BEHAVIORAL AND BRAIN SCIENCES (2011) **34**, 293–347
doi:10.1017/S0140525X11000057

Drugs as instruments: A new framework for non-addictive psychoactive drug use

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Abstract: Most people who are regular consumers of psychoactive drugs are not drug addicts, nor will they ever become addicts. In neurobiological theories, non-addictive drug consumption is acknowledged only as a "necessary" prerequisite for addiction, but not as a stable and widespread behavior in its own right. This target article proposes a new neurobiological framework theory for non-addictive psychoactive drug consumption, introducing the concept of "drug instrumentalization." Psychoactive drugs are consumed for their effects on mental states. Humans are able to learn that mental states can be changed on purpose by drugs, in order to facilitate other, non-drug-related behaviors. We discuss specific "instrumentalization goals" and outline neurobiological mechanisms of how major classes of psychoactive drugs change mental states and serve non-drug-related behaviors. We argue that drug instrumentalization behavior may provide a functional adaptation to modern environments based on a historical selection for learning mechanisms that allow the dynamic modification of consummatory behavior. It is assumed that in order to effectively instrumentalize psychoactive drugs, the establishment of and retrieval from a drug memory is required. Here, we propose a new classification of different drug memory subtypes and discuss how they interact during drug instrumentalization learning and retrieval. Understanding the everyday utility and the learning mechanisms of non-addictive psychotropic drug use may help to prevent abuse and the transition to drug addiction in the future.

Keywords: addiction; drug instrumentalization, drug memory; evolution; mental states

1. Introduction

1.1. Non-addictive drug use

The use of drugs is a widespread phenomenon in many societies of the world, even though there are cultural differences influencing the kinds of drugs used and the ways in which drugs are taken (Heath 2000; Kuntsche et al. 2006). The U.S. National Survey on Drug Use and Health (NSDUH 2007) revealed that approximately 19.9 million Americans (8% of the population) aged 12 or older consumed at least one illicit drug such as marijuana/hashish, cocaine, heroin, hallucinogens, solvents, or prescription-type psychotherapeutics. More than 50% of Americans aged 12 or older reported they were current drinkers of alcohol, and more than 28.6% of Americans aged 12 or older used tobacco products. European surveys revealed that in the general population of the 15-to-64-year-olds, about 324 million people (84%) drank alcohol daily. A recent survey (EMCDDA 2009) estimating illicit drug use by response to a question about "last month's use" determined current cannabis users at 12.5 million people (3.7%) and cocaine users at 2.0 million people (0.5%).

It has been established beyond any doubt that drug addiction is a major psychiatric disorder that causes harm to the individual, to the social environment, and to society (American Psychiatric Association 1994). Much research is devoted to understanding and curing drug addiction. Epidemiological data show, however, that the majority of people who consume psychoactive drugs with an addiction potential are not addicts and will never become addicted (Glynn et al. 1983; O'Malley & Johnston 2002; Zinberg & Jacobson 1976; Zinberg et al. 1978). Of those people who are classified as current alcohol drinkers in the United States, 14.9% are diagnosed as addicts based on the SAMHSA (2005) report. Among the 20.4 million current users (use in the previous month) of illicit drugs in the United States – which include marijuana, cocaine,

 0140-525X/11 $40.00

heroin, hallucinogens, solvents, and prescription-type drugs – 34.3% have been estimated to be addicts (SAMHSA 2005). European Union estimates are similar. In the European Union, about 7.1% of the daily drinkers of alcohol are alcohol dependent (Anderson & Baumberg 2006), whereas about 32% of the current cannabis consumers show a problematic consumption (EMCDDA 2009). In a U.S. National Comorbidity Survey, the cumulative risk until the age of 54 to fulfill criteria for dependence to marijuana is 10%; for cocaine, up to 21% (until age 40); and for alcohol, about 20% (Chen & Anthony 2004; Wagner & Anthony 2002). From surveys of this kind, it is clear that the majority of psychoactive drug users are not and will never be drug addicts (Heyman 1996). Although drug addiction is an undeniable, major burden to society, to a considerable degree, use of psychoactive drugs is unrelated to addiction.

1.2. Psychoactive drug use

In this article, we regard a drug (a single chemical compound with unique structure) as psychoactive when it (a) interacts with the function of the central nervous system (CNS) and (b) changes subjective experience, behavior, or both. Whereas considerable research effort has been made to understand drug addiction and how it develops (Hill & Newlin 2002; West 2006), an adaptive role or beneficial effect for psychoactive drugs is often categorically denied (e.g., Sullivan et al. 2008). Without an account of non-addictive drug use, conceptualizing the transition between non-addictive to addicted drug use is difficult. In this article, we suggest that people use psychoactive drugs not because their reward systems have been "hijacked," but to advance specific behaviors relevant for their own "fitness."

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2. Widening the explanatory scope for drug use

The consumption of psychoactive drugs is usually considered a maladaptation, particularly in people with genetic or environmental risks that make them prone to addiction (e.g., Campbell et al. 2009; Schumann 2007; Schumann et al. 2003; 2008). Many drugs that humans consume are plant toxins, such as nicotine, cocaine, or cannabis, which serve as plant defenses and prevent plant consumption. The widely accepted evolutionary adaptation of these toxins for plants is to deter herbivores (e.g., Nathanson et al. 1993). Why certain plants develop substances that reinforce plant consumption and why any organism should have a mechanism that reinforces the toxin consumption are therefore a puzzle. This apparent evolutionary contradiction has been termed the "paradox of drug reward" (Hagen et al. 2009; Sullivan & Hagen 2002; Sullivan et al. 2008).

Dosage is one aspect of the resolution of this paradox. Drugs like cocaine induce euphoria only at low to medium doses. At higher doses, cocaine induces highly aversive paranoia and behavioral stereotypes (Gawin 1991; Gawin & Kleber 1986; Kramer et al. 1967). Drugs with a low euphoria component, such as nicotine or caffeine, are voluntarily consumed, usually at low, non-toxic doses (Cauli & Morelli 2005). It is important to realize that the doses in which humans and animals voluntarily consume psychoactive drugs are usually below the acute toxic range (Gable 2004; Hagen et al. 2009). As such, the general "paradox of drug reward" may be resolved at the dose-response level: In a low- to medium-dose range, the drug effect is not toxic in the sense of being an immediate threat to life. In the range of medium to low doses, therefore, a role for drugs in functional adaptation can reasonably be considered (Chisholm 1999).

A number of alternative views seek to explain the development and persistence of psychoactive drug consumption. The behavior may, hence, be based on (1) a fitness-irrelevant hijacking of generic motivational systems, (2) a fitness-irrelevant but subjectively perceived improvement in a variety of fitness-relevant motivational states specific to important goals, or (3) an actual improvement in success in these same motivational states.

1. Nesse and Berridge (1997) have argued that those psychoactive drugs that induce positive emotions might provide at the same time a false fitness benefit signal, which in turn "hijacks" incentive salience mechanisms, such as "wanting" and "liking" in the brain. For positive as well as negative emotions, a clear fitness benefit can be identified, in that these emotions can be conceptualized as "specialized states shaped to cope with situations that involve the opportunities or gains and a great number of different kinds of situations that involve threats or losses" (Nesse & Berridge 1997). This evolutionary approach expanded the reinforcement-centered explanations for drug taking by an emotional perspective in that drugs are consumed to change emotions in a broad sense, not

https://doi.org/10.1017/S0140525X11000057 Published online by Cambridge University Press

just for relatively narrow euphoria/hedonia. Although this can be done safely in some circumstances, it might leave the organism with less fitness when the natural function of emotion is constantly circumvented or "hijacked" (Nesse & Berridge 1997; Panksepp et al. 2002).

