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Evolutionary game theory and multiple chemical sensitivity[†]

DAVID B. NEWLIN

National Institute on Drug Abuse—Intramural Research Program, Baltimore, Maryland 21224

Newlin's [Newlin D.B. Evolutionary game theory of tolerance and sensitization in substance abuse. Paper presented to the Research Society on Alcoholism, Hilton Head, SC, 1998] evolutionary game theory of addictive behavior specifies how evolutionarily stable strategies for survival and reproduction may lead to addiction. The game theory of multiple chemical sensitivity (MCS) assumes that: (1) the MCS patient responds to low-level toxicants as stressors or as direct threats to their survival and reproductive fitness, (2) this activates the cortico-mesolimbic dopamine system, (3) this system is a survival motivation center—not a 'reward center', (4) the subject emits a counter-response that is in the same direction as the naive response to the chemicals, (5) previously neutral stimuli associated with chemicals also trigger conditioned responses that mimic those to the chemicals, (6) these counter-responses further activate the dopaminergic survival motivation system, and (7) this produces a positive feedback loop that leads to strong neural sensitization in these structures and in behavior controlled by this system, despite a small initial response. Psychologically, the MCS patient with a sensitized cortico-mesolimbic dopamine system is behaving as though his/her survival is directly threatened by these chemicals. Non-MCS subjects have counter-responses opposite in direction to those of the chemicals and show tolerance. An autoshaping/sign-tracking model of this game is discussed. This evolutionary game makes several specific, testable predictions about differences between MCS subjects, non-MCS controls, and substance abusers in laboratory experiments, and between sensitized and nonsensitized animals.

Introduction

Evolutionary game theory (EGT) provides mathematical models of how animals optimize their chances for survival and maximize their reproductive fitness (Maynard Smith, 1973, 1998; Weibull, 1996). The most common evolutionary game is the 'Prisoner's Dilemma' which has been used to model cooperative and competitive behavior among pairs of animals (Dugatkin and Reeve, 1998; Mesterton and Adams, 1998), humans (Wilson, 1998), and even nations (Zagare, 1984). It is a two-player game, meaning that it involves actions and counteractions between pairs of contestants, although there are some evolutionary games with multiple players.

An evolutionarily stable strategy is one that reaches equilibrium over succeeding generations (Maynard Smith, 1973, 1998). For example, Sinervo and Lively (1996) reported evidence of a three-player evolutionary game of the child's 'rock–paper–scissors' game in the side-blotched lizard. Orange-, blue-, and yellow-throated lizards cycle through 6-year periods in which the three types of males trade dominance in a manner that follows the rock–paper–scissors typology. Evolutionary game theory was very helpful in elucidating and modeling this behavior across generations of lizards (Sinervo and Lively, 1996).

Another example of an evolutionary game involves 'stotting' or jumping in the air several times before fleeing a predator in the gazelle. This stotting behavior appears counter-adaptive because it actually impairs the gazelle's ability to elude the predator. This self-handicapping strategy (Zahavi and Zahavi, 1997) has been understood in evolutionary game theory as signalling to a predator that the animal can flee even with this behavioral handicap. Therefore, the adaptive nature of the behavior is understood as a successful strategy in the context of an unusual evolutionary game.

Another example of self-handicapping involves mate selection by female gray tree frogs. Welch et al. (1998) found that male frogs with longer duration mating calls, which could attract a predator, were selected by females over males with shorter mating calls. They argued that the longer mating calls reflected an advertisement by males of 'good genes,' and that the only benefit to the females was in greater viability of their offspring. This self-handicapping strategy was supported in a mating situation that ruled out direct benefits to the females. We will return to self-handicapping (Tucker et al., 1981; Bordini et al., 1986) as a strategy concerning intoxication from alcohol in humans (below).

1. Address all correspondence to: David B. Newlin, NIDA-IRP, 5500 Nathan Shock Dr., Baltimore, MD 21224. E-mail: dnewlin@irp.nida.nih.gov

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EGT has been particularly helpful for understanding animal behavior, such as stotting, that appears to be counterproductive (i.e., seems to reduce chances for survival or impairs reproductive fitness). This ability to model contingencies of survival functioning and reproductive fitness may make EGT suitable to understand maladaptive behaviors and human disease. Multiple chemical sensitivity (MCS) is a human disorder with characteristic behavior that appears to bring no obvious benefits to the individual. In fact, the phenomenology of the disorder (Miller, 1994) involves pronounced discomfort, distress, and negative affect (i.e., fear, anger, anxiety, and disgust). The goal of this paper is to apply EGT to the disorder of MCS. This application may reveal ways in which MCS can be understood in terms of the universal motivations to increase chances for survival and to improve reproductive fitness. The present theory views these motivations as pervasive in everyday functioning.

