animal model of the disorder. Miller's four postulates (1) provide an ideal starting point for determining whether an existing animal model is adequate as a nonhuman analogue for MCS. For example, the alcohol preferring (P) and alcohol avoiding (NP) strains of rats and the high alcohol drinking (HAD) and low alcohol drinking (LAD) strains developed through genetic selection by Li and colleagues (23) have been shown to meet criteria for an animal model of alcoholism. Miller's postulates could serve the same function in MCS research.

### Alcohol Preference

Although a number of rodent models of alcohol and drug abuse have been developed, the P versus NP and HAD versus LAD lines of rats are perhaps the best validated (23). Therefore, these strains of animals need to be tested in terms of their physiological and behavioral responses to high and low levels of toxic chemicals. To the extent that MCS and alcoholism represent polar opposites, we would expect the NP and LAD rat lines to be highly avoidant of low-level toxic chemicals compared to the P and HAD lines, respectively. Conversely, if it were found that MCS and alcoholism represented alternative phenotypes of the same underlying diathesis in humans, then we would expect the P and HAD rats to be more avoidant.

### Methods

Wood (24,25) has developed sophisticated experimental procedures for measuring

behavioral aversion to chemicals in rodents. In addition, the conditioned place-preference paradigm (26) has been used extensively in the behavioral pharmacology literature to assess both preference for drug effects and aversion to them.

### Limitations

An important limitation of the present discussion might be that it appears to assume a psychiatric etiology of MCS (and substance abuse). However, both the behavior genetic designs outlined in the first part of this discussion and the animal models in the second part are compatible with etiologic mechanisms that are either central nervous system (CNS) or non-CNS. For example, a twin or adoption study would be equally informative for psychiatric and immunologic diatheses. Similarly, animals predisposed to chemical aversion or attraction would be useful for studying different mechanisms, whether CNS or non-CNS, that determined this orientation. Therefore, a limitation of these approaches is that they are not intended to distinguish between different etiologic models of MCS but only to reveal and study genetic and environmental mechanisms.

### Conclusion

The behavior-genetic approach to psychopathology may be particularly useful in the study of MCS. This discussion has emphasized ways in which future research can proceed in this direction using both human volunteers and animal subjects. The suggestions are not exhaustive, but may provide useful starting points. It has been the experience of many psychologists and psychiatrists that new diseases/disorders/problems/complaints are taken more seriously by professionals and by the public after they have been shown to have a significant genetic component. This does not imply that environmental diseases are any less valid or distressing than those with genetic diatheses. It more likely reflects a political or societal bias in the medical and lay communities.

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