2. Newlin (2002) suggested that drugs are taken to "inflate" the "self-perceived survival ability and reproduction fitness" (SPFit). SPFit is a concept for the mammalian motivation to enhance and protect survival and reproductive fitness, much related to the feelings of personal power and sexual attractiveness. Indeed, it could be shown that common drugs like alcohol, if taken in moderate amounts, increase the subjective perception of power in humans (Wilsnack 1974). Although it was argued that drugs enhance this subjective feeling, Newlin (2002) denies a potential evolutionary benefit.

3. Some authors have at least raised the possibility of actual short- (Lende & Smith 2002) and long-term beneficial effects of drug use (Hagen et al. 2009). Viewing drug use as an evolutionary adaptation, Lende and Smith (2002) argued that the adaptive function of drug use is to provide an individual with a predictable short-term pleasure in an unsafe environment, where the pursuit of natural reinforcers can only be poorly established. Drug addiction is then seen as a maladaptation based on a missing built-in regulatory function in the salience signaling mesolimbic dopamine (DA) system (Lende & Smith 2002). Lende and colleagues (2007) analyzed the behavioral function of methamphetamine in a population of heavy users in Atlanta, Georgia (United States). They interviewed users for their perceived functions of use and identified three main categories: (1) enhanced function, (2) increased productivity, and (3) functioning normally. This study revealed an important detail: methamphetamine users did not perceive their drug use to impair their daily functioning, but rather to enhance it (Lende et al. 2007).

Several authors have acknowledged the subjectively perceived psychological benefits of drug consumption (Baum-Baicker 1985; Chick 1999; Peele & Brodsky 2000). These subjectively reported and objectively measured benefits are related to a moderate and non-compulsive– that is, non-addictive – consumption of alcohol and comprise fields such as subjective health, mood enhancement, stress reduction, sociability, mental health, long-term cognitive functioning, and work performance (Chick 1999; Molnar et al. 2009; Peele & Brodsky 2000). In addition, there is evidence for beneficial effects of methamphetamine use on everyday function (Lende 2007; Lende et al. 2007).

Overall, several researchers have recognized subjectively reported beneficial effects of certain consumption patterns and have reviewed in much detail the evidence for it. However, a systematic analysis of drug taking as either a functional adaptation or, alternatively, as a beneficial effect of current adaptations is still in its infancy. As such, a general principle for non-addictive psychoactive drug consumption has yet to emerge. The presented functional analysis of non-addictive psychoactive drug consumption suggests that psychoactive drug use does indeed result in an improvement of fitness-relevant behavior. It also suggests that humans are able to subjectively perceive or cognitively reflect – or both – not only the improved outcome of behavior, but also the rather systematic use of the behavior "psychoactive drug consumption."

3. Why do human beings consume psychoactive drugs? A drug instrumentalization framework

We propose that the large majority of non-addicted humans who consume psychoactive drugs as a normal part of their lives, take drugs because the drugs' effects are useful for their personal goals. Psychoactive drugs can be *instrumentalized*. We refer to *drug instrumentalization* as a two-step behavioral process: (1) the seeking and consumption of a psychoactive drug in order to change the present mental state into a previously learned mental state, which then allows for (2) better performance of other, previously established behaviors and better goal achievement.

An *instrument* may be defined as something that helps to achieve a goal that would not be achievable or which would require a higher workload without the use of the instrument. As such, behavior itself can be an elaborate instrument (Frolov & Pavlova 2003; Skinner 1938). A *goal* is referred to here as the outcome of an already established behavior. If a behavioral goal is, for example, to socialize and to maintain a social network, instrumental behaviors would be seeking a place where other people are to be found and starting social interaction with them.

How can a psychoactive drug be considered an "instrument"? The instrument is, in this case, the effect of the drug on the organism's *mental state*. The nervous system of human beings and other vertebrates displays different modes of action, which can be referred to as *mental states* (also termed *internal* or *affective states*). Mental states are the brain's working modes that are held stable over longer periods of time (minutes to hours) during which they provide the functional setting for fast computational processes in the millisecond-to-minutes range. Mental states govern an organism's subjective perception, memory retrieval, and autonomic and behavioral responses (White 1996). It is suggested that the brain's mental states are determined by the different functional states of the modulatory transmitter systems, such as the dopaminergic, serotonergic (5-HT), acetylcholinergic (ACh), noradrenergic (NA), and various neuropeptidergic systems, which control the information processing in diencephalic and telencephalic target regions of the brain (Castren 2005). These systems display different modes of basal activity depending on various external factors, such as time of day, season, or environment, as well as on various internal factors, such as glucose, oxygen, or hormone levels in the blood (e.g., Aston-Jones et al. 1999; Jacobs & Fornal 2010; Sarter & Bruno 1997; Schultz 2000; Steriade et al. 1990). Under different tonic activity modes, environmental stimuli can elicit very different phasic responses. Tonic, as well as stimulation-dependent phasic, responses determine stimulus processing and behavioral responses generated by the brain.

These mental states predispose an organism's responses to the options that its environment offers. These responses, in turn, determine an organism's success in performing previously established instrumental behaviors and, hence, how effectively the organism can reach its goals. As such, an organism's mental state essentially determines if a previously established behavior will be performed to reach a certain goal. Furthermore, if an organism pursues a goal, there is a particular mental state that allows the organism to most effectively perform the behavior with respect to the outcome. For example, if the goal is to get from place

A to B by the behavior "driving a car," an organism can perform this action best in an attentive mental state and less well in a tired and distracted state.

By definition, all psychoactive drugs change an organism's mental state (e.g., Fischman & Schuster 1982; Post et al. 1974). However, this would be a trivial explanation for drug-taking behavior and does not acknowledge the full extent of the *behavioral complex* involved in non-addictive drug consumption. Here, we argue that the *set* of the organism, the surrounding *settings*, and the *subsequent behaviors* that follow the change in mental state are pivotal (Zinberg 1984) for a full appreciation of drug seeking and consumption, and the resulting mental state change. On the one hand, drug consumption arises in a particular environment and in particular mental states. Drug-unrelated behaviors are performed, however, when the drug is on board and the drug-induced change in mental state is in full swing. These behaviors can be viewed as drug-independent, in that they were established independently from drug use and could be performed without anteceding drug use and mental state change. For example, most adults can drive a car from A to B undrugged. After a long working day, however, having a last coffee and a subsequently "refreshed" and attentive mind may enable the driver to better drive home. In this example, the effects of caffeine on the mental state are the instrument. The *A process* of psychoactive drug instrumentalization would be the "coffee preparing and drinking," whereas the *B process* would be "driving the car." The individual instrumentalization goal would be "driving home," which might belong to the goal class of "improving cognitive performance and counteracting fatigue." A superior goal achievement would outweigh the additional effort of seeking and consuming a psychoactive drug before performing the behavior, for example, an instrumental behavior (Heyman 1996).

4. Psychoactive drug use from an evolutionary perspective

In an evolutionary approach to non-addictive psychoactive drug consumption, we discuss the evidence for "drug instrumentalization" at four different levels of behavioral analysis: (1) its evolutionary history, (2) in its adaptive function for reproduction and survival, (3) the proximate causation of the behavior, and (4) the ontogeny of the behavior – that is, its development in the life history of a single individual (Hill & Newlin 2002; Nesse 2002; Tinbergen 1963). A distinct behavior, to be acknowledged as a true adaptation, needs to solve an adaptational problem that would not be solved by chance without specific selection pressure (Miller 2000). Is there any adaptational problem to which drug consumption could reasonably offer a solution? We suggest that the adaptational problem is the occurrence of multiple distinct microenvironments for single individuals who must make fast transitions among those microenvironments (Bronfenbrenner 1994).

