Individual Differences in Neural Sensitization and the Role of Context in Illness from Low-level Environmental Chemical Exposures

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This paper summarizes the clinical phenomenology of multiple chemical sensitivity (MCS), outlines the concepts and evidence for the olfactory–limbic, neural sensitization model for MCS, and discusses experimental design implications of the model for exposure-related research. Neural sensitization is the progressive amplification of responsivity by the passage of time between repeated, intermittent exposures. Initiation of sensitization may require single toxic or multiple subtoxic exposures, but subsequent elicitation of sensitized responses can involve low or nontoxic levels. Thus, neural sensitization could account for the ability of low levels of environmental chemicals to elicit clinically severe, adverse reactions in MCS. Different forms of sensitization include limbic kindling of seizures (compare temporal lobe epilepsy and simple partial seizures) and time-dependent sensitization of behavioral, neurochemical, immunological, and endocrinological variables. Sensitized dysfunction of the limbic and mesolimbic systems could account in part for many of the cognitive, affective, and somatic symptoms in MCS. Derealization (an alteration in perception making familiar objects or people seem unfamiliar or unreal) is a common MCS symptom and has been linked with limbic dysfunction in clinical neuroscience research. Sensitization is distinct from, but interactive with, other neurobiological learning and memory processes such as conditioning and habituation (compare adaptation or tolerance). In previous studies, hypotheses for MCS involving sensitization, conditioning, and habituation (adaptation) have often been considered in isolation from one another. To design more appropriate chemical exposure studies, it may be important to integrate the various theoretical models and empirical approaches to MCS with the larger scientific literature on individual differences in these potentially interactive phenomena. — Environ Health Perspect 105(Suppl 2):457–466 (1997)

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This paper outlines the possible relationships between the olfactory–limbic system and neural sensitization model for multiple chemical sensitivity (MCS) (*1*) and certain exposure-related symptoms; and discusses potential interactions between individual differences in neural sensitization, conditioning (context), and habituation (tolerance; adaptation) that might affect experimental design in MCS studies. We describe the model briefly, using data and conclusions from our laboratory studies on chemically sensitive human subjects to illustrate certain points. Research on chemically intolerant subjects thus far indicates that they *a*) exhibit bidirectional variability around an unstable set point (*2*) or failure of habituation over time; *b*) report certain lifetime patterns of medical (*3–5*) and psychiatric (*6–9*) conditions that require explanation in any MCS model; *c*) present more complex clinical phenomenology than chemical avoidance behaviors alone (*3,4*).

Multiple Chemical Sensitivity Clinical Observations That Require Explanation

It is essential to note that the clinical observations summarized below represent a mixture of anecdotal and controlled data from the published literature, with relevant citations. Much of the specific epidemiologic and laboratory study evidence needed to support particular points is not available. At the same time, these concepts represent a core of clinical information that requires articulation in order to design proper studies for testing the assumptions and various mechanistic hypotheses for MCS. MCS is a chronic, polysymptomatic condition. Affected individuals report recurrent flares of illness when exposed to low levels of environmental chemicals (e.g., pesticides, solvents), common foods (e.g., milk, chocolate, wheat, sugar), multiple drugs, and other ingestants (e.g., alcohol, chlorinated water) (*10*). Women represent 70 to 80% of the affected population (*10*). The illness process involves two steps: initiation and elicitation (*10*). Many (*11*), but not all (*12*), MCS patients report an identifiable, acute, or subacute exposure event in which they inhaled, absorbed, or ingested toxic levels of a particular chemical agent. Typically, the initiating substances are pesticides or solvents (*4,5*). Patients report recovery from the more classical, substance-specific toxic effects, followed by a deterioration in overall health over a period of weeks to months. Subsequent eliciting agents are numerous and diverse in chemical structures, but often similar in their adverse effects. Triggers can include previously tolerated levels of pesticides, perfumes, deodorizers, gasoline, paint, new carpet, fresh newsprint, or traffic exhaust, as well as foods, drugs, and alcohol (*4*). Patients report the ability to return to a relatively normal baseline if they avoid exposures to inciting agents (*13*). Some investigators postulate

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Abbreviations used: ADHD, attention-deficit/hyperactivity disorder; ASI, Anxiety Sensitivity Index; CNS, central nervous system; CS, conditioned stimulus; DA, dopamine; EEG, electroencephalogram; MCS, multiple chemical sensitivity; SCL-90-R, Symptom Checklist 90 (revised); TDS, time-dependent sensitization; TLE, temporal lobe epilepsy; UCS, unconditioned stimulus.

that adaptation to chronic exposures dampens the degree of reactivity to exposures under certain circumstances (*5*). They suggest that this adaptation necessitates removal from chronic exposures prior to acute sensitivity testing to avoid type II error (*5,10*).