The success of applying EGT to MCS rests on its ability to account for characteristics of MCS that are known currently, and to predict specific responses in the experimental laboratory in future empirical research. In addition, the models have heuristic value when they lead to new experiments (even those that disconfirm the model) that might never have been performed if EGT had not been applied to MCS.

Assumptions of the game

An EGT analysis of MCS makes several basic assumptions that are plausible but which require substantiation by empirical research. The first assumption is that MCS patients are motivated to increase or to protect their self-perceived survival ability and reproductive fitness (SPFit). SPFit (Newlin, 1998) is a proposed psychological structure in humans that provides a buffer between survival and reproductive motivations on the one hand and biobehavioral interactions with the individual's ecology (life situation) on the other. The second assumption is that MCS patients behave as though various low-level chemicals in the environment threaten their ability to survive and their reproductive fitness; in other words, they respond to chemicals as direct threats to SPFit. A third assumption is that this biobehavioral response to chemicals and to signals for chemicals (such as characteristic odors) represents a stress response that involves activation of cortico-mesolimbic dopamine (DA) circuitry (Sorg and Prasad, 1997). This follows from evidence that the ventral striatum is not a 'reward center', as has been assumed (Kalivas and Samson, 1992), but instead represents a survival motivation system that is activated by threatening stimuli.

A fourth assumption is that MCS and substance-use disorders represent polar opposites, perhaps with a common biological diathesis or constitutional vulnerability (Newlin, 1994a, 1994b, 1997). MCS patients view chemicals as threats to SPFit so they seek 'to move away from' them, while substance abusers view particular chemicals as boosting SPFit so they seek 'to move toward' and to amplify their responses to them. Both disorders may involve hyperactivation and chronic sensitization of the cortico-mesolimbic DA system (Sorg and Prasad, 1997), which serves to amplify the motivation to survive and to increase SPFit.

The current model proposes that MCS reflects right anterior brain activation while intoxication from abused drugs is associated with left anterior brain activation. Greater right frontal brain activity has been found to be associated with moving away from psychological stimuli, while greater left frontal activity has been associated with moving toward stimuli (Davidson, 1992; Sutton and Davidson, 1997). MCS may involve sympathetic (beta-adrenergic) cardiovascular activation that is consistent with a stress response (Berne and Levy, 1977), and use of abused substances has been found to involve withdrawal of vagal inhibition of the heart (Newlin, 1992, 1995; Newlin et al., 1990). Both abused drugs and 'anxiety' responses produce increases in locomotor activity, an apparent output function from the cortico-mesolimbic DA system (Wise and Bozarth, 1987). In learning terms, MCS represents aversive autoshaping/sign-tracking, while substance abuse represents appetitive autoshaping/sign-tracking (Newlin, 1992). Finally, secondary gain in MCS patients involves a self-handicapping strategy that is similar to that for intoxication from alcohol (Tucker et al., 1981; Bordini et al., 1986). Secondary gain also resembles self-handicapping strategies for survival in certain animals, modelled by Zahavi and Zahavi (1997). These assumptions, each of which is testable, will be discussed in more detail below.

SPFit

SPFit is a new psychological construct. SPFit, which is defined only in humans, reflects the tendency for people to symbolize and internalize their functioning. The motivations to survive and to reproduce are therefore experienced as attempting to maximize feelings of personal power (McClelland, 1974) and control—related to survival—and feelings of sexual attractiveness, sexiness, and social desirability (Wilsnack, 1974)—related to reproductive function. SPFit is a symbolic psychological system that organizes and prioritizes behavior in a complex world. Figure 1 illustrates how SPFit can be understood in relation to universal human goals and motivations. Note that cortico-mesolimbic DA is the proposed biological substrate of SPFit, which is the psychological system related to the motivations to survive and to reproduce.

This human capacity to internalize motivational systems allows considerable complexity in adaptive behavior, but

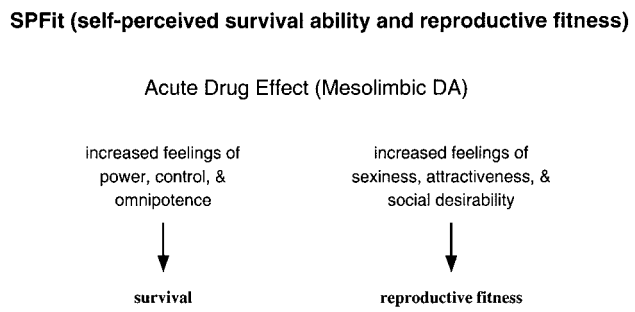

Figure 1. Schematic diagram of SPFit, a psychological structure or system driven by survival and reproductive functions.