Microadaptations as specific adaptations to each microenvironment may be supported best by behaviors that are under opposing selection pressures (Cosmides & Tooby 1994; Crawford 2000). Static behavioral traits that are constant over a developmental period, or even over the whole life span, may appear as less advantageous than a mechanism that allows flexibly adjusting behavioral traits according to each microenvironment (Cosmides & Tooby 1994; Tooby & Cosmides 1992). An example for this may be "social disinhibition" as a behavioral trait in humans. Although certainly appropriate and rewarded in a close social setting, it is inappropriate and even punished in a professional work environment. An adaptation to flexibly shift between enhanced and suppressed "social disinhibition" when changing microenvironments may provide an optimal net adaptation.

4.1. The ultimate cause of psychoactive drug use

Evolutionary psychologists suggest that many of our current behaviors can be viewed as adaptations to our ancestral environment. Furthermore, these historical adaptations should have solved a problem ultimately enhancing lifetime reproduction of self or kin (Cosmides & Tooby 1994; 1999). The consumption of psychoactive plants has occurred for at least 10,000 years, according to oldest human records (Abel 1980; Dudley 2002; Heath 2000; Seefelder 1996; Streatfeild 2001). One origin of psychoactive drug instrumentalization may be found in the selective acquisition and preparation of food. The selective consumption of psychoactive compounds may be based on selective food seeking and consumption behavior and its flexible modification by psychological learning processes (Dudley 2000; Lozano 1998). Seeking and consumption of a particular type of food can be very specific depending on nutritional needs. Phylogenetically old learning mechanisms associate sensory parameters such as taste and visual cues of foods with their ingredients and physiological effects. The lack of a particular nutrient can trigger a focused search and consummatory behavior for a particular type of food. Based on whether the consumption maintained or failed to maintain homeostasis, this particular food will either be searched out and consumed in the future or avoided (Johnson et al. 1975, Lozano 1998; Rozin & Kalat 1971).

Ethological research in chimpanzees has shown that the choice of food may be guided not only by the nutrient content, but also by non-nutritional properties of plant compounds, in particular secondary plant metabolites (Robles et al. 1995). Wild chimpanzees selectively consume plants to self-medicate for infections, gastrointestinal problems, and other physically stressful conditions (Glander 1994; Page et al. 1992; Rodriguez et al. 1985; Wrangham & Nishida 1983), referred to as "'zoopharmacognosis" (Huffman 2003; Rodriguez & Wrangham 1993). Zoopharmacognosis appears to be learned as much as food preference or avoidance (Lozano 1998). Depending on the physical state of the body, self-medication can be a conditional behavior in mammals – that is, consuming a particular food only when stressed, but less in recovery (Lisonbee et al. 2009; Villalba et al. 2010). Consummatory choices are made either as a prophylactic/preventive self-medication, which reduces the risk of physical distress, or as therapeutic/curative self-medication, which may reduce the physical stress once it occurred (Kester & Barbosa 1994; Hagen et al. 2009; Singer et al. 2009; Sullivan et al. 2008). The ability to dynamically adapt food choice according to the organism's physical state based on a learning mechanism may hence be a basic adaptive trait in mammals, enhancing survival

and reproduction (Clayton & Wolfe 1993; Hagen et al. 2009; Sullivan et al. 2008). We speculate that those learning systems, which can dynamically adapt individual food choice for nutritional needs and self-medication, are the same as those involved in choosing food to change mental state.

We also suggest that two major changes between our ancestral environment and modern environments have taken place, and these changes are crucial for understanding current drug-taking behavior (Lende 2007):

1. Only recently, with the isolation and purification of natural compounds and with the advent of synthetic chemistry, psychoactive drugs became available in pure (e.g., cocaine, amphetamine) or highly concentrated form (e.g., alcohol). For other drugs, selective breeding of the crops increased their drug content significantly (e.g., Δ9-THC in cannabis plants). Recently available purified psychoactive substances may represent a new "niche" we have constructed; and this niche has the potential to modify the future basis of natural selection (Laland et al. 2000; 2010). Psychoactive drug consumption is now considered a polygenetically determined behavior (Stacey et al. 2009) influenced by environment and culture (Blomeyer et al. 2008; Clarke & Schumann 2009; Laland et al. 2010). The availability of purified psychoactive substances is now part of the environment in many societies (Lende 2007), which may then interact with a genetically determined predisposition for drug use and drug addiction (Bierut et al. 1998; Kendler et al. 2003a; 2003b; Schumann 2007).

Psychoactive drug seeking and consumption can be observed in fruit flies (Devineni & Heberlein 2009), rodents (Arroyo et al. 1998; Witkin et al. 1999; Yokel & Pickens 1973), dogs (Risner & Jones 1980), and monkeys (Fantegrossi et al. 2004; Howell & Byrd 1995; Johanson et al. 1976; Ritz & Kuhar 1989) when given access to a drug. Although the availability of purified psychoactive drugs is a new environmental feature (Nesse 2002), the behavioral capacity to consume drugs – the learning mechanisms – developed much earlier in evolution.

2. In industrialized societies, an individual's workload is so high that a person may need to perform many different behaviors with contrasting types of effort. It is speculative whether single behaviors need to be performed with more effort now than in the past when considering available resources (there are more tools now) and relative outcomes (tool-supported behaviors are usually more effective). One may, nevertheless, reasonably guess that the modern environment contains more and stronger differentiated microenvironments. This may become evident, for example, by the availability of technical tools that can now be very specific for a microenvironment and yet require a high degree of training and effort in their use (e.g., a computer for work or a bicycle for spare time). We can also guess that transitions between these settings occur at a much faster rate than they did for our pre-agricultural ancestors. This may put a selection pressure not only on single behaviors, but even more on behavioral flexibility – that is, the transition from one behavior to another.

We suggest that non-addictive psychoactive drug instrumentalization helps to solve an adaptational problem, employing species-general learning mechanisms that dynamically adapt the search for and consumption of plants and plant compounds. In a modern environment, however, the problem changed together with the emergence of supportive "'instruments." As for many functional adaptations (Cosmides & Tooby 1999; Wakefield 1999), psychoactive drug use behavior may, under these relatively recently occurring environmental changes, have led a minority of individuals to evolutionary dysfunctional behaviors, one of which is drug addiction (American Psychiatric Association 1994).

4.2. Proximate mechanisms of psychoactive drug use

A consideration of the evolution of psychoactive drug consumption suggests a number of different proximate mechanisms that provide unique adaptations to particular microenvironments (Lende 2007). An organism's environment can therefore be considered the sum of its microenvironments (Bronfenbrenner 1994), in which distinct behavioral flexibility is the best adaptation. Each of these behaviors may be seen as a microadaptation. In fast-changing microenvironments, short transition times between mental states may be advantageous because they allow behavioral flexibility. We suggest the proximate adaptive problem that may be solved by psychoactive drug use is (a) to facilitate the transition between different mental states and (b) to enhance the magnitude or duration – or both – of an ongoing mental state.

