Context gives meaning. Commentary on Badiani & Robinson 'Drug induced neurochemical plasticity: the role of environmental context'.

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Abstract

A Badiani and TE Robinson (2004) review findings which show that the neurobiological profile of sensitization to a drug depends on the context of the drug experience. The commentary notes that such findings are consistent with the concept of drugs as functional stimuli and that the meaning of stimuli is provided by context. Furthermore, it suggests that psychostimulant drugs generate cues that are affective in nature and that the organism overlays a meaning on these signals that is congruent with the motivational state in the current surroundings. Finally, it questions whether sensitization lacks specificity in animal models of psychiatric disorders but points out that models of specific disorders may be produced by inducing sensitization in the appropriate context.

INTRODUCTION

Sometimes the meaning of a word is ambiguous or even contradictory and its intended meaning can be gathered only in the context of a sentence. Consider, for instance, how Wilson (1993) in The Columbia Guide to Standard American English cautions the reader regarding the importance of context for the word *artless*:

> artless (adj.) is a two-edged word: it can mean "naive, without guile, innocent, and natural" all words of an ameliorative character: *He was a simple, artless young man, with no harm in him*. Or it can mean "clumsy, ignorant, uncultured, and crude"—all pejorative words: *The young man was artless and rough, an unmannerly boor*. Control its meaning carefully through context (http://www.bartleby.com/68/27/527.html).

At first it may seem surprising but the extensive and interesting findings reviewed by Badiani and Robinson (2004) on environmental modulation of sensitization to amphetamine, cocaine or morphine, can be interpreted as revealing that the meaning of an event (here, drug exposure) may depend, similarly, on the circumstances in which the event occurs (that is, context). In other words, the enhanced locomotor sensitization to psychostimulant drugs in novel surroundings that is described by the authors suggests that differential behavioural outcomes reflects correspondingly different meanings of the drug experience in dissimilar contexts (novel environment vs. home territory). Such a conceptual framework raises questions such as: What is it about drugs that may lead to different experiences? What is the 'meaning' to the animal of amphetamine, cocaine or morphine exposure in the different circumstances and can the described

brain findings help us to understand it? And more generally, how does such a perspective on sensitization impact the development of animal models of drug addiction and animal models of psychiatric disorders in general? I consider some possible answers below.

NOT MAGIC BULLETS BUT STIMULI

One of the points stressed by Badiani and Robinson (2004) is that "drug-induced neurobehavioral plasticity is not a mere function of the neuropharmacological actions of drugs." Why did the authors choose to emphasize this point, which in certain respects seems rather obvious? My guess is that the need to state this conclusion reflects the necessity to counteract a deeply ingrained and common (mis)conception about drugs. Notions of magical powers are deeply ingrained in human myths and folklore; often such magical powers were contained in some brew made of special compounds, compounds that in today's vernacular could be seen as isomorphic with drugs. The legacy of magic has crept into scientific language (and, perhaps inadvertently, into scientific thinking). Indeed, one of the first drugs rationally developed to specifically target a disease (syphilis), was dubbed a "magic bullet" by its discoverer, the 1908 Nobel-prize winner in Physiology and Medicine, Paul Ehrlich (The Official Web Site of The Nobel Foundation, 2004). Ehrlich's search for "magic bullets" was focussed on compounds that would target foreign invaders of the human body, invaders that possessed a set of unique receptors not present in the human (Ehrlich, 1908). Today, this quest seems to have expanded to target particular features of human behaviour and psychology, even though it is not at all obvious (and indeed probably unlikely) that each feature of interest can be characterized by a particular set of unique receptors. The underlying notion of psychoactive drugs as potential "magic bullets" aimed at particular psychiatric disorders or capable of selectively altering specific moods or behaviours,

can be discerned in the use of a language that draws a distinction between a drug's "effects" and "side-effects". In reality, all are equally "effects" of the drug in question.