also permits behavior that is maladaptive despite the appearance to the individual that it is adaptive. A good example of this is evidence that intoxication from alcohol increases 'power motivation' (McClelland, 1974) and feelings of gender-appropriate masculinity and femininity (Wilsnack, 1974), at the same time that behavior may be grossly impaired and sexual performance is hampered. This paradox illustrates ways in which maladaptive behavior, such as that associated with MCS, can be fuelled by and responsive to survival motivation, which is normally adaptive. Nesse and Berridge (1997) argued that "drugs of abuse create a signal in the brain that indicates, falsely, the arrival of a huge fitness benefit" (p. 64). Although they were discussing nonhuman animals, one might say that in humans, drugs of abuse increase SPFit at the same time that they decrease actual biological fitness. In other words, SPFit determines behavioral response (i.e., taking harmful drugs) rather than actual fitness, which is lowered by drugs.

Toxicants as Threats to SPFit

The second assumption, that MCS patients respond to signals for low-level chemicals (or to symptoms of actual chemical exposure) as direct threats to SPFit, is consistent with the phenomenology of the disorder (Miller, 1994; Ashford and Miller, 1998) Testing this assumption involves laboratory studies in which MCS patients are compared to non-MCS controls in relation to their psychophysiological responses to signaled and unsignaled low-level chemicals (Bell et al., 1997a, 1997b). Stress hormones may increase in this situation, supporting a stress interpretation of the response. Non-MCS control subjects may demonstrate a response that is qualitatively different from MCS patients—that is, opposite in direction to the response of the MCS patients. Presentation of the signal alone (i.e., with no actual toxicant present), such as an odor, light, tone, or visual slide with instructions that it signals the delivery of a chemical, can provide evidence of psychological stress in response to the signal. This is important in studying the *perception* of threat as opposed to the adverse consequences of the chemical, itself. Presentation of the unsignaled chemical eliminates the perception of threat, and can be interpreted as evidence of the aversive response to the chemical, itself.

Table 1 illustrates this four-cell experimental design, called the balanced placebo design in the alcohol literature (Rohsenow and Marlatt, 1981; Hull and Bond, 1986). The balanced placebo design has a strong resemblance to designs used in the animal literature for drug conditioning in rodents (illustrated in Table 1). Moreover, this experimental design has been advocated (Siegel and Kreutzer, 1997) as a way to disentangle conditioned from unconditioned responses to toxicants in MCS patients. The balanced placebo design provides a powerful methodology for testing some of the assumptions of the EGT model of MCS.

Activation of Cortico-Mesolimbic Dopamine DA

Based on evidence that virtually all abused drugs increase DA levels in the ventral striatum, the latter has been viewed as a 'reward center' in the brain (Kalivas and Samson,

Table 1. Experimental design and hypothesized effects in MCS.

		Typical	Placebo	Anti-placebo	Null control
Balanced placebo	Expect (CS)	'toxicant'	'toxicant'	'vehicle'	'vehicle'
design (humans)	Receive (US)	toxicant	vehicle	toxicant	vehicle
Pavlovian conditioning	History	conditioning history	conditioning history	vehicle history	vehicle history
model (animals)	Administer	toxicant	vehicle	toxicant	vehicle
Animals	Response	both CR and UR	CR alone	UR alone	neither
	Mesolimbic DA	large increase	increase	increase	0
Humans	EEG asymmetry	right frontal L>>R	right frontal L>R	right frontal L>R	L=R
Animals and humans	Heart rate	strong tachycardia (sympathetic)	tachycardia (sympathetic)	tachycardia (sympathetic)	0
Animals and humans	Locomotor	strong locomotor activation	locomotor activation	locomotor activation	0
Animals and humans	Subjective	fear and stress	fear	stress	0
Humans	SPFit	increase	increase	increase	0

1992). The fact that stressful stimuli also increase DA in the ventral striatum presents serious problems for this interpretation, particularly since stressful stimuli usually produce negative affect rather than positive. A more appropriate interpretation is that the ventral striatum is a survival motivation center (Newlin, 1998). This accounts well for the effects of stressful stimuli, but also accounts for the actions of abused drugs if we assume, like Nesse and Robinson (1997) that these drugs give a false sense of enhanced survival and reproductive fitness (increased SPFit in humans). Nothing is under more pressure from natural selection than basic survival and reproductive functions in an organism. Therefore, this interpretation of the similar properties of stressful and drug stimuli in terms of survival motivation is consistent with empirical evidence concerning biologically relevant stimuli.