This generally stated hypothesis can be quickly made empirical by asking non-addicts why and under which circumstances they consume psychoactive drugs. Epidemiological data indicate that people give a wide range of different answers on the question why they consume psychoactive drugs (e.g., Brown 1985; Brown et al. 1980; Cooper et al. 1995; Maloff et al. 1981). Baum-Baicker (1985) has summarized five areas of benefit for alcohol consumption: (1) stress reduction, (2) mood enhancement, (3) cognitive performance, (4) reduced clinical symptoms of depression, and (5) improved function in the elderly. Reviews of the growing experimental evidence by Chick (1999), Heath (2000), and Peele and Brodsky (2000) and a functional analysis of methamphetamine use by Lende et al. (2007) confirmed these earlier observations. Of course, not all motivations for consumption are consciously accessible and reportable (Davies 1997; O'Brien et al. 1998; Skog 2000). Overall, these themes of drug consumption may ultimately serve efforts directed to reproduction or efforts directed toward one's own survival. Therefore, psychoactive drug use should, like any important human behavior, be considered with regard to these two life themes raised by behavioral ecologists when considering the continuous trade-off between allocations of finite human resources (Hill & Chow 2002).

In the following paragraphs, we describe different proximal mechanisms of psychoactive drug use in terms of unique instrumentalization goals. Their general functions for reproduction or survival and maintenance (or both) are discussed. To substantiate these views, we suggest plausible neuropharmacological mechanisms for improved functioning.

4.2.1. Improved social interaction. The establishment and maintenance of social groups and networks is essential for many species (Axelrod & Hamilton 1981; Hamilton 1964). For obligatorily social animals, including humans, social interaction becomes an incentive by itself (e.g.,

Matthews et al. 2005; Panksepp & Lahvis 2007). In modern societies, most adults spend a great deal of their time in training- or work-related microenvironments. A large body of explicit and implicit rules governs interactions between people in these microenvironments. Although social encounters are manifold, private social interactions are systematically suppressed in order to enhance work performance. Professional interactions require a high degree of attention and cognitive effort, as well as a suppression of overt emotional responses. These microenvironments appear to make the establishment of social bonds deliberately difficult. The formation of social bonds is rather facilitated by a state of emotional openness and accessibility and some display of private individuality. Transitory periods between professional and private microenvironments, such as after-school or after-work gatherings or activities, are where peer groups and social networks are formed and maintained.

Interestingly, a number of drugs change mental states in a way that appears to facilitate the transition from a professional to a private behavioral repertoire. It is important to note that it is not the pharmacological effect of the drug alone that enhances social behavior; rather, it is the interaction with the social environment. In a drug-free state, social settings alone induce social behavior, but perhaps less effectively and more briefly.

Psychoactive drugs that can facilitate social behavior under various circumstances are alcohol (Bradizza et al. 1999; Glynn et al. 1983; Kuntsche et al. 2005), marijuana (Bonn-Miller et al. 2007; Zvolensky et al. 2007), cocaine (Lende 2005; O'Malley et al. 1985), and other psychostimulants (Davey et al. 2007; O'Malley et al. 1985), when used in a low- to medium-dose range (Boys & Marsden 2003; Boys et al. 1999; 2001; Cato 1992; Segal 1985; Simons et al. 2000). Also, some effects of nicotine and caffeine may be useful to maintain social interactions (Cauli & Morelli 2005; Eissenberg & Balster 2000).

Alcohol reduces social inhibition, discomfort in social situations, and social anxiety; increases talkativeness; and increases the tendency to talk about private affairs (Baum-Baicker 1985; Booth & Hasking 2009; Carrigan et al. 2008; Peele & Brodsky 2000). These "beneficial effects" are brought about by the multiple pharmacological targets of alcohol in the brain (Harris et al. 2008; McBride et al. 2002; Spanagel 2009; Tupala & Tiihonen 2004). Most important for these effects is probably the interaction of alcohol with $GABA_A$-receptors in the brain. γ-Aminobutyric acid (GABA) is the most abundant inhibitory transmitter in the brain (Feldman et al. 1997). Alcohol at low to medium doses enhances GABAergic activity, leading to reduced anxiety levels and a behavioral disinhibition. An indirect neurochemical effect of alcohol is to increase dopamine (DA) levels in the nucleus accumbens (NAc; Di Chiara & Imperato 1988). This neurochemical effect was shown to reduce the brain's reward threshold (Koob et al. 1998) and, thus, may enhance the incentive value of social interaction (Ikemoto & Panksepp 1999). No claim is made here that each and every effect of alcohol on the nervous system is beneficial for social interaction. For example, alcohol affects pharmacological targets in subcortical brain regions, shown to be involved in social bonding or social recognition (Ross & Young 2009). Social cognition, in contrast, involves also cortical networks, including the medial prefrontal cortex and anterior cingulate cortex (Burnett et al. 2010). Although the disinhibitory effects of alcohol mediated at subcortical level may facilitate social behavior, alcohol effects at the cortical level may at the same time have no effect or even impair social cognition (Uekermann & Daum 2008). We suggest that it is the sum of alcohol effects on social behavior that requires investigation.

Psychostimulant drugs, such as cocaine, amphetamine, methylphenidate, methamphetamine, and methylenedioxymethamphetamine (ecstasy, MDMA), are also used in a social context with enhanced self-exposure, such as at parties or in club settings (Britt & McCance-Katz 2005; White et al. 2006). In addition to being more generally aroused and having increased attention, people become more talkative, disinhibited, and self-confident after consuming these drugs. In addition, psychostimulants suppress fatigue, which also enables prolonged social interaction (Fischman & Schuster 1980). An increase in aggression after psychostimulant consumption (Emley & Hutchinson 1983) may result in dominating social gatherings and the "competition" for partners, further enhancing the beneficial effects for the individual (King et al. 2009). Psychostimulant drugs increase extracellular activity of DA, 5-HT, and noradrenaline (NA) in the CNS by their interaction with the monoamine transporters (Ritz & Kuhar 1989; Ritz et al. 1990). They block or reverse monoamine transport (Green et al. 2003; Johanson & Fischman 1989; Müller et al. 2007a; Pum et al. 2007; Seiden et al. 1993). Although high NA levels may account for the suppression of fatigue (Aston-Jones et al. 1999), 5-HT may mediate the anxiolytic (Ho et al. 2004; Müller et al. 2008; Schwarting et al. 1998) and aggression-enhancing effects of these drugs (Licata et al. 1993; Quadros et al. 2010).

Also, various dissociative anesthetic drugs, such as phencyclidine (PCP), ketamine, and γ-hydroxybutyrate (GHB), can at low doses stimulate social interactions. They can induce a feeling of empathy, reduce anxiety, and increase relaxation. At the same dose range, they are locomotor stimulants. These drugs are noncompetitive glutamate *N*-methyl-D-aspartate (NMDA)-receptor antagonists (Jentsch & Roth 1999). Glutamate is the most abundant excitatory transmitter in the brain (Feldman et al. 1997). Blocking NMDA receptors is considered the predominant mechanism for the observed behavioral effects (Britt & McCance-Katz 2005; Weir 2000; Wolff & Winstock 2006).

A number of psychoactive drugs can be used to change an individual's mental state in ways to facilitate social interactions. A state in which conditioned and unconditioned anxiety and behavioral suppression are attenuated can be achieved by enhancing GABAergic inhibition and reducing glutamatergic excitation. Alternatively, a state in which the energization of social interaction is required can be achieved by enhancing monoaminergic modulatory transmission. Exaggerated drug use for this instrumentalization goal, however, may result in more pronounced euphoria or high effects, which may facilitate the transition to habitual drug use and addiction (e.g., Chen & Anthony 2004; Wagner & Anthony 2002). An acute overdose reverses the sought effects and may even result in a schizophrenia-like psychotic state for psychostimulants or hallucinations and delirium for alcohol (e.g., Rich & Singer 1991; Siegel 1978).