Individual reactions to many chemically unrelated substances include cognitive difficulties with concentration and memory, neuromuscular, gastrointestinal, affective, musculoskeletal, respiratory, and cardiac dysfunctions, and fatigue (*3,4,11,14*). Miller and Mitzel (*4*) found that cognitive symptoms of MCS such as slowed thinking, memory problems, and concentration difficulty are among the most severe dysfunctions, whereas feelings of unreality/spaciness and lightheadedness are among the most frequent features of the condition (*15*). Symptoms of a given adverse reaction can begin within minutes or be delayed for up to 24 hr after a given exposure or ingestion (*16*). Once triggered, reactions last from minutes to several days, even if the exposure is terminated promptly (*16*). Different phases of the same reaction can involve activated states such as insomnia, anxiety, or irritability, and deactivated states such as sleepiness or depression in the same person, i.e., bidirectionality (*5,10,16*). MCS patients also report increased lifetime rates of physician-diagnosed rhinitis, sinusitis, menstrual disorders, irritable bowel, arthritis, migraine headaches, breast or ovarian cysts, depression, and panic disorder (*3,6–8*). MCS patients usually show marked avoidant behaviors toward inhaled chemicals (for which onset of adverse reactions is within minutes), but often extreme cravings for foods such as sweets (for which onset of adverse reactions is delayed by hours) (*5*). MCS reactions include somatic manifestations as well, involving autonomic dysfunction or inflammation at multiple sites (*17–19*).

A recent study indicated that MCS patients make an average of 23 health care provider visits per year (*20*). This poorly understood condition is costly in terms of worker's compensation, personal injury litigation, and health care utilization. Although definitive population-based studies have not been published, the estimated prevalence of MCS ranges from 0.2 to 4% of the general population (*21,22*). Morrow et al. (*23,24*) found that 60% of solvent-exposed industrial workers manifested symptoms of illness from chemical odor. Bell et al. (*21,25–27*) demonstrated less severe self-reported chemical odor intolerance in 15 to 30% of young adult college student (mean ages 18–19 years) and active retired community elderly (mean ages 68–76 years) samples. In contrast with MCS populations (*3,4,6*), neither the college students nor the elderly individuals with chemical odor intolerance worked in the chemical or associated industries or perceived themselves as disabled by chemical-related illness at the time of the study.

MCS is a complex condition that, once established, defies traditional dose–response relationships of toxicology. That is, in MCS, low doses trigger large responses. The symptom of illness from low-level chemical odors is common in populations not motivated by secondary gain in terms of worker's compensation or disability claims (*22*). The manifestations of adverse reactions are multiple and individualized, and often include involvement of the central nervous system (CNS) (*3,4*).

Olfactory–Limbic and Neural Sensitization Model

The olfactory–limbic and neural sensitization model proposes that individual differences in reactivity to environmental substances in MCS derive from neurobiologically based sensitization of the olfactory, limbic, mesolimbic, and related pathways of the CNS (*1,28*). The nose is a direct pathway into the limbic system both for neural signals (odor–olfactory and irritant–trigeminal) (*29,30*) and for transport of many molecules (*31,32*). Among the sensory systems, only the olfactory system lacks a blood–brain barrier (*29,30*). The olfactory bulb, amygdala, and hippocampus are interconnected parts of a phylogenetically older portion of the brain that is particularly vulnerable to sensitization processes (*33,34*). Repeated intermittent exposures to a given stimulus lead to progressively increased levels of responsivity over time in those structures (*1,33,34*). Sensitization then persists without reexposures for long periods of time. As a result, Stewart and Badiani (*35*) refer to sensitization as a basic form of learning and memory. Indeed, drugs that can interfere with the neurobiology of learning, such as excitatory amino acid antagonists or protein synthesis inhibitors, can also block acquisition of sensitization (*36–38*). The limbic region participates in regulation of a broad range of psychological and physiological functions, including anger, fear, learning and memory, reproduction, eating, drinking, autonomic activity, and pain (*39–41*). Limbic dysfunction could lead to polysymptomatic conditions involving neurobehavioral and somatic manifestations (*1*).

Kindling

Kindling is the prototypical sensitization process, in which a low-level electrical or chemical stimulus that initially had little or no effect on behavior eventually elicits persistent vulnerability to electrographic and behavioral seizures after daily repetition for 10 to 14 days (*42*). Kindling is considered an animal model for temporal lobe epilepsy (TLE) in humans. Full kindling is unlikely to provide an explanation for most MCS cases, as increased rates of TLE per se and other clinically obvious seizure disorders are not present in the majority of MCS patients. However, partial kindling to a point short of seizures produces persistent changes in electrical firing patterns and in aggressive and social behaviors of animals (*43*). Many environmental chemicals, especially pesticides (*44–46*) and the solvent toluene (*34*), induce chemical kindling or partial kindling, or facilitate electrical kindling of the amygdala in animals. Rossi (*42*) has recently published a detailed examination of the basic neurobiology issues in kindling as a model for MCS.

No studies have yet directly examined MCS patients for electrophysiological evidence of partial kindling, TLE (complex partial seizures), simple partial seizures, or subclinical seizure disorders. In view of the association of high rates of polycystic ovary disease in women with TLE (*47*), a history of ovarian cysts (*3*) could suggest focal amygdala or hypothalamic dysfunction resulting in reproductive hormone dysregulation in MCS patients. Moreover, Bell et al. have shown that young adults (*48*) and middle-aged women (*49,50*) with chemical odor intolerance have higher scores than do their chemically tolerant peers on the McLean Limbic Symptom Checklist. This scale is based on self-ratings of the frequency of ictal symptoms of TLE such as somatic, sensory, behavioral, and memory dysfunctions (*51*).