MCS and Substance Abuse as Polar Opposites

Newlin (1994a, 1994b, 1997) and others (Miller, 1997) have argued that MCS and substance abuse disorders represent opposites, but with a common diathesis (biological vulnerability). In a bivariate (i.e., measuring both MCS and substance abuse) twin study of these disorders, a common diathesis would be indicated by a significant genetic correlation between these two disorders. However, they should have no shared environmental variance if they reflect opposing expressions or alternate manifestations of the same underlying vulnerability.

There is evidence that MCS and substance abuse are related in families. Bell et al. (1996) found that drug abuse was more prevalent in the families of MCS patients, and Black (1998) reported increased prevalence of alcoholism in the families of MCS patients. To date, there have been no twin or adoption studies of MCS.

Moving Away vs. Moving Toward

A fundamental dichotomy exists between 'moving away' from specific psychological stimuli and 'moving toward' them. MCS patients are moving away from chemicals and substance abusers are moving toward chemicals of abuse. There is consistent evidence (Davidson, 1992; Sutton and Davidson, 1997) that this dichotomy is reflected in frontal brain asymmetry, with moving away associated with greater anterior right hemisphere activity and moving toward associated with greater anterior left hemisphere activity. This has been measured in several ways, but most often with electroencephalography (EEG). The functionally activated frontal area demonstrates beta activity—low voltage, desynchronized EEG activity at approximately 13 to 35 Hz—while the contralateral hemisphere shows alpha activity—high voltage synchronized EEG activity at 8 to 12 Hz—thought to be an 'idling' rhythm. Right frontal activation is associated with beta activity at the F4 electrode site and alpha activity at F3, and left frontal activation with beta at F3 and alpha at F4.

While it is often the case that we move toward stimuli that we find pleasurable and away from stimuli that are aversive, anger is negative affect that is associated both with 'moving toward' and with greater left frontal activity (Harmon-Jones and Allen, 1998). Therefore, the dichotomy between moving away or moving toward (Sutton and Davidson, 1997) is more fundamental in describing these asymmetric brain activation patterns than is a dichotomy between positive and negative affect (Davidson, 1992).

This asymmetry in anterior brain activation suggests straightforward predictions concerning the ways in which MCS patients should respond to signaled exposure to low-level chemicals. Table 1 presents these empirical predictions in relation to the balanced placebo design. Specifically, signals for low-level toxicants should produce relative right anterior brain activation, and relief from chemical exposure should produce relative left anterior brain activation. Moreover, resting patterns of EEG asymmetry (with no discrete stimulus) should reflect the MCS patients' biases in favor of moving away from environmental pollutants.

Following the idea that MCS and substance abuse represent opposite approaches to chemicals (Newlin, 1994a, 1994b, 1997), we would predict that substance abusers would respond to cues for drugs and to ingestion of abused drugs with relative left anterior brain activation.

Cardiovascular measures may provide other psychophysiological measures that may be equally important in understanding reactions to low-level toxicants in MCS patients and the opposite characteristics of MCS and substance abuse. Under the assumption that the response to signals for toxicants and the response to the toxicants, themselves, are stress responses, then we would predict sympathetic (beta-adrenergic) cardiovascular responses to these stimuli. This would be reflected in tachycardia (increased heart rate) and systolic blood pressure, and increased myocardial contractility (Newlin and Levenson, 1979; Obrist, 1981).

There is substantial evidence that the cardiovascular response to ingestion of abused drugs is qualitatively different from this—tachycardia due to withdrawal of vagal tone (Newlin, 1995; Newlin et al., 1990). Reduction in parasympathetic inhibition allows heart rate to increase markedly, although the cardiovascular mechanism is parasympathetic rather than sympathetic (Berne and Levy, 1977). Some researchers have argued that this tachycardia reflects activation of the cortico-mesolimbic DA system (Newlin, 1994a, 1994b). While most view this DA system as a 'reward center,' the present view is that the ventral striatum is a survival motivation center that is activated both by stressful stimuli and by euphoriant drugs.

In a comparison of MCS, non-MCS controls, and individuals at elevated risk for substance abuse, we would predict that MCS and substance abuse would be associated with sensitization of cardiovascular responses, but that non-MCS controls would show tolerance. Newlin and Thomson (1991, in press) found precisely this effect (sensitization in sons of alcoholics and tolerance in sons of nonalcoholics) using various autonomic variables, although they did not study MCS patients.