4.2.2. Facilitated sexual behavior. Closely related to an instrumentalization of psychotropic drug effects for social interaction is their use to facilitate the possibility of sexual behavior (Cooper 2006; Patrick & Maggs 2009; Taylor et al. 1999). Sexual behavior may still be considered the sine qua non of natural selection. However, many of the same rules that control social interactions in society also restrict occasions for sexual behavior. A "scheduled" and time-dependent (e.g., Saturday night; Patrick & Maggs 2009) transition from professional to private microenvironments may therefore significantly enhance the chances of finding a partner or allow already formed couples to escape daily routines. It may, therefore, not be a surprise that drugs that can be instrumentalized to improve social interactions also serve well for sexual behavior.

An important variable determining reproductive success and social behavior in humans is personality (Alvergne et al. 2010). Certain personality traits, such as introversion, may be disadvantageous in some settings but advantageous in others. Because it is argued that psychoactive drugs change mental states, one might view drug instrumentalization also as a self-induced, time-restricted personality change. For example, extroversion may change the likelihood of sexual behavior. The ability of a controlled personality trait change in a certain context may, therefore, help to improve sexual behaviors by overcoming the disadvantages of certain personality traits (e.g., Booth & Hasking 2009).

In support of popular belief, there is strong evidence for an association among alcohol drinking, drunkenness, and the likelihood for sexual intercourse, in particular in adolescents and young adults (e.g., Lavikainen et al. 2009; Patrick & Maggs 2009; Sen 2002; Wells et al. 2010). In addition to the pharmacological effects of alcohol, the expected (conditioned) disinhibitory effects mediate the higher chances of sexual intercourse (Cooper 2006; Crowe & George 1989; Patrick & Maggs 2009) and may predict future alcohol use (Mooney 1995). Cooper (2006) suggested that those expectations may even be "instrumental in setting up situations that may lead to alcohol-related disinhibition of sex." Behavioral disinhibition may also result from diminished cognitive abilities and a narrowed range of perception focusing in a "myopic" way on highly salient stimuli that can drive sexual arousal (Steele & Josephs 1990). We do not know if situational alcohol consumption in any way improves contemporary "reproductive success," but this would be an interesting opportunity to distinguish perceived from actual success in the realm of sexual interaction.

As before, psychostimulant drugs may have mixed effects, serving to improve chances for sexual behavior, but may later interfere with physical performance during sexual intercourse in males (Maier 1926; Waldorf et al. 1991). In particular, the elevated DA levels in the mesolimbic system may contribute to a mental state that makes the individual respond more effectively to sexual cues, making a potential partner appear more "attractive" (Ikemoto & Panksepp 1999; Koob et al. 1998).

One often reported function of drug use is to "enhance sex." Drugs frequently reported to be used for this purpose are alcohol, cannabis, amphetamines, ecstasy, and cocaine (Boys & Marsden 2003; Boys et al. 1999; 2001; Maier 1926). Although mating behavior can be conceptualized as a flexible approach behavior, sexual intercourse, in contrast, is a consummatory behavior, which is controlled by other neuronal mechanisms (Ikemoto & Panksepp 1999). The verbal reports on enhanced pleasure taken from sexual intercourse after psychoactive drug consumption may, therefore, be based on mechanisms that enhance incentive salience.

Altogether, psychoactive drugs facilitate sexual behavior, even enhancing pleasure during sexual intercourse. The mental state they induce is for several drug classes similar to that serving social interaction. Hence, it may be assumed that neuronal mechanisms of this drug instrumentalization are largely overlapping with those facilitating social behavior.

4.2.3. Improved cognitive performance and counteracting fatigue. Highly developed societies put a high cognitive demand on individuals in education and work microenvironments (Arria & Wish 2006). Long working hours lead to fatigue and to decline in cognitive performance. Having the means to "artificially" prolong full cognitive capacity may consequently appear to be beneficial for the individual by increasing external resources for reproduction of self or kin (e.g., money). Although little is known about whether any drug can actually increase cognitive performance in a healthy person with full mental capacity, there is considerable evidence suggesting that mild impairments resulting from exhaustion, fatigue, or mood swings can be compensated with psychoactive drugs (Boys & Marsden 2003; Lende et al. 2007). In this case, no new mental state is desirable, only maintenance of a baseline state over prolonged cognitive effort. Many psychoactive drugs, both legal and illicit in Western societies, improve cognitive performance in this case.

Caffeine, a major psychoactive ingredient of coffee, tea, chocolate, and soft drinks, is a legal drug frequently used to keep people awake. During waking periods, the brain levels of the neurotransmitter adenosine steadily increase and trigger fatigue and sleepiness (Hong et al. 2005; Huston et al. 1996; Porkka-Heiskanen et al. 1997). As an antagonist at the adenosine A_1 and A_{2A} receptors, caffeine effectively blocks adenosine action in the brain (Cauli & Morelli 2005). It is thought this action of caffeine is responsible for preventing fatigue and reducing the decline in cognitive performance after prolonged activity.

Another widely used legal drug is nicotine, the active compound in tobacco (Le Foll & Goldberg 2006). Nicotine is an agonist at the nicotinic ACh-receptor (Markou 2008). Nicotinic ACh-receptors in the brain are essentially involved in mediating the action of the neurotransmitter ACh to promote attention and to facilitate learning and memory (Blokland 1995; Sarter et al. 2005). Nicotine improves attention (Hahn et al. 2002; Hahn & Stolerman 2002) and cognitive performance in animals (Decker et al. 1995) and in nonsmoking humans (Rezvani & Levin 2001). In human smokers, there is a decline in cognitive abilities after smoking cessation that can be reversed by nicotine administration (Mansvelder et al. 2006). Nicotine was also found to ameliorate cognitive deficits in patients with Alzheimer's disease. It can reduce the cognitive deficits induced by neuroleptic drug treatment in schizophrenic patients (Rezvani & Levin 2001). The stimulation of nicotinic ACh-receptors by nicotine increases not only ACh, but also NA activity (Mitchell 1993; Wonnacott 1997), which might contribute

to the attention promoting effects of nicotine. Nicotinic ACh-receptors also modulate the activity of the mesolimbic DA system (Markou 2008; McBride et al. 1999; Wonnacott 1997), which could be one mechanism for how nicotine might increase the reinforcing value of non-drug reinforcers (Harrison et al. 2002; Kenny & Markou 2006) and hence support goal-directed behavior.

Psychostimulant drugs have been widely used to increase cognitive performance over long periods of time, in particular to maintain arousal and attention. Truck drivers in the United States and Australia use amphetamine and other psychostimulants to stay attentive during long driving hours (Davey et al. 2007; Grinspoon & Hedblom 2005). Students use prescription stimulants, such as methylphenidate, demethylphenidate, amphetamine, and methamphetamine, non-medically to promote concentration, to stay awake, to increase alertness, and to help with studying (Arria & Wish 2006; Lende et al. 2007; McCabe et al. 2005; Sussman et al. 2006; Teter et al. 2010; White et al. 2006). Psychostimulants were shown to effectively increase arousal and attention in humans for long periods of time at doses that induce only a minor and short-lasting "high" and no signs of dysphoria thereafter (Higgins et al. 1990; Stillman et al. 1993). In line with increased attention, improved learning and memory was shown after small doses of cocaine in occasional users (Higgins et al. 1990). Attention deficits induced by sleep-deprivation can be ameliorated by a low to medium dose of cocaine (Fischman & Schuster 1980). Phasic and tonic NA activity in the brain is well known to control cognitive performance in tasks with a high attention load and potential distraction (Usher et al. 1999). Cocaine and amphetamines interact with NA transporters in the brain and effectively block NA reuptake at the synapse (Ritz & Kuhar 1989; Ritz et al. 1990). This increases extracellular NA levels and causes a hyperactivation of NA receptors (Green et al. 2003; Johanson & Fischman 1989; Seiden et al. 1993), which may account for beneficial effects of small doses of psychostimulants on cognition.