Several different studies have shown that MCS patients have an inordinately high rate of past or comorbid depression and panic disorder (*6–8*), conditions also associated with limbic system dysfunction. Notably, a subset of panic disorder patients with symptoms of derealization and other sensory distortions actually exhibit electrophysiological patterns of simple partial seizures (e.g., unilateral delta-theta slowing over temporal regions) during attacks in supermarkets and

malls monitored with ambulatory electroencephalogram (EEG) (*52*). In addition, nasal inhalation of an olfactory stimulus odor (sweet orange in propylene glycol) to stimulate the temporolimbic regions in such panic disorder patients who were not experiencing an attack elicited increases in EEG delta (slow wave, 2–4 Hz) activity not seen in panic patients without the derealization symptom or in normals (*53*). In other words, panic patients with temporolimbic symptoms of derealization and other sensory distortions show epileptiform EEG alterations with ambulatory monitoring and/or odor inhalation. By analogy, odor-elicited temporal lobe dysfunction could explain in part the derealization symptom in MCS patients. However, such odor reactivity may be present only under conditions of sensitization, not necessarily in a single, isolated test (*28*).

Time-dependent Sensitization

Animal studies have permitted systematic examination of the phenomenology and mechanisms of time-dependent sensitization (TDS). Among various efferents, the amygdala sends excitatory input to the nucleus accumbens of the dopaminergic mesolimbic pathway (*54*). As a result, the amygdala can modulate (but is not necessarily required for) another nonkindling type of neural sensitization known as time-dependent sensitization (*55*). TDS is the progressive increase in responsivity of a given outcome measure with the passage of time between the initial and later exposures to a pharmacological or nonpharmacological stimulus or stressor (*56*). Agents that differ widely in their structural and pharmacological properties can all induce, elicit, and/or modulate TDS (*56–60*), including stimulants, μ opioids, glucocorticoids, tranquilizers, antidepressants, immunosuppressants, pertussis or cholera toxins, and neuromodulators such as substance P, and volatile organic agents such as ethanol (*61*), toluene (*62*), or formaldehyde (*63*). Sensitizable outcomes may be behavioral, neurochemical, immune, or endocrine. Outcomes may also be bidirectional (increases or decreases), depending on the individual's past history with the sensitizing or cross-sensitizing agent (*61,64*). Convulsions are not necessarily involved in TDS, and drugs such as anticonvulsants that block kindling do not prevent TDS-type effects (*65*).

Previous research suggests that the patterns of response to exposures under different time factors can distinguish sensitization from other neurobehavioral processes such as classical conditioning or habituation (Table 1). For example, the initial response to a given stimulus may be of magnitude 1+ in sensitization and habituation. The magnitude of the initial response to a conditioned stimulus (CS) would be 0 in conditioning. Namely, only the unconditioned stimulus (UCS) can elicit the 1+ biological response, and the UCS would not be retested; the initial response to the unconditioned stimulus that is paired with the UCS is 0. Thus, the response magnitude upon initiation could distinguish conditioning from sensitization and habituation. However, if the stimulus is given again soon after the initial exposure, the response is dampened to 0 in habituation, while it remains 1+ in sensitization and grows from 0 to 1+ to the CS in conditioning. Thus, rapid repetition of a stimulus could distinguish habituation from the other two phenomena. After the passage of time, the magnitude of the response in sensitization (amplification of responsivity by passage of time) would be 3+, whereas it would be 1+ in habituation (restoration of responsivity by passage of time without reexposures). In contrast, the magnitude of the response to the CS in conditioning would diminish because of a lack of repeated pairings with the UCS or even oppose that of the UCS (*66*). Thus, delay between reexposures to a stimulus could distinguish sensitization from the other two phenomena.

Sensitization is further complicated by the potential for interaction with conditioning processes in a context-dependent manner (Table 2). That is, if the initiating and eliciting stimuli are given in the same physical environment, then it is possible to elicit the sensitized response only in that same, familiar environment (*35,67*). Testing for elicitation of sensitization in an environment different from the one where the process was initiated, (e.g., testing in a laboratory when the illness is reported at work) will elicit only a baseline magnitude of response. In this circumstance, the sensitization may still be present, but not observable. By analogy, the degree of novelty of environments, in ascending order would be home, work, MCS laboratory (Table 2). In context-dependent sensitization, it is preferable to both initiate and elicit sensitization in the laboratory; otherwise, testing in a novel site after initiation in a familiar setting (*4*) could fail to elicit sensitization when it is actually present.