The language of magic bullets detracts our attention from the obvious - drugs in the body, and psychostimulant drugs in particular, act as stimuli (Carlton, 1983) and consequently posses the normal properties of natural stimuli including their cue, arousing, affective, and reinforcing functions. Badiani and Robinson (2004) make note of some of these properties in their search for factors to account for the influence of novelty on sensitization. They note a tight relationship between detection of the cue properties of amphetamine and the development of locomotor sensitization, as evidenced by the observation that the profile of amphetamine discrimination in novel and home environments follows the same pattern as locomotor sensitization in the two contexts. Although the specific amphetamine-like sensory qualities are not yet defined, the results reviewed by the authors nevertheless show that the sensitization response involves perception of an experience initiated by the drug.

From the perspective of drugs as functional stimuli (Carlton, 1983), it follows readily that the action of drugs necessarily would be subject to modulation by context, as is the case for natural stimuli. The significance of most natural stimuli is not hardwired. Rather, the meaning of most stimuli is acquired through various forms of learning, is generally determined by the spatial and/or temporal relationship of the stimulus to other events in the environment, and may depend on the motivational state of the organism as well as its experiential history. A compelling illustration of the importance of such context is provided by the rat's varied responses to one and the same stimulus, namely, a mild tail-pinch (Antelman & Szechtman, 1975; Antelman *et al.*, 1975). Context modulates the behavioural response to tail-pinch in that the response is influenced by the

sort of stimuli present in the environment, by the rat's physiological and motivational state, and by the animal's experiential history (Szechtman, 1980). For instance, tail-pinch behaviour takes the form of eating when food pellets are available (Antelman & Szechtman, 1975; Levine & Morley, 1981) but turns into gnawing in the presence of wooden blocks (Koob *et al.*, 1976) or maternal behaviour when there are rat pups in the vicinity (Sherman, 1972; Szechtman *et al.*, 1977) or increased bar-pressing for brain stimulation when there exists the opportunity to obtain rewarding brain stimulation (Katz *et al.*, 1980); however, tail-pinch does not induce drinking of water (Antelman *et al.*, 1976; Mufson *et al.*, 1976; Marques *et al.*, 1979) and rarely rearing or grooming (Picone & Hall, 1979; Szechtman & Hall, 1980; Szechtman, 1980), suggesting some specificity to the tail-pinch stimulus. Motivational states also influence the response to tail-pinch. For instance, with both rat pups and food available, nursing mothers choose pups but non-maternal virgin female rats prefer food pellets (Sherman, 1972); similarly, cholecystokinin, a hormone that signals satiety, inhibits tail-pinch-induced eating (Nemeroff *et al.*, 1978). Finally, past experiences modulate the rat's response to tail-pinch; for instance: there is little eating during tail-pinch if the food is unfamiliar (Antelman *et al.*, 1976; Guder & Kornblith, 1979) or had been paired with lithium chloride poisoning (Antelman *et al.*, 1976); similarly, practise (Antelman *et al.*, 1976; Koob *et al.*, 1976) and early housing experience (Sahakian & Robbins, 1977) facilitate the response to tail-pinch and practise of one type of response to tail-pinch favours this response when several alternate options are subsequently available (Szechtman, 1980).

The parallel between tail-pinch and psychostimulant drugs as examples of stimuli modulated by context is particularly striking when one considers that both tail-pinch and amphetamine-like drugs activate the dopamine systems (Brake *et al.*, 2004). Badiani and Robinson (2004) consider that this system may be crucial for mediating the effects of novelty on

sensitization, but they were disappointed by a failure to observe novelty-enhanced dopamine release induced by amphetamine. However, the sensitization effect may not be related to enhanced dopamine release because quinpirole, a direct dopamine receptor agonist which inhibits dopamine release (Imperato *et al.,* 1988; Koeltzow *et al.,* 2003), also produces locomotor sensitization that is similarly modulated by context (Willner *et al.,* 1992; Szechtman *et al.,* 1993; Einat & Szechtman, 1993; Einat *et al.,* 1996; Szumlinski *et al.,* 1997). Such data suggest that the mechanism of sensitization may involve postsynaptic dopamine changes (Koeltzow *et al.,* 2003) rather than simply enhanced neurotransmitter release.

Regardless of the physiological mechanisms, the concept that drugs in the body constitute functional stimuli provides a way to understand why exposure to the same drug may yield different behaviours in different contexts—the meaning of a stimulus is set by the context surrounding the stimulus event and, consequently, different settings may impart different meanings or significance to the drug experience.