Autoshaping/Sign-Tracking

Newlin (1992) presented an autoshaping/sign-tracking model of substance abuse. Autoshaping represents Pavlovian conditioning with a skeletal conditioned response that tends to mimic the unconditioned response (Hearst and Jenkins, 1968). For example, when a key light is predictive of the presentation of water to a thirsty pigeon, the animal directs skeletal responses toward the key light that are similar to those while actually drinking water. There is strong evidence that autoshaping is not so-called 'superstitious conditioning,' which would be operant or instrumental conditioning, but is instead an example of Pavlovian conditioning in which the conditioned response involves skeletal, voluntary behavior (Brown and Jenkins, 1968). This is also referred to as 'sign-tracking' (Hearst and Jenkins, 1968) because the animal is strongly attracted to the 'sign' that water is imminent (i.e., 'drinking' the key light when it comes on).

The advantage of an autoshaping/sign-tracking model of substance abuse (Newlin, 1992) is that behavior in this experimental situation is remarkably resistant to changes in schedules of reinforcement (Brown and Jenkins, 1968). Therefore, the model appropriately mimics the pervasive evidence that addiction to drugs and alcohol is highly resistant to change, and relapse to substance abuse is the rule rather than the exception (Jaffe, 1990; O'Brien, 1996). Autoshaping to signaled injections of cocaine in rats has been reported (Carroll and Lac, 1993).

Figure 2 presents an aversive autoshaping/sign-tracking model of MCS. This model of MCS would suggest that patients are moving away from and amplifying stimuli (such as characteristic odors) that signal the delivery of environmental pollutants. Again, this is an example of Pavlovian conditioning in which the conditioned response is skeletal behavior directed away from predictive stimuli. The model accounts well for the remarkable resistance to extinction of avoidant behavior in MCS, as well as the hypothesized strong response to signaled as opposed to unsignaled responses to toxicants. The sign of imminent exposure to a toxicant attains dramatic importance in a manner similar to the sign of an aversive stimulus in aversive sign-tracking in laboratory animals.

The critical test of an autoshaping model of MCS is an experiment in which laboratory animals have developed an

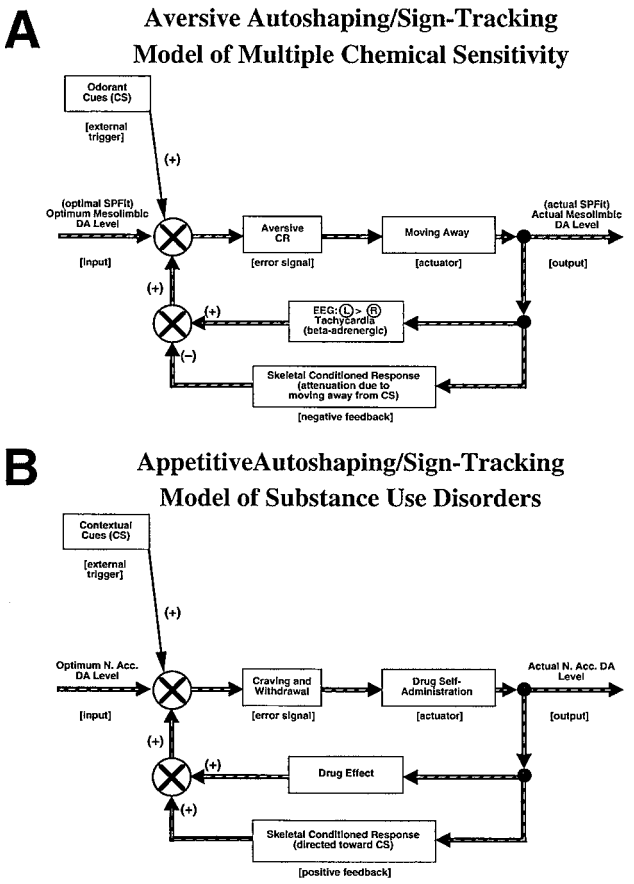

Figure 2. Control theory or linear dynamical systems diagram of MCS (Figure 2A) and substance abuse (Figure 2B).

aversion to an arbitrary cue (such as an odor) which is highly predictive of presentation of a chemical toxicant. Following such autoshaping, the contingencies are changed such that if the animal moves away from a cue for the toxicant, then it will receive the toxicant, but if it moves toward the cue, then it will *not* receive the toxicant. In this system, the animal is rewarded for moving toward the cue and punished for moving away from it. If the autoshaping/sign-tracking model is correct, the animal should continue to move away from the cue, even though it is punished for doing so, and rewarded for approaching the cue. This result would be inconsistent with operant conditioning. It would also be a good example of the tenacity of behavior in an autoshaping/sign-tracking paradigm.