These context-related concepts derive from previous animal research. Badiani et al. (*67*) studied the interaction of stimulant drugs with the environment (home versus novel cage for both initiating and test exposures) and with individual differences in behavior over a 1-week protocol. They found that it was possible to induce a greater degree of sensitization of rotational behavior if both initiating and test exposures were given in a novel cage, rather than if the exposures were all given in the home cage. This design parallels previous

Table 1. Predicted size of response compared with unexposed controls to a repeated stimulus in sensitization, conditioning, and habituation, based on time since the individual's previous exposure.

	(*a*) Reactivity to initial exposure in environment	(*b*) Effect of time with rapid reexposure	(*c*) Effect of more time, without rapid reexposure
Sensitization[a]	+	+	+++
Conditioning	0 (CR)	+ (CR)	0 (CR)
Habituation[a]	+	0	+

CR, conditioned response to a previously neutral, biologically inactive stimulus (conditioned stimulus [CS]) initially paired with a biologically active stimulus (unconditioned stimulus [UCS], which initially causes a positive unconditioned response [UCR]). NOTE: All three processes can occur in the same individual for a given exposure. The net observed effect will be a complex summation of their respective underlying effects. Within this table, assume the responses represent outcomes for each process by itself. Sensitization proceeds by the passage of time after the initial exposure without further reexposures. Retests produce progressively larger responses. Conditioning proceeds by repeated pairing of UCS and CS starting with the initial exposure until CS alone elicits CR. Repeated retests of CS without repairing with UCS over time extinguishes CR and produces progressively smaller responses. Habituation proceeds by continuous exposure or frequent repetition of exposures. Retests produce progressively smaller responses. [a]If repeated chemical exposures were to induce both sensitization and habituation together in varying degrees, then the net observed response might be modified from the simple examples in the table above. That is, under time pattern *b*, the net response would be present but dampened [i.e., 0 to 1/2 +, masked or adapted by concomitant habituation (*5,10*)]. Under time pattern *c*, the net response would be present and amplified as in the sensitized state [i.e., +++, unmasked or de-adapted by the removal of habituation (*5,10*)]. If repeated chemical exposures were to induce both sensitization and conditioning together, then the net observed response might be one of the scenarios shown in Table 2.

Table 2. Predicted size of context-dependent response to a given chemical during challenge testing by interaction with environmental factors, from the sensitization model for MCS without dishabituation or de-adaptation (*35,67*). Assume a baseline level of chronic symptoms at 1+.

Live in environment	Sensitize to chemical in environment	Test chemical in environment	Response vs baseline: Predicted size after test chemical	Response vs baseline: Predicted size after placebo
[i] Home	Home	Home	2+	1+
[ii] Home	Work	Work	3+	1–2+
[iii] Home	MCS laboratory	MCS laboratory	4+	2+
[iv] Home	Home	MCS laboratory	1–2+	1–2+
[v] Home	Work	MCS laboratory	1–2+	1–2+

The degree of novelty of a given environment (scenarios *ii* and *iii* should heighten sensitization if the initiation and elicitation both occur there. A novel environment should dampen the size of an elicited response if the initiation is removed from the environment in which testing for elicitation occurs (scenarios *iv* and *v*). Research scenario *iii* is more likely than *iv* or *v* to distinguish active from placebo. However, fluctuations in baseline symptomatology without dishabituation make it difficult to differentiate active from placebo in all scenarios, especially *iv* and *v*.

human studies in which investigators gave the sensitizing exposures (session a) and test exposures (session b) in the same novel laboratory setting (*49,50,68*). Badiani et al. (*67*) also demonstrated that the animals with lower responses to amphetamine during the first session exhibited the greater sensitization of rotational behavior after 7 days when sensitizing and test doses were given in a novel environment. In contrast, animals with higher responses to amphetamine during session a exhibited habituation, not sensitization, of rotational behavior after 7 days when all sensitizing and test doses were given in the home environment. Similarly, Sorg et al. (*63*) noted differential sensitization to formaldehyde as a function of initial locomotor responsivity to a novel environment.

Sensitization is not merely a type of conditioning. Animal studies have demonstrated the ability to extinguish the conditioned responsivity to the experimental context by giving sham exposures (e.g., saline injections) without eliminating the sensitized response to the actual substance (e.g., a drug) in the same setting (*69*). Reexposure to the original stimulus immediately elicits the sensitized response despite extinction of the context responsivity. It is also possible to initiate and elicit sensitization in a context-independent manner (*70*). For this type of sensitization, the environment in which the initiating stimulus is given varies among exposures; whenever the stimulus is readminstered, the later responses will be amplified, i.e., sensitized, regardless of the environment in which the reexposures occur. One animal study suggests that animals with the greatest behavioral reactivity to novelty are more prone to develop both stimulant drug self-administration (*71*) and context-dependent rather than context-independent sensitization. These findings raise the possibility of studying analogous individual differences in human subjects to explain why one person progresses into severe MCS and another does not.