Because drugs are generally administered systemically, it is likely that the action of a particular drug in the body does not represent a single functional stimulus but rather a range of stimuli, perhaps even contradictory ones. For instance, the dopamine agonist apomorphine had been shown to possess both rewarding and aversive properties (Wise *et al.,* 1976).

The focus of this commentary thus far has been on the variety of possible behavioural responses to drug action. And yet, there is usually a fair amount of consistency in the drug response across a population of animals studied in a particular environment, as evidenced for instance by the differential locomotor response to amphetamine in novel *versus* home environments (Badiani and Robinson, 2004). This suggests that the external context not only is a

factor in drug action but, also, that it can strongly constrain the selection of possible meanings of the drug experience. Badiani and Robinson (2004) provide an extensive examination of endocrine and neural systems that may be activated differentially in the two environments and contribute to the novelty effect on sensitization to psychostimulant drugs. As seen in their Table 1, there is an extensive neural network that is more active during the acute amphetamine experience in the novel environment compared to the experience at home. Furthermore, some of these differences are exacerbated by chronic exposure to amphetamine in the novel environment. Given the observed differences in neural systems activated, what are the corresponding psychological differences in the drug experience in the two environments? I consider this question next.

DIFFERENT MOTIVATIONAL STATES IN DIFFERENT ENVIRONMENTS

It is reasonable to suppose that the forms of behaviour under amphetamine in the home and novel environments would provide a clue as to the nature of the psychological experience and, perhaps, motivational states under the drug in the two settings. Unfortunately, Badiani and Robinson (2004) did not provide information on the rats' behaviour in the two environments except for higher locomotion in the novel apparatus. Yet, there clearly is a relationship between the dominant behaviour exhibited in a particular environment and the behaviour that gets enhanced by chronic drug treatment. For instance, Willner *et al.* (1992) observed that rats treated chronically with quinpirole showed more locomotor sensitization if they experienced the drug in an environment that favoured locomotion (a movable running wheel) *versus* an environment that did not (a locked running wheel). Similarly, Einat and Szechtman (1993) found that the higher sensitized locomotion for rats treated chronically with quinpirole in a novel *versus* home cage was related to the differential display of locomotion *versus* mouthing in the two environments: rats

administered quinpirole at home showed more mouthing than locomotion during the course of chronic treatment while the opposite was true for the animals injected in the novel apparatus, a finding consistent with the hypothesis that sensitization reflects an enhancement of the behaviour displayed during the onset of drug action (Cools *et al.*, 1977; Willner *et al.*, 1992; Einat & Szechtman, 1993). While it is generally the environmental context that directs the predominating drug response, the response can be influenced pharmacologically as well. For instance, the co-injection of the MAOI inhibitor clorgyline changes the dominant response to acute quinpirole from locomotion to self-directed mouthing, and from this time on, it is mouthing rather than locomotion that sensitizes during the course of chronic treatment with clorgyline plus quinpirole (Culver *et al.*, 2000; Culver & Szechtman, 2004).

But what does the higher locomotion under amphetamine in the novel environment reveal about the possible psychological states there? In and of itself, increased locomotion is not revealing because it can represent enhanced attempts to move away (escape) from the situation, or conversely, it can indicate increased curiosity about the environment and exploration of it, or none of these alternatives and reflect merely an increase in the exercise of running. Based on an extensive literature on the properties of novelty, Badiani and Robinson (2004) examined the possibility that enhanced locomotion may reflect a greater stress response. However, the authors did not find good support for this hypothesis in terms of the expected effects of adrenal hormones on sensitization. Nevertheless, the authors are probably correct in not yet rejecting the stress hypothesis because, as they note, mediators other than adrenal hormones also contribute to the stress response.