Secondary Gain and Self-Handicapping Strategies

Secondary gain is indicated when an individual finds that having certain symptoms, particularly those associated with pain and discomfort, leads to relatively positive outcomes in addition to their negative effects (Kendall and Norton-Ford,

1982). For example, patients with terminal cancer may discover that friends and relatives are very sympathetic to their complaints, that they do not have to work at their usual employment, or that they receive special attention from physicians and other medical personnel. Experiencing secondary gain does not imply that there is no underlying disease or suffering, but only that the advantages of the disease are realized in addition to the adversity. For example, cancer patients who focus on their pain in a way that maximizes sympathetic responses from others may experience secondary gain, but they still have cancer.

Pennebaker (1994) has conducted extensive studies in which he has found that the degree of complaint by patients with many different diseases is relatively unrelated to the severity of the illness or to the degree of discomfort. This finding says nothing about the seriousness of the disease, but only that medical complaints are verbal operants that are under separate control from the symptoms, themselves. In the same way, the presence of secondary gain in MCS may be entirely separate from the disorder, itself. An EGT model of MCS must be able to account for secondary gain in a manner that is apart from the primary symptoms of the disorder.

Self-handicapping has been studied in relation to intoxication with alcohol (Tucker et al., 1981; Bordini et al., 1986). In this model, drinkers protect their self-esteem in the face of poor performance under the influence of alcohol by emphasizing that their intoxication impaired their performance. Therefore, they would be motivated to drink alcohol to provide a self-handicap that they could use to protect self-esteem.

It is clear that self-handicapping is a form of secondary gain. The drinker uses the fact of his/her impairment to prevent loss of face. In the SPFit model of substance abuse of Newlin (1998), we would say that secondary gain was used to protect SPFit. In the current model of MCS, self-handicapping is a form of secondary gain that is used by some MCS patients to protect SPFit in the face of life problems. Such patients would be motivated to emphasize their impairment from the disorder, and would be less motivated to avoid chemical exposure because it would provide secondary gain.

The SPFit game

Game Forms

Using these assumptions an evolutionary game can be constructed that models fundamental aspects of MCS. In this model, the concepts of orientation toward chemicals (moving toward vs. moving away), and response gain (amplification vs. attenuation) are characteristic counter-moves of MCS patients in the evolutionary game of MCS. These counteractions by MCS patients are in response to cued or uncued chemical toxicants. The game is presented graphically in three different ways: the normal form (Figure 3), the extensive form (Figure 4), and a control theory diagram (Figure 2).

The normal form, which is by far the most common form, includes the pay-off matrix for different moves and counter-moves. The extensive form is useful for modeling moves that occur repeatedly over time, something that is simply assumed in the normal form. Finally, the control theory form emphasizes that this game includes a positive feedback loop that is inherently 'explosive' in nature. Therefore, it can model situations in which the MCS patient is totally overwhelmed by their response to chemicals. In addition, the MCS game is compared to a similar game for substance abuse (Figures 2B, and 4C). This comparison is useful because constructs such as neural sensitization and environmental cues have been studied more thoroughly in psychopharmacology (Kalivas and Samson, 1992) than in MCS.

Normal Form of the Game

The normal form of this evolutionary game is illustrated in Figure 3. The counter-moves by the MCS patient to toxicants or to cues for toxicants can lead to different payoffs depending on how the orientation and gain effects combine. The payoff can be understood as a change in SPFit, and the goal of the game is to improve or to protect SPFit. In this way, the game models maladaptive behavior (in either MCS or substance abuse) that is actually motivated by universal human goals. Reliable and valid measurement of SPFit will be necessary to test some of the predictions of the game, but this is beyond the scope of the current discussion.

If MCS patients move away from chemicals, which would be their preferred response, then this inherently reduces their exposure and thus the gain of the system. This implies that efforts to move away from chemicals are rewarded, but unsuccessful efforts to move away fail to improve the payoff. If they tend to amplify their response to

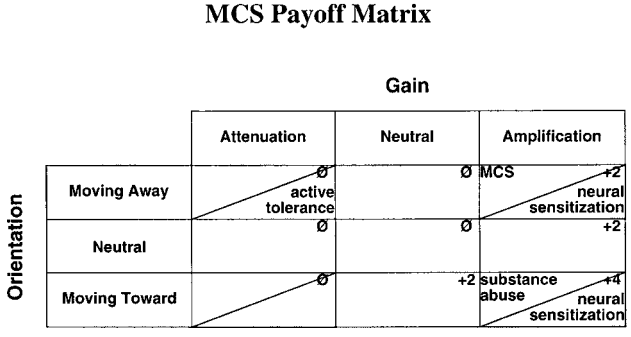

Figure 3. 'Normal' form of SPFit game with payoff matrices for MCS and substance abuse.