A sensitization model also accomodates possible comorbid psychiatric disorders and stress factors in MCS. TDS is a neurobiological process, but drugs and stress (physical or psychological) can cross-sensitize (initiate TDS) when tested later in time (*56,72,73*). Hormones present in the physiological stress response (compare with glucocorticoids) may be required for initiation of TDS to stress (*74*), though not necessarily to pharmacologic agents (*75*). Estrogens favor acceleration of the development of TDS in animals (*76*), and females sensitize more readily than do males (*77*). TDS is emerging as a leading model for various chronic recurrent disorders such as drug craving and addiction (*78*), posttraumatic stress disorder (*79*), bipolar disorder (*80*), recurrent unipolar depression (*80*), and eating disorders such as bulimia (*56*). Various investigators have linked MCS with all of these disorders with the notable exception of drug abuse (*81*). Antelman (*57*) and Bell (*28,81*) have reviewed the extensive overlaps between MCS and TDS. Bell et al. have found increased histories of drug problems in the families of chemically intolerant young adults (*48*) and of alcohol problems in the families of chemically intolerant middle-aged adults (*50*). Thus, the genetic vulnerability to substance abuse problems may be present, but may not be expressed as such in MCS patients.

Another leading MCS symptom is concentration difficulty (*4,15*). This symptom may have neurophysiological correlates in the slow EEG frequency, absolute theta (4–8 Hz). That is, normal young adults trained to produce increased amounts of EEG theta perform more poorly on tests of vigilance than do controls trained to produce decreased amounts of theta (*82*). We have studied temporoparietal theta activity among young adults with depressed affect by using nasal inhalation of filtered room air immediately following a series of low-level chemical exposures (*n*-butanol, galaxolide, propylene glycol) and other tasks. Under those conditions, we found increased theta at rest after the chemicals within the chemically intolerant subset compared with those who reported tolerating chemicals (*83*). Notably, children with attention-deficit/hyperactivity disorder (ADHD) also exhibit increased levels of EEG theta activity, especially during cognitive tasks (*84,85*), which researchers have linked with feelings of unreality (*84*). In a recent survey, chemically intolerant young men reported an increased rate of childhood ADHD diagnoses (*86*). The dopaminergic pathways involved in TDS have also been implicated in ADHD (*87*).

Bell et al. also have evidence for TDS of the endogenous opioid, plasma β-endorphin (*2*), and of cardiovascular measures (*88*) over multiple laboratory sessions involving foods and stress in older adults with moderate levels of chemical odor intolerance. The endorphin levels of the chemically intolerant subjects were generally elevated, but changed direction from session to session relative to those of the normals. In addition, greater initial psychological distress correlated with lower endorphin levels later in the study for the chemically intolerant as contrasted with higher endorphin levels under the same conditions for the normals (*2*). The chemically intolerant group also had waking diastolic blood pressures that were higher on the second than on the first days in the laboratory, whereas the normals showed the opposite pattern (*88*). Despite this variability, averaged over six measurements, waking blood pressures of the chemically intolerant elderly were higher overall than those of their normal peers. Bell et al. have found increased diastolic blood pressures and/or heart rate over time in two subsequent laboratory studies of chemically intolerant individuals in which chemical exposures were given (*49,50*). Together, the data suggest instability of certain physiological variables between measurements and paradoxical reversals in the direction of some stress-related responses for chemically intolerant individuals over time. The findings are

consistent with Antelman et al.'s (*61,64*) data on bidirectionality in TDS. Higher peripheral endorphin levels could lead to nonimmunological release of histamine from mast cells (*89*). If so, endorphin could account for some of the allergylike symptoms such as rhinitis, breathing problems, or hives reported in MCS patients without atopy (*3,4,90*). Moreover, μ opioids such as β-endorphin can initiate TDS in animal studies (*58*) and can modulate cardiovascular tone in human subjects (*91*).

The same group of chemically intolerant elderly described above also exhibited objective polysomnographic sleep patterns such as decreased total sleep time, increased waking, and decreased rapid-eye movement sleep, despite only slightly elevated subjective ratings of sleep disturbance compared with chemically tolerant controls (*92*). Milk, a commonly implicated food incitant in MCS (*4*), was associated with poorer sleep than was soy beverage in the chemically intolerant group. One of several possible neurochemical bases for the aroused sleep pattern that would be consistent with TDS is increased dopamine activity and/or responsivity (DA) (*93*), e.g., in mesolimbic pathways (*94*). Many but not all animal studies of TDS have reported progressive increases in mesolimbic DA activity during induction of TDS (*54,59*). DA is also a major neurotransmitter in the olfactory bulb for odor discrimination (*94*) and in the hypothalamus for inhibition of the reproductive/stress hormone prolactin (*95*).