The contrast in the neural maps of *c-fos* activation by amphetamine in the novel *versus*

home environments (Table 1 in Badiani and Robinson, 2004) shows greater recruitment of limbic and basal ganglia circuits in the novel environment, a pattern suggestive of more extensive processing of affective information and motor programs. Close coupling of affective and motor programs is a characteristic of motivated behaviour, and there is an intuitive appeal to the idea that a novel environment would bias the organism towards concerns about danger (and thus activation of the security motivation system (Szechtman & Woody, 2004)). Along the same lines, feelings of safety instead should predominate at home. Accordingly, if the amphetamine-like sensory qualities are affective in nature, signalling a feeling of energy (Szechtman *et al.,* 1994) or heightened arousal, for instance, then such a cue is prone to different appraisals in different surroundings: in the context of potential danger, it is likely to add to the sense of threat and distress, but in the context of safety and boredom, a mild increase in arousal may add to the sense of well-being and provide the impetus for activity that is pleasant and positive. Clearly, while speculative, the notion that a single psychomotor stimulant drug may potentiate different motivational states set-up through dissimilar environmental contexts is consistent with the general thesis advanced by Badiani and Robinson (2004) that environmental context modulates the effects of drugs on behaviour and brain function.

CONTEXT OF SENSITIZATION CRUCIAL FOR DIFFERENT ANIMAL MODELS

Sensitization induced by psychostimulant drugs has been proposed as an experimental model for various psychopathologies including schizophrenia, mania, post-traumatic stress disorder, panic disorders, obsessive-compulsive disorder and drug addiction (e.g., Ellinwood, Jr., 1968; Ellison, 1979; Post & Contel, 1981; Angrist, 1983; Antelman, 1988; Post & Weiss, 1988; Robinson & Berridge, 1997; Kalivas *et al.,* 1998; Szechtman *et al.,* 2001; Tizabi *et al.,* 2002;

Szechtman & Eilam, 2004; Badiani & Robinson, 2004). The list seems at first rather daunting because its wide range suggests a possible lack of specificity. However, Badiani and Robinson (2004) counter the non-specificity argument by showing that the neurobiological profile of sensitization to a drug is dependent on the context of drug experience. Hence, specificity for the different disorders is likely to come from the context in which sensitization is induced. As noted above, the context includes not only the physical attributes of the environment but also the experiential history of the organism as well as its motivational and physiological states. In other words, chronic exposure to a psychostimulant drug in one context may potentiate the particular set of neural systems that lead to a particular kind of disorder but in another context, the drug may potentiate another set of neurobiological mechanisms that underlie a different disorder.

In terms of modelling psychiatric disorders, Badiani and Robinson (2004) show that it is inadequate to focus on the mechanisms of "sensitization"—it must be of "sensitization" in a particular context. This leads us to the next challenge: to identify how the animal's history and surroundings can be structured to form the appropriate psychological context in which exposure to a given drug turns this experience into a particular psychopathology. This perhaps would constitute a useful animal model for improving our understanding and treatment of the particular psychiatric disorder.

Acknowledgements

The author's research is supported by the Canadian Institutes of Health Research (MOP-64424) and the Natural Sciences and Engineering Research Council of Canada (544-2001 RGPIN).

REFERENCES

Angrist B (1983). Psychosis induced by central nervous system stimulants and related drugs. In: *Stimulants, neurochemical, behavioral, and clinical perspectives.* Creese I (editor). New York: Raven Press. pp. 1-30.

Antelman SM (1988). Stressor-induced sensitization to subsequent stress: Implications for the development and treatment of clinical disorders. In: *Sensitization in the Nervous System.* Kalivas PW, Barnes CD (editors). Caldwell, NJ: Terford Press. pp. 227-254.

Antelman SM, Rowland NE, Fisher AE (1976). Stimulation bound ingestive behavior: a view from the tail. *Physiol Behav* 17:743-748.

Antelman SM, Szechtman H (1975). Tail pinch induces eating in sated rats which appears to depend on nigrostriatal dopamine. *Science* 189:731-733.

Antelman SM, Szechtman H, Chin P, Fisher AE (1975). Tail pinch-induced eating, gnawing and licking behavior in rats: dependence on the nigrostriatal dopamine system. *Brain Res* 99:219-237.

Badiani A, Robinson TE (2004). Drug induced neurochemical plasticity: the role of environmental context. *Behav Pharmacol* in press.