Good evidence supports the view that several psychoactive drugs are instrumentalized to enhance cognitive performance by counteracting exhaustion and fatigue. Although little enhancement can be achieved in healthy and "fresh" individuals, the decline in function during fatigue, or in several mental disorders, can be effectively overcome, if temporarily, by these drugs. Likely mechanisms of action are the blockade of adenosine A_1 and A_{2A} receptors, activation of nicotinic ACh-receptors, or the enhancement of NA activity in the brain. Exaggerated use of these drugs may acutely result in hyperarousal, restlessness, and a decline in cognitive abilities (e.g., Quednow et al. 2006; 2007). Long-term regular use of these drugs can induce tolerance for the cognitive effects and might lead to an escalation of consumption and to drug addiction.

4.2.4. Facilitated recovery from and coping with psychological stress. Modern societies not only request constant high cognitive and physical performance, but they also allow decreasingly little time for the individual to recover from periods of intense or high work load (Anders 1956). This leaves the individual with the pressure of finding a fast recovery and an effective way to cope with the related psychological stress. The goal is then to change the mental state from "tired and stressed" to "fresh and relaxed" in a short period of time. Ideally, after recovery, resources are replenished and stress is under control. Using drugs to accelerate recovery and to enhance coping with stress in a "spare but limited time" microenvironment may, therefore, increase the success of many behaviors in other microenvironments (Amendt 2003; Baum-Baicker 1985; Peele & Brodsky 2000; Segal 1985).

A number of pharmacologically different drugs are instrumentalized to facilitate recovery from and coping with psychological stress. Humans as well as animals self-administer alcohol (Cooper et al. 1988; 1992; Kuntsche et al. 2005), cannabis (Bonn-Miller et al. 2007; Zvolensky et al. 2007), cocaine (Lende 2005; Waldorf et al. 1991), methamphetamine (Lende et al. 2007), barbiturates, benzodiazepines, and other sedative anxiolytic drugs (Boyd et al. 2009) to cope with stress (Boys & Marsden 2003; Boys et al. 1999; 2001; Bradizza et al. 1999; De las Cuevas et al. 2003; Griffiths et al. 1991; Heberlein et al. 2009; Lader 1994; Perkins 1999; Segal 1985). In the last decade, evidence for a survival promoting effect of moderate alcohol consumption in humans accumulated. Moderate alcohol consumption, which can be maintained with a high degree of stability, was associated with better health, more close friendships, and more family support than was total abstinence (Mondaini et al. 2009; Peele & Brodsky 2000; Rodgers et al. 2000;Skogen et al. 2009; Taylor et al. 2005; but see also: Sareen et al. 2004). Moderate drinkers were also found to face less depression than abstainers in the presence of stress (Lipton 1994). Chronic moderate, but not high, alcohol consumption can reduce the risk of somatic diagnoses, as well as mental disorders such as anxiety and depression (Peele & Brodsky 2000; Skogen et al. 2009).

Alcohol inhibits excitatory glutamatergic transmission and enhances inhibitory GABAergic activity at the $GABA_A$-receptor (Spanagel 2009). Barbiturates and benzodiazepines also modulate the $GABA_A$-receptor (Ito et al. 1996), though at other binding sites than alcohol, and allosterically enhance responses to the inhibitory transmitter GABA (Allison & Pratt 2003). Enhanced GABAergic activity is believed to reduce anxiety and the impact of conditioned aversive stimuli. This is one way in which these drugs may attenuate the processing of stress-related stimuli at a subconscious level. For conscious processing of stress-related stimuli, neocortical circuits, which also contain a high number of $GABA_A$-receptors, are more likely to be involved (Feldman et al. 1997). By their interaction with neocortical $GABA_A$-receptors, sedative drugs can dampen cognitive activity and memory of aversive events (Curran 1991).

The most widespread illicit psychoactive drug instrumentalized to ameliorate pressure and to reduce stress is cannabis (Boys et al. 1999; 2001). The main psychoactive compound of cannabis is Δ9-tetrahydrocannabinol (THC; Iversen 2000). THC is an exogenous ligand at the brain's cannabinoid 1 (CB1)-receptors, which among others control the emotional impact of external stimuli and thoughts (Mechoulam et al. 1998). CB1-receptor activation was shown to control the extinction of aversive memories (Marsicano et al. 2002), which might contribute to the stress ameliorating effects of THC.

Interestingly, social stress was also found to increase the self-administration of nonsedating drugs, such as cocaine

in animals and humans. The drug-induced increase in arousal (Haney et al. 1995) might involve another coping mechanism that resembles more a "fight" than a "flight" response. Psychostimulant drugs increase aggression levels and physical strength and can suppress fatigue (Green et al. 2003; Johanson & Fischman 1989; Seiden et al. 1993), which are useful effects for an active stress coping mechanism. However, animal studies showed that an increase in cocaine self-administration in order to cope with social stress was only observed in animals with low spontaneous activity (Kabbaj et al. 2001). Several findings suggest that the ways in which psychoactive drugs are instrumentalized for coping with stress may largely depend on the individual's personality traits and coping strategies.

A number of different classes of drugs can be used to facilitate recovery from and coping with stress. They can be consumed to self-induce a mental state in which conditioned and unconditioned anxiety and mental preoccupation with them are attenuated. This is predominantly achieved by enhancing GABAergic inhibitory activity or by activating cannabinoid receptors. However, an acute overdose of sedating drugs may have fatal effects (Charlson et al. 2009). For some individuals, an aroused and attentive state of mind might serve to actively cope with stress, when behavioral action is required. This is served by enhanced monoaminergic activation. Chronic exaggerated drug use for this instrumentalization goal may result in restlessness, a hyperanxious state during withdrawal, and compulsive drug use to overcome this state.

4.2.5. Self-medication for mental problems. Psychiatric or mental disorders are characterized by the prolonged persistence of a mental state that is perceived as aversive (American Psychiatric Association 1994). They can be considered as a temporary, recurrent, or continuous breakdown of the homeostatic mechanisms in the neuronal systems that determine mental states. Behavioral functions and reproduction rates are significantly impaired in these disorders (Uher 2009).

Certain psychiatric disorders seem to correlate with an increased consumption of psychoactive drugs with a particular neurochemical profile. Although psychoactive drugs do not persistently restore homeostasis in psychiatric patients, they may cause a temporary change to a less aversive mental state. In that, they may provide at least a temporary relief from suffering and an enhanced "functioning" in everyday life (e.g., Lende et al. 2007). The self-medication might improve the adaptation to the adverse condition (Nesse & Berridge 1997). This might also apply to mental states that are perceived as aversive (e.g., being in a depressed mood), but do not fulfill the diagnostic criteria of a psychiatric disease (Boys & Marsden 2003; Boys et al. 1999; 2001).

It is well known that people suffering from negative affect use psychoactive drugs to self-medicate and regain some sense of control over their mental state (Boys et al. 1999; 2001; Glynn et al. 1983; Khantzian 1985; 1997; Markou et al. 1998; Sher et al. 2005). Considerable evidence supports the view that alcohol is consumed to provide relief from negative affect (Peele & Brodsky 2000), although it is still unclear whether this is a causal or associative relationship (Room 2000). The effectiveness of alcohol depends on several factors such as genetic predisposition, expectancies, and environmental factors (Sher et al. 2005).