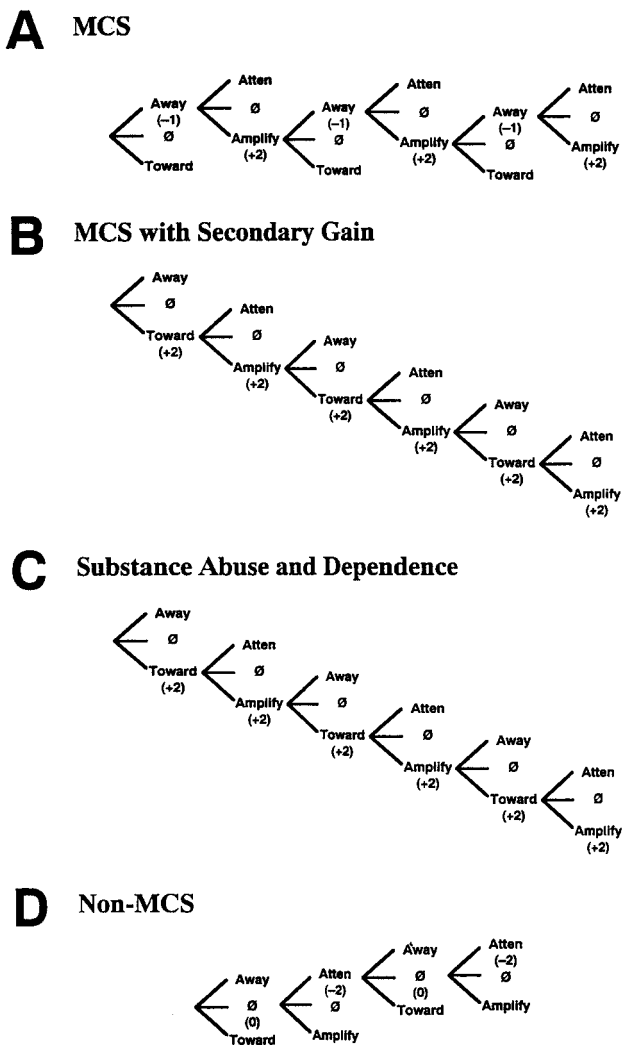

Figure 4. 'Extensive' form of SPFit game, comparable to Figure 3. Movement is from left to right.

the chemicals, which along with moving away can be viewed as defining characteristics of MCS, then the cortico-mesolimbic DA system is sensitized and fear and stressful reactions occur. The MCS patient will be symptomatic in this situation. If the individual moves away from and attenuates their response to chemicals, the result is active tolerance to their effects. This may be the preferred mode of an individual without MCS. In many cases, the MCS patient and the unsymptomatic individual have daily exposures to chemicals that are comparable in intensity. Tolerance also occurs if they move toward chemicals but attenuate their effects, a result consistent with nonproblematic use of drugs (such as caffeine or alcohol). Finally, if the individual moves toward drugs and amplifies their response to them, the likely result is substance abuse. This outcome also involves a sensitized cortico-mesolimbic DA system, with characteristic euphoria and temporarily inflated SPFit.

The payoff matrix in Figure 3 specifies the relative effects of orientation and gain, and their interaction, in a manner that leads to testable hypotheses. Some of these empirical predictions appear in Table 1. For simplicity, Figure 3 assumes linear combination of orientation and gain.

The Extensive Form of the Game

The SPFit game in extensive form is illustrated in Figure 4 as a branching tree diagram. There is a 'choice' point at each branch, with movement through the tree determined by counter-moves indicated in the normal form (Figure 3). The term 'choice' does not imply any conscious decision, but only that the organism is constructed in such a way that characteristic branching takes place to define MCS or drug addiction.

The extensive form emphasizes that there are many choice points in the daily life of an individual as environmental cues for toxicants are perceived and actual exposures to toxicants occur. The presence of disease is indicated by stereotyped, repetitive counter-moves that are clearly maladaptive, but ultimately motivated by the desire to improve or to avoid losing SPFit. This leads to a well-worn path in the MCS patient from sensing chemicals to excessive responses to them. A history of making these moves repeatedly makes this the 'path of least resistance.' This has parallels to the extensive form of drug addiction (Figure 4C) in which the path of least resistance is to use drugs and to amplify the response to them (i.e., sensitization).

A second extensive form (Figure 4B) illustrates the game with the addition of secondary gain. In this form, the MCS patients move toward chemicals (instead of moving away from them) and they amplify their response to them. This pattern leads to very strong neural sensitization because it eliminates the inherent tendency for moving away to limit exposure and to reduce the gain of the system. It is possible that only a small subset of MCS patients experience secondary gain, although it is important to model this effect in those patients.