Brake WG, Zhang TY, Diorio J, Meaney MJ, Gratton A (2004). Influence of early postnatal rearing conditions on mesocorticolimbic dopamine and behavioural responses to psychostimulants and stressors in adult rats. *Eur J Neurosci* 19:1863-1874.

Carlton PL (1983). *A primer of behavioral pharmacology: Concepts and principles in the*

behavioral analysis of drug action. New York: W.H. Freeman.

Cools AR, Broekkamp CL, Van Rossum JM (1977). Subcutaneous injections of apomorphine, stimulus generalization and conditioning: serious pitfalls for the examiner using apomorphine as a tool. *Pharmacol Biochem Behav* 6:705-708.

Culver KE, Rosenfeld JM, Szechtman H (2000). A switch mechanism between locomotion and mouthing implicated in sensitization to quinpirole in rats. *Psychopharmacology (Berl)* 151:202-210.

Culver KE, Szechtman H (2004). Hypophysectomy does not block sensitization to the dopamine agonist quinpirole or its modulation by the MAOI clorgyline. *Horm Behav* 45:23-30.

Ehrlich, P (1908). Partial cell functions. In: *Nobel Lectures, Physiology or Medicine 1901-1921*, Elsevier Publishing Company, Amsterdam, 1967. [Electronic Version] Available at http://www.nobel.se/medicine/laureates/1908/ehrlich-lecture.html

Einat H, Einat D, Allan M, Talangbayan H, Tsafnat T, Szechtman H (1996). Associational and nonassociational mechanisms in locomotor sensitization to the dopamine agonist quinpirole. *Psychopharmacology (Berl)* 127:95-101.

Einat H, Szechtman H (1993). Environmental modulation of both locomotor response and locomotor sensitization to the dopamine agonist quinpirole. *Behav Pharmacol* 4:399-403.

Ellinwood EH, Jr. (1968). Amphetamine psychosis. II. Theoretical implications. *Int J Neuropsychiatry* 4:45-54.

Ellison GD (1979). Animal models of psychopathology: studies in naturalistic colony

environments. In: *Psychopathology in animals: Research and clinical implications.* Keehn JD (editor). New York: Academic Press. pp. 81-101.

Guder LD, Kornblith CL (1979). Tail pinch-induced eating does generalize to a nonpreferred but familiar food. *Physiol Behav* 22:179-183.

Imperato A, Tanda G, Frau R, Di Chiara G (1988). Pharmacological profile of dopamine receptor agonists as studied by brain dialysis in behaving rats. *J Pharmacol Exp Ther* 245:257-264.

Kalivas PW, Pierce RC, Cornish J, Sorg BA (1998). A role for sensitization in craving and relapse in cocaine addiction. *J Psychopharmacol* 12:49-53.

Katz RJ, Roth KA, Schmaltz K (1980). Tail pinch facilitation of self-stimulation in the rat--dependence upon dopamine and independence of opiates. *Pharmacol Biochem Behav* 12:389-391.

Koeltzow TE, Austin JD, Vezina P (2003). Behavioral sensitization to quinpirole is not associated with increased nucleus accumbens dopamine overflow. *Neuropharmacology* 44:102-110.

Koob GF, Fray PJ, Iversen SD (1976). Tail-pinch stimulation: sufficient motivation for learning. *Science* 194:637-639.

Levine AS, Morley JE (1981). Stress-induced eating in rats. *Am J Physiol* 241:R72-6.

Marques DM, Fisher AE, Okrutny MS, Rowland NE (1979). Tail pinch induced fluid ingestion: interactions of taste and deprivation. *Physiol Behav* 22:37-41.

Mufson EJ, Balagura S, Riss W (1976). Tail pinch-induced arousal and stimulus-bound behavior in rats with lateral hypothalamic lesions. Further evaluation of hypothalamic control of feeding and drinking. In: *Brain, Behavior and Evolution.* Riss W (editor). Basel, Switzerland: S. Karger. pp. 154-164.

Nemeroff CB, Osbahr AJ 3d, Bissette G, Jahnke G, Lipton MA, Prange AJ (1978). Cholecystokinin inhibits tail pinch-induced eating in rats. *Science* 200:793-794.