Plasma prolactin levels are accessible indicators of CNS dopamine (*95,96*). That is, increased hypothalamic dopamine has been shown to act as prolactin inhibitory factor, i.e., decreasing prolactin output into the blood. Prolactin is often elevated in cases of psychological or physiological stress (*97*). Consequently, serum prolactin could offer an objective correlate of sensitization and of stress responses. As part of a study of subsequent blood pressure sensitization (*49*), Bell et al. examined baseline 4 P.M. resting serum prolactin levels (drawn upon study enrollment and assayed with a standard commercial kit) in middle-aged women with and without self-rated chemical odor intolerance. Data from the depressed and nondepressed controls without chemical intolerance were averaged in this analysis; the resulting two groups (CI and non-CI) did not differ in mean levels of psychological distress (SCL-90-R Global Severity Index, $p = 0.969$). Sitting and standing blood pressures were then taken without concomitant chemical exposures at the beginning and end of two sessions, spaced one week apart. During each session, blinded, placebo-controlled chemical exposures were given, using identical procedures. Significantly more of the chemically intolerant women (8/10, 80%) exhibited increased sitting diastolic blood pressure from week one to week two than did the chemically tolerant women (4/17, 24%) (Fisher's Exact Test, $p = 0.007$). Furthermore, the chemically intolerant women who showed laboratory evidence of blood pressure sensitization had lower baseline prolactin levels, in contrast with chemically tolerant women who did not sensitize blood pressure (when a single hyperprolactinemic outlier was removed) (serum prolactin—CI: 7.8, SD 2.9; non-CI: 11.9, SD 4.1, $F(1,19) = 6.1$, $p = 0.024$). While these observations are preliminary, the lower prolactin level suggests either: increased baseline CNS dopamine activity in the hypothalamus; or decreased CNS hypothalamic dopamine with heightened DA receptor sensitivity in the pituitary of the chemically intolerant individuals. The direction of the group difference for prolactin levels is consistent with sensitization of dopaminergic activity to a low-level initiating stimulus (*61*), rather than sensitization to a simple stress response model for chemical intolerance (in which more stress should lead to higher prolactin). However, in view of the variability of the β-endorphin data and one prolactin outlier, it will be essential to replicate and extend the blood studies to multiple measurements over different days and different times of day, at rest, and after chemical exposures, in larger samples of subjects. Nonetheless, the data overall suggest a labile but generally activated neurochemical internal milieu in chemically intolerant individuals that may involve at least opioids and dopamine.

Design Implications of Time-dependent Sensitization

Sensitizable and Previously Sensitized Individuals

For present purposes, hypotheses that derive from a TDS model have major design implications for future studies of exposure-related symptoms in MCS (*81*). First, an important hypothesis is that a subset of MCS patients may be highly sensitizable individuals, not only to environmental chemicals, but also to foods, drugs, other environmental factors, and life stressors (*2,21,27,81,88,98*). This implies that environmental chemicals may be the initiating stimulus for the sensitizing process and that chemicals may act synergistically with other classes of stimuli to initiate MCS (*21,73*). For example, it may be difficult retrospectively to distinguish the sensitizing physiological effects of an acute toxic chemical spill of a single agent from the sensitizing psychophysiological effects of the associated stress response (e.g., β-endorphin, cortisol) (*99*). It may still be possible to try prospective pharmacological agents (e.g., dopamine antagonists to block certain types of TDS initiation) (*35,59*) or nonpharmacological interventions (e.g., brief cognitive psychotherapy to minimize the perceived stressfulness of the event) at the time of emergency treatment in patients exposed to a chemical spill, to determine if a given class of intervention might prevent the later development of MCS on a TDS basis.

In the laboratory, cross-sensitization between pharmacologic and nonpharmacologic stimuli in TDS means that demonstrating current reactivity to psychological stressors such as placebo will not prove a lack of reactivity to chemical stimuli, and vice versa. The initial question then becomes whether certain MCS patients are sensitized to multiple environmental factors (*98*), rather than the dualistic question of a toxogenic versus psychogenic etiology for MCS (*100*). It is also possible that different subsets of MCS patients experience different types of initiation factors, i.e., some may have had early life psychological or physical trauma without chemicals (*21,49*) whereas others may have undergone only an identifiable chemical exposure event in mid-adulthood (*12*). Some chemical exposure events such as a toxic spill could invoke both stress and chemical effects to initiate TDS, perhaps via the physiological stress response pathways (*72–75*). Chemical and stress responses may be dependent on some of the same final common biological mechanisms for initiation or elicitation of sensitization (*72,73*). A key factor in TDS may be the experienced or perceived threat to the individual from the environment (*101,102*). Studies must be designed to manipulate systematically not only chemical exposure levels and awareness of chemicals, but also the perceived stressfulness of the setting in which the chemical exposures occur (*67,102*).

Animal studies suggest that between-group (different groups receiving the active and sham treatments) rather than within-group/crossover (the same groups receiving the active and sham treatments