Control Theory Form

The final form of the game is illustrated in a control theory diagram (Luenberger, 1979) in Figure 2. An advantage of this systems form of modeling is that highly disparate elements can be related together in one system. For example, this system for MCS integrates in one system, cortico-mesolimbic DA (a brain substrate), SPFit (a psychological construct), environmental cues (sensory stimuli), movement relative to chemicals (behavior), and EEG and cardiovascular responses (psychophysiological measures). This ability to relate across different domains of

functioning may be needed with a complex disorder such as MCS.

A second advantage of this control theory model is that it identifies critical elements that control the system's behavior. In this case, the positive feedback loop, denoted by a '(+)' for the effect of psychophysiological stress responses to increase sensitivity to toxicants, suggests a 'vicious cycle' in MCS patients. This positive feedback loop is limited only by the tendency to move away from toxicants, denoted by a '(−)' for negative feedback of skeletal motor behavior on adverse responding. In other words, if the MCS patient is unable to avoid toxicants, or if secondary gain prevents them from moving away from toxicants, then the vicious cycle will lead to extremely adverse responses to toxicants. The unstable or 'explosive' nature of positive feedback systems makes them rare in normal functioning. However, these properties seem appropriate to model the behavior of some MCS patients.

A third advantage of control theory models is that they facilitate comparison between different systems. The autoshaping/sign-tracking model (Newlin, 1992) of addiction and craving for abused drugs is illustrated in Figure 2B. This figure is almost identical to that of MCS (Figure 2A) except for the negative feedback loop in MCS provided by movement away from the stimulus. This structural similarity is consistent with comparable biological substrates in the two disorders and with neural sensitization as potential mechanisms of each disease.

Note that these models of sensitization do not distinguish between classic neural sensitization (Bell, 1994; Bell et al., 1997a, 1997b) and toxicant-induced loss of tolerance (Miller, 1997; Miller et al., 1997). If the response under study reflects increased activation (which is the case with both MCS and substance abuse), then sensitized activation is equivalent to loss of tolerance to activating effects.

Finally, autoshaping/sign-tracking is a laboratory paradigm that suggests relatively simple experiments to test certain aspects of MCS. Autoshaping is an exclusively animal paradigm, although sign-tracking has been demonstrated in human volunteers (Newman et al., 1980).

Summary and conclusions

The central paradox of substance abuse is that people (and animals) take drugs and become addicted to them when this is clearly harmful to the individual. The EGT of addiction of Newlin (1998) proposes that abused drugs artificially inflate SPFit, a psychological structure with cortico-mesolimbic DA as its biological substrate, at the same time that these chemicals impair actual biological fitness. The central paradox of MCS is that patients report overwhelming responses to chemicals that are at such low levels that they may be harmless. The EGT of MCS attempts to resolve this paradox by considering that patients are highly motivated to preserve SPFit, which they view as threatened by the presence of toxicants. This model emphasizes the psychological meaning of the disorder (i.e., perceived threat to SPFit) which resembles a chronic stress condition.

In a classic study in psychosomatic medicine, Graham (1962) and Graham et al. (1962) developed cartoons depicting specific attitudes that their research team had found previously were associated with specific psychosomatic disorders. For example, they found that hives was associated with the attitude that the patient is "taking a beating and feels helpless about it," and so they made a cartoon of an individual being beaten with a whip. They argued further that these specific attitudes were associated with characteristic patterns of psychophysiological responses. Using these cartoons, patients tended to pick the appropriate cartoon that depicted their primary attitude toward life. So, for example, the hives patients tended to pick the whipping cartoon among a number of unrelated cartoons. Moreover, they were able to produce specific psychophysiological responses by asking the subjects to adopt these and other attitudes (Graham et al., 1962). Note that these results do not distinguish between causes or results of the different illnesses.

If MCS patients were included in such a study, their central complaints might be, 'the world stinks' or 'the world makes me sick.' One can easily imagine cartoons that depict these sentiments. We would predict that adopting these attitudes should result in right frontal brain activation, sympathetically mediated tachycardia, and locomotor activation (Table 1). These central metaphors have important basic and clinical implications, although these sentiments could either predate or postdate the development of MCS.

Psychological Disposition

One implication of these conclusions is that the conditioned response to cues for the toxicant in MCS patients may be more informative to the researcher or clinician than the unconditioned (unsignaled) response to the toxicant, itself. In the same way, the psychological disposition of the MCS patient, such as the 'central metaphor of their life (above)', their maintaining SPFit in the face of toxicants, their moving away from chemicals, their behavior reflecting secondary gain, may all be more characteristic of the disorder of MCS than are their inflammatory processes.

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