Picone TA, Hall RD (1979). Effects of early malnutrition on tail pinch-induced behavior of the rat. *Physiol Behav* 22:149-155.

Post RM, Contel NR (1981). Cocaine-induced behavioral sensitization: A model for recurrent manic illness. In: *Biological psychiatry 1981.* Amsterdam: Elsevier/North-Holland Biomedical Press. pp. 746-749.

Post RM, Weiss SRB (1988). Sensitization and kindling: Implications for the evolution of psychiatric symptomatology. In: *Sensitization in the Nervous System.* Kalivas PW, Barnes CD (editors). Caldwell, NJ: Terford Press. pp. 257-291.

Robinson TE, Berridge KC (1997). The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Res Rev* 18:247-291.

Sahakian BJ, Robbins TW (1977). Isolation-rearing enhances tail pinch-induced oral behavior in rats. *Physiol Behav* 18:53-58.

Sherman, K. A. (1972) Tail-pinch induced maternal behavior: evidence for the role of internal state in response selection during tail-pinch activation. Unpublished master's thesis,

University of Pittsburgh.

Szechtman H (1980). Redirected oral behavior in rats induced by tail-pinch and electrical stimulation of the tail. *Physiol Behav* 24:57-64.

Szechtman H, Eckert MJ, Tse WS, Boersma JT, Bonura CA, McClelland JZ, Culver KE, Eilam D (2001). Compulsive checking behavior of quinpirole-sensitized rats as an animal model of Obsessive-Compulsive Disorder (OCD): form and control. *BMC Neurosci* 2:4. [Online] Available at http://www.biomedcentral.com/1471-2202/2/4

Szechtman H, Eilam D (2004). Animal models in psychiatry. In: *The Behavior of the Laboratory Rat: A Handbook With Tests.* Whishaw IQ, Kolb B (editors). London: Oxford University Press. pp. in press.

Szechtman H, Hall WG (1980). Ontogeny of oral behavior induced by tail pinch and electrical stimulation of the tail in rats. *Journal of Comparative & Physiological Psychology* 94:436-445.

Szechtman H, Siegel HI, Rosemblatt JS, Komisaruk BR (1977). Tail-pinch facilitates onset of maternal behavior in rats. *Physiol Behav* 19:807-809.

Szechtman H, Talangbayan H, Canaran G, Dai H, Eilam D (1994). Dynamics of behavioral sensitization induced by the dopamine agonist quinpirole and a proposed central energy control mechanism [published erratum appears in Psychopharmacology (Berl) 1994 Sep;116(1):124]. *Psychopharmacology (Berl)* 115:95-104.

Szechtman H, Talangbayan H, Eilam D (1993). Environmental and behavioral components

of sensitization induced by the dopamine agonist quinpirole. *Behav Pharmacol* 4:405-410.

Szechtman H, Woody E (2004). Obsessive-compulsive disorder as a disturbance of security motivation. *Psychol Rev* 111:111-127.

Szumlinski KK, Allan M, Talangbayan H, Tracey A, Szechtman H (1997). Locomotor sensitization to quinpirole: environment-modulated increase in efficacy and context-dependent increase in potency. *Psychopharmacology (Berl)* 134:193-200.

The Official Web Site of The Nobel Foundation 2004. Paul Ehrlich – Biography. Retrieved July 8, 2004 from http://www.nobel.se/medicine/laureates/1908/ehrlich-bio.html/

Tizabi Y, Louis VA, Taylor CT, Waxman D, Culver KE, Szechtman H (2002). Effect of nicotine on quinpirole-induced checking behavior in rats: implications for obsessive-compulsive disorder. *Biol Psychiatry* 51:164-171.

Willner P, Papp M, Cheeta S, Muscat R (1992). Environmental influences on behavioural sensitization to the dopamine agonist quinpirole. *Behav Pharmacol* 3:43-50.

Wilson KG (1993). *The Columbia guide to standard American English*. New York: Columbia University Press.

Wise RA, Yokel RA, Dewit H (1976). Both positive reinforcement and conditioned aversion from amphetamine and from apomorphine in rats. *Science* 191:1273-1275.