in counterbalanced order) designs may be optimal to differentiate the chemical effects from those of experimental stress (*56,69,71,101,102*). The difficulty for within-subjects designs is that the sensitizing effects of either an active or a sham exposure may change the subsequent responsivity to the next test (sham or active) in the same individual (*56,61,64*). For example, Badiani et al. (*67*) found a much less intense but nonetheless increased response to saline injections in animals that had been pretreated with active stimulant drug in a novel environment, when sensitizing and the test drug doses were all given in a novel environment. However, the saline effect was apparently conditioned to specific circumstances. It was not present for saline when the pretreatment had involved active drug in a home environment, or saline in either home or novel environment. These latter observations may affect the interpretation of studies such as those of Staudenmayer et al. (*103*), who reported an unreliable pattern of MCS patient symptom data in differentiating chemical from sham challenges. The within-subjects design and the pretesting of masking odors to determine initial lack of reactivity in that study may have initiated a sensitization process to the testing procedures or the masking odors in the MCS patients. Consequently, subjects could have been reactive in a seemingly unreliable manner to various test exposures when they were in fact sensitized to both active and sham agents. This point is important because of recent findings that mint odor, for instance, used repeatedly as a masking odor in Staudenmayer's human MCS study (*103*), can initiate olfactory–limbic sensitization in animals (*34*). Similarly, examination of the study designs of nonatopic adverse food reactions in MCS patients suggests that a failure to appreciate the implications of sensitization can lead to widely divergent experimental outcomes (*15,26*). Systematic designs to test for sensitization with awareness of its potential interactions with contextual conditioning and with adaptation are essential to avoid methodological pitfalls in future MCS chemical and sham exposure studies.

Context-dependent and Context-independent Sensitization

Second, as discussed above, TDS can develop in either context-dependent (conditioned) or context-independent ways (*35,55,59,67,102*). That is, varying the setting in which the sensitizing substance is encountered will enable the individual to exhibit a sensitized response in any setting (context-independence). However, if the chemical exposure is usually paired with particular environmental, nonchemical cues (context-dependence), then single session studies in a novel laboratory situation may miss a true effect. Studies have shown that animals with established sensitization who receive the test agent in a new cage different from the one in which the drug was usually given during initiation of sensitization will not show a sensitized response. When returned to the original, drug-paired setting, sensitized animals will again exhibit heightened responsivity to the drug (*35*) (Table 2). Furthermore, in established context-dependent TDS, environmental chemicals may not be the only eliciting stimulus for symptoms. Some degree of heightened response may occur in animals given saline in the cage previously paired with active drug (*67*). Consequently, the inherent stressfulness, familiarity, or novelty of the experimental setting and procedures themselves may play a substantial role in the outcome of MCS studies involving TDS (*35,67,69,71,75,104*). Both context-dependent and context-independent sensitization theoretically might occur in the same person. However, animals prone to drug self-administration (*71*) may be particularly susceptible to the context-dependent form; whereas animals not prone to stimulant drug self-administration (compare with a large subset of MCS patients) (*63*) may be particularly susceptible to the context-independent form (*71*).

This argument implies that field studies in familiar settings such as office, factory, shopping malls, car, and home environments may be as important as laboratory studies. In this manner, it may be possible to detect sensitized responses to chemicals that would be obscured in acute tests within a novel and often threatening laboratory setting. However, multiple test sessions over periods of days and weeks in the same setting would also help avoid type II error by facilitating development and elicitation of context-dependent sensitization to the experimental procedures (*67*), even if the ability to elicit pre-existing sensitization were initially inhibited (*35*).

It is also possible to design studies to differentiate conditioned from sensitized response. For example, Stewart's group (*69*) extinguished the conditioned component of a heightened response with saline injections by repeated reexposure of the animals to the previously drug-paired environment until the size of the response returned to baseline. However, when they gave the drug again, the sensitized response immediately reappeared, suggesting that extinction addressed only the context-dependent part of the process, not the sensitization itself. Certain investigators have claimed the ability to desensitize MCS patients to chemicals by particular psychological extinction procedures (*103*). It would be crucial to determine not only if the procedures are actually effective in some MCS patients, but also if such extinction eliminates chemical sensitization completely, or simply the conditioned elicitation of adverse reactions in certain situations (*69,71*). The long-term health implications of remaining sensitized, even though not exhibiting context-dependent sensitized reactions in some settings, are unexamined at this time.

Sensitization and the Adaptation Hypothesis

The sensitization hypothesis is compatible with the MCS-derived adaptation hypothesis; that is, a long-standing precept in MCS is that the heightened reactivity and another process, called masking or adaptation, can develop at the same time (*5,10*). The corollary hypothesis is that adaptation may obscure the ability to detect sensitized responses during challenge tests (Tables 1, 2). Complete removal from all adaptation-inducing exposures for 4 or more days is required prior to attempting definitive testing for true adverse reactions to chemicals (*10*). Simple environmental chambers are insufficient, as subjects can remain in them for only a few hours during a day, with little impact on the adaptation process (*5,10*). The practical and financial limitations of developing environmentally controlled units for research have impeded progress in testing the adaptation hypothesis.

Historically, many neurobiological researchers have noted that sensitization and habituation (compare tolerance, adaptation) are distinct but interactive processes (*71,105,106*). Post (*106*) pointed out that continuous or frequent exposures to a given stimulus favor development of tolerance, whereas intermittent exposures favor development of sensitization. Studies have shown that sensitization and habituation are not opposite ends of the same process, but independent, concomitant processes that can summate. Habituation added to an otherwise sensitized response could result in

mutual cancellation of effects, i.e., an apparent lack of change over time (*105*). Moreover, habituation to the test environment itself in an acute test of a substance can interact with individual differences in inclination to drug self-administration to alter drug response (*35,67,71*). Animal studies indicate that MCS patients (who do not tend to be drug abusers) might not show their capacity for heightened reactivity to a chemical during an initial, one-session test. Thus, the basic neuroscience literature supports the MCS contention that adaptation and cross-adaptation to chronic chemical exposures could obscure evidence of heightened reactivity (Table 1). Days, not hours, of withdrawal from the sensitizing substance are needed to be able to elicit a heightened response in TDS (*54,59,71*). Individual differences in responses to habituation to the total (chemical, physical, and psychosocial) environment in which the substance is encountered also may alter the outcome of a given chemical challenge (*35,71,102,107,108*).