Increased consumption of nicotine and cannabis has been demonstrated in schizophrenic individuals (Hughes et al. 1986). It is believed that these drugs may exacerbate positive symptoms such as hallucinations (Perry & Perry 1995). However, the aversive negative symptoms, such as the flattening of affect, and possibly cognitive impairments, might improve with cannabis (Potvin et al. 2003). Nicotine might improve cognitive deficits in schizophrenic individuals with prescribed neuroleptics (Rezvani & Levin 2001). At present, it can only be speculated that the nicotinic ACh-receptor activation, which enhances cognitive performance under certain circumstances in healthy subjects, might also account for the benefits in cognitively impaired schizophrenics.

THC was shown to alleviate anxious states and to reduce pain in chronic neurological disorders such as multiple sclerosis (Williamson & Evans 2000). There is a high rate of substance abuse in patients suffering from posttraumatic stress disorder (PTSD) to self-medicate the PTSD symptoms (Jacobsen et al. 2001). Benzodiazepines are used to self-medicate other forms of anxiety disorders and sleep-disturbances off prescription (Heberlein et al. 2009). Opiate drugs were reported to be used by people who suffer from physical pain (Boyd et al. 2006; McCabe et al. 2007b; Zacny & Lichtor 2008). People with tendencies for rage and strong violence reported opiate use because they felt that the drug effects help to control the outbursts (Khantzian 1985; 1997).

This instrumentalization goal might also explain why non–clinically diagnosed people use psychostimulant drugs to deal with the distress caused by their depression, dysphoria, hypomania, hyperactivity, and attention-deficit problems (Khantzian 1985; 1997; Lende et al. 2007; Teter et al. 2010). It was suggested that some biomarkers of depression resemble those of drug withdrawal, such as a chronic down-regulation in the activity of the DA- and 5-HT-systems (Maisonneuve et al. 1995; Wyatt et al. 1988). Drug use could possibly restore homeostasis and ameliorate depressive symptoms (Markou et al. 1998). Nevertheless, attempted self-medication may increase the risk of disease progression in the long run (McLellan et al. 1979; Weiss et al. 1986).

Sullivan and Hagen (2002) suggested that at least part of the motivation to use psychoactive drugs for self-medication might be a neurotransmitter deficit in the brain, leading to psychiatric diseases. Indeed, a reduction in DA- and 5-HT transmission can dramatically reduce behavioral activity and incentive motivation (Carey et al. 2004; 2008). Several psychoactive plant compounds resemble structural motifs of those key neurotransmitters that are known to be involved in psychiatric diseases. Sullivan and Hagen (2002) argued that the drug might compensate for the deficit. This might be true for some drugs. For example, people suffering from depression use cocaine as a preferred drug to ameliorate a negative affective state (Khantzian 1985; 1997). Depression is associated with disturbed 5-HT activity (Carr & Lucki 2010). Acute administration of cocaine, as well as synthetic antidepressant drugs, increases 5-HT levels (Müller et al. 2004; 2007a; 2007b). For the long-term antidepressant effects, however, chronic drug taking is required to increase basal 5-HT levels and 5-HT throughput (Carr & Lucki 2010).

An altered mental state and inadequate behavioral responses characterize psychiatric disorders. Several psychotropic drugs were found to be useful by individuals to temporarily ameliorate at least part of their disease-related mental or/and cognitive disturbances. Because disease etiology for major psychiatric disorders is still little understood, it appears difficult to identify those pharmacological actions of the drugs that might serve this instrumentalization goal. Exaggerated drug use for this goal, however, was often found to potentiate disease symptoms in the long term and might add a comorbid addiction to the original disorder (Robbins & Everitt 1999).

4.2.6. Sensory curiosity – Expanded perception horizon. Novel stimuli and novel environments carry the potential of new reward contingencies that would allow for the establishment of new behaviors that can lead to a higher overall "reward income" for an individual. The greater the number of distinct behaviors leading to rewards that are established, the more independent an individual will become from changes in the environment when single stimulus-behavior-reward associations lose their contingency. As such, the non–drug related search for novelty and new environments is a driving force to expose an individual to stimuli and environments where new stimulus-reward contingencies exist and can be learned (Kelley et al. 1990; Thiel et al. 1999).

At least in humans, insight may not only be gained by de novo experience of the external world, but also by restructuring of knowledge already gained. As such, a qualitatively or quantitatively altered cognitive performance (Lende et al. 2007; Stillman et al. 1993) may also count as an example of novelty. Although the first is associated with learning and the formation of new representations (McGaugh 2000; Kandel 2001), the later may involve the coincident activation of previously unrelated representations that are then interlinked. Novelty and new sensations can be considered as primary reinforcers in humans and animals (Weil 1998; Zuckerman 1990). They were shown to increase DA activity in the mesolimbic system of the brain in a similar way to other primary reinforcers (Feenstra et al. 1995; Martel & Fantino 1996). The active enhancement of this exposure may contribute to reward learning as a major behavioral adaptation that enhances an organism's survival chances and reproduction.

Psychoactive drugs, by definition, change mental states. This constitutes a novelty effect on the first consumption episodes for each drug. It is unique to particular substances and is reflected in a drug's discriminative stimulus properties (Overton 1968; Stolerman 1992). It is believed that the distinct pharmacological profile of each drug results in unique discriminative stimulus properties. After repeated exposure, the discriminative stimulus properties still exist, but they are not novel anymore, and something other than the novelty effects are needed to motivate continuation of drug use. If no other motives or instrumentalization goals arise, the "experimental" consumption of the drug may cease. This is supported by drug consumption surveys that collectively show considerably higher rates for trying a particular drug once in a lifetime versus regular consumption, measured as, for example, monthly use (SAMHSA 2005; EMCDDA 2009).

From consumer reports, it can be inferred that some psychoactive drugs may not provide a completely new sensory stimulus or environment but rather change an organism's mental state such that present stimuli or already established memories thereof are perceived and dealt with in a new fashion, including self-perception (Weil 1998). However, the psychotropic drug–induced changes in the perception of the external and internal world do not expose the individual to new reward contingencies and may finally offer little improvement in "reward income." It may, therefore, drive psychotropic drug consumption only for a relatively short period of time – that is, until an individual has learned that the drug-induced changes in stimulus perception are not providing new reward-contingencies. This view is in line with self-administration studies in animals. These studies showed that animals do not regularly self-administer those drugs that humans consume primarily for their sensory perception changing properties, such as hallucinogens (Nichols 2004).

Hallucinogenic drugs, a particular group of psychoactive drugs, are used to change sensation and perception of the external world and to increase self-understanding and self-discovery (Boys & Marsden 2003; Boys et al. 1999; 2001; Cato 1992; Nichols 2004). These drugs include natural compounds, like mescaline and psilocybin, as well as semisynthetic drugs, like lysergic acid diethylamide (LSD). They induce a mental state characterized by perceptual hypersensitivity, illusions, and hallucinations. The experience of time and space and the perception of the self are changed. Highly dependent on expectations and setting, hallucinogens can produce a loss of ego boundaries with an elevated mood but may also cause psychotic ego dissolution with fear, paranoid ideation, and a split ego (Geyer & Vollenweider 2008; Nichols 2004). In this state, environmental stimuli can be perceived in a new way that is reported to be an enrichment of one's perceptual world.