Time Factors in Experimental Approaches

Available data indicate two primary ways to design human studies testing for heightened reactivity to environmental chemicals: *a*) place patients in an environmentally controlled unit and remove them from all sources of the suspect chemicals and cross-sensitizing stimuli for a period of days prior to challenge tests (*10*). This effectively removes habituation while providing optimal time for emergence of sensitization; *b*) use inherently more versus less sensitizable individuals and induce context-dependent sensitization to common chemicals in an initially novel laboratory setting over multiple sessions, separated by days from one another (*2,68,98*). Such a procedure would make the heightened reactivity to an otherwise familiar and habituated substance dependent upon the new setting in which it is encountered (*67*).

Design *a* relies largely on deadaptation to reveal pre-existing, context-independent sensitization. It is important to emphasize that both sensitization and habituation are likely to contribute to the reported patterns of reactivity in MCS patients in an environmental control unit (design *a*). That is, if adaptation to ambient exposures outside the unit were the only issue, then removing adaptation by avoidance for a few days would restore not hyperreactivity, but simply reactivity. Instead, clinicians observed a marked hyperreactivity (*10,16*), matching that of a sensitized response (*35,102*).

Design *b* relies largely on experimentally initiated, context-dependent (conditioned) sensitization. The individual may or may not have had preexisting sensitization to the substance. The underlying assumption is that the patient is inherently more sensitizable than a normal person. Design *b* takes advantage of the possibility of inducing and then testing for sensitization by using the laboratory setting itself to make the first exposure to the substance novel and the later exposures familiar, i.e., to foster context-dependent sensitization (Table 2). Newlin and Thomson (*68*) have already demonstrated the feasibility of design *b* in human subjects. They compared changes in autonomic nervous system responses to ingestion of alcohol on three different days in sons of alcoholics and sons of nonalcoholics (all of whom used alcohol socially and nonabusively). The outpatient sessions were spread over a two-week period in the National Institute of Drug Abuse laboratory. The sons of alcoholics exhibited less ability to habituate and more capacity to sensitize the autonomic measures over sessions than did the control subjects. They also tested for conditioned responses to the laboratory setting alone, without alcohol after the last session. Autonomic patterns reverted to baseline levels in the absence of alcohol. Thus, a context-dependent sensitization to alcohol was observed in sons of alcoholics, in which the conditioned component relied on concomitant exposure to the substance and to the setting, not to the setting alone.

Our own preliminary polysomnographic, quantitative EEG, endorphin, and cardiovascular data suggest the feasibility of the multiple, identical-session design for MCS studies. This approach may permit induction and elicitation of sensitized responding in chemically intolerant human subjects without necessitating use of an environmentally controlled hospital unit. However, designs *a* and *b* facilitate asking different types of questions. For design *a*, the main question can be whether the individual is currently sensitive to a given substance. For design *b*, the main question can be whether the individual is unusually sensitizable.

Another important methodological consideration is that exposure levels must be intermittent and perhaps fluctuating, with breaks of hours and even days from one exposure to the next, if sensitization is to develop (*106*). The constant levels of chemicals used in many toxicology studies could minimize sensitization and favor tolerance. Real-world exposures in human populations are generally intermittent and fluctuate over time. Previous investigators have treated inconsistencies in dose during laboratory studies as a potential procedural flaw. On the contrary, the constancy and lack of interruptions in experimental dosing may help explain why tolerance has been reported more often than sensitization in toxicology research., The major ethical consideration for this research in humans is the need to limit the number of repeated exposures during the research protocol. Kalivas et al. (*59*) point out that sensitization to a few scattered exposures is temporary and reversible, but massed daily exposures for a week induce permanent sensitization in animals.

Conclusions

MCS is much more than behavioral avoidance of chemicals; explanations of MCS must account for a broad range of clinical observations (*100*). These observations include low rates of drug use and abuse despite elevated levels of affective distress (*28*). The partial limbic kindling and TDS model has a limited, but growing, amount of empirical evidence in humans (*2,27,88,109*) and in animals (*34,44,45,62,63*) to support its involvement in the multiple symptoms, phenomenology, and medical/psychiatric pictures of MCS patients (*81*). In particular, the sensitization model suggests specific experimental design considerations, without which one risks missing a true effect (type II error). Previous hypotheses for MCS involving sensitization, conditioning, and adaptation have often been considered in isolation from one another. To design more appropriate chemical exposure studies, it may be important to integrate the various theoretical models and empirical approaches to MCS with the larger scientific literature on individual differences in these potentially interactive phenomena (*35,59,67,69,71,105,106*).

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