LSD and other hallucinogenic drugs are 5-HT_2-receptor agonists, activating predominantly 5-HT_{2A} and 5-HT_{2C} receptors. There is now wide agreement that the effects on the 5-HT_{2A} receptor are crucial for the hallucinogenic action (Gonzalez-Maeso & Sealfon 2009; Halberstadt & Nichols 2010). They also reduce 5-HT turnover and 5-HT neuronal firing in the raphe nuclei. This suggests a further enhancement of the contrast in activation between 5-$HT_{2A/2C}$ and all other 5-HT receptors. 5-HT_{2A} receptors are found in a high density in the neocortex (Mengod et al. 2010) where they fine-tune principal- and inter-neurons (Sheldon & Aghajanian 1990; Aghajanian & Marek 1997). 5-HT and 5-HT_2 receptors play an important role in sensory stimulus processing (Jacobs & Fornal 2010; Pum et al. 2008; Quednow et al. 2008; 2009). The artificial disturbance of this fine-tuning leads to an altered mental state that is relatively selective for the processing of the physical properties of the stimulus without enhancing its incentive salience. However, an interaction of subcortical 5-HT_2 receptors, e.g., with the mesolimbic DA system may also affect the emotional properties of a stimulus resulting in, e.g., "horror trips." Although 5-HT_{2A} and 5-HT_{2C} receptors control DA activity at the level of mesocorticolimbic DA systems (Adell et al. 2010; McMahon et al. 2001; Müller & Carey 2006), the effects of hallucinogenic drugs are not considered to induce euphoria or have a major addictive potential (Nichols 2004).

A similar instrumentalization might also apply to the entactogenic drug, MDMA (Boys et al. 1999; 2001), which has a hallucinogenic profile and induces a unique feeling of "divine oneness" with the world. This particular effect might be mediated by an interaction with the peptide transmitter oxytocin, which facilitates social bonding and the feeling of attachment (Halberstadt & Nichols 2010). MDMA increases 5-HT activity in the brain (Sprouse et al. 1990), which also hyperactivates 5-HT_{2A} receptors. This effect was shown to be involved in the perceptual changes and emotional excitation following MDMA administration, but did not appear to contribute to the positive effects on mood (Liechti et al. 2000). In contrast to LSD, MDMA has a significant effect on DA and NA activity, which might motivate MDMA's use beyond the sensory curiosity.

Phencyclidine, ketamine, and gammahydroxybutyrate (GHB) are drugs used in the club and rave scenes. They are dissociative anesthetics used in the clinic. At high dose, they can have profound hallucinogenic effects. They are unique in that they induce a dissociative state, characterized by sensory deprivation, dreamlike visions, and feelings of the "self" separated from the body. Even near-death experiences were reported. In contrast to serotonergic hallucinogens, they are antagonists at the glutamate NMDA receptor. It is assumed that blocking this receptor, together with an interaction with opiate receptors and monoamine transporters, leads to a functional dissociation of thalamo-cortical and limbic stimulus processing. This was suggested to be the mechanism for the dissociation of the subjective perception from actual environment (Britt & McCance-Katz 2005; Weir 2000; Wolff & Winstock 2006).

Also, cannabis was reported to be consumed to expand self- and environmental perception (Bonn-Miller et al. 2007; Zvolensky et al. 2007). In particular, the perception of time is much slower after cannabis consumption (Iversen 2000). It has been speculated that activation of the CB1 receptors in the association cortices of the brain and the presynaptic inhibition of DA, NA, 5-HT, and glutamate release may mediate the changes in self- and environmental perception (Felder & Glass 1998; Porter & Felder 2001).

Several drugs can be used to change one's mental state such that environmental stimuli and the self are perceived in a new fashion, without significant effects on euphoria or on the incentive properties of the stimuli. This can be achieved by drugs that either directly or indirectly activate 5-HT_{2A} receptors or by blocking NMDA receptors. Exaggerated drug use for this instrumentalization goal may result in dangerous activities and schizophrenia-like psychoses.

4.2.7. Euphoria, hedonia, and high. "Euphoria," "happiness," "hedonia" – all these concepts describe a more-or-less intense feeling of well-being (the terms are used here synonymously). The pursuit of euphoria, or happiness – as either a series of short-lasting feelings or as a long-lasting mental state – is probably the greatest desire in human life (Marcuse 1984; Tatarkiewicz 1976). Human brains work toward linking this subjective feeling with either the receipt of a primary or secondary reward or with the change in reward contingencies – when a formerly meaningless stimulus now predicts reward availability or a formerly useless behavior now yields a reward. Although the biological function of the subjective perception of euphoria is far from clear, it appears that the amount of euphoria we perceive is related to human well-being. It was argued that mood enhancement alone is a psychological benefit gained from psychoactive drug use (Lende & Smith 2002; Peele & Brodsky 2000). An enhanced mood by itself – one without an impact on physical health and behavior – however, would rather constitute a mock benefit. In this respect, the view of drugs "hijacking" the reward system was developed (Nesse & Berridge 1997), which is mostly supported by psychoactive drugs with a strong euphoria component. Alternatively, an enhanced mood can be seen as one example of a mental state change, which might allow more efficient performance of many other goal-directed behaviors and, hence, enhance chances for survival and reproduction.

Psychoactive drugs such as heroin, morphine, cocaine, amphetamine, methamphetamine, methylphenidate, and MDMA can induce a potent feeling of euphoria and an emotional "high" (e.g. Javaid et al. 1978; Resnick et al. 1977) and are used for this reason by nonaddicts (Boyd et al. 2006; McCabe et al. 2007a; Teter et al. 2010; Zacny & Lichtor 2008). A certain degree of euphoria can also be induced by other drugs of abuse, such as alcohol, cannabis, LSD, benziodiapines, and nicotine (e.g., Boys & Marsden 2003; Boys et al. 1999; 2001; Sher et al. 2005). However, the latter are usually not consumed primarily for this reason. The neuronal correlate for the profound euphoria-inducing effects of psychoactive drugs was long believed to be an increase of the extracellular DA activity in the NAc. This view developed from research on the brain's reward circuitry (Olds & Milner 1954; Wise 1980; 1994; 2002) supported by the hugely influential finding that drugs of abuse increase DA levels in the NAc in vivo, whereas nonabused drugs do not (Di Chiara 1995; Di Chiara & Imperato 1988).

It is now well understood how pharmacologically different classes of drugs converge in their acute neurophysiologic effects of increasing mesolimbic DA activity (Ameri 1999; Di Chiara & North 1992; Koob 1992; McBride et al. 1999). Of special importance for the role of DA in these effects appeared to be the D2 receptor (Volkow et al. 1997), which becomes hyperactivated during acute drug exposure. In humans, drug-induced euphoria is usually more intense than naturally occurring euphoria. There subsequently appeared to be several conceptual problems with the DA hypothesis, however (Salamone 1996), which led to the view that DA may not code for the euphoria, but rather signal a reward-related prediction error (Hollerman & Schultz 1998; Schultz 2000). This is not only the case for appetitive (i.e., pleasant) stimuli, but also for aversive stimuli (Brischoux et al. 2009; Matsumoto & Hikosaka 2009; Young et al. 1993). Although these findings may have preserved an outstanding role for DA in reinforcement learning and addiction (Ikemoto & Panksepp 1999; Robbins & Everitt 1996), they further moved reinforcement learning away from the subjective perception of euphoria.

Robinson & Berridge (1993) suggested that DA in the NAc may be the mechanism to attribute incentive salience (i.e., the "wanting") to cues associated with either natural or pharmacological reinforcers. However, euphoria,

which is most closely conceived as the "liking" of a stimulus, should be independent from its incentive salience and may be mediated by endogenous opioid- and GABAergic mechanisms (Berridge 1996; Berridge & Robinson 2003). In their incentive-sensitization theory, Berridge and Robinson (2003) suggested that during repeated drug consumption, a sensitization of neural systems, which attribute incentive salience, occurs. This sensitization increases the "wanting" of a drug, which results in compulsive drug seeking and taking. Thereby, the problems with the original DA hypothesis gave way to an opening for a role of other neuronal adaptations beyond NAc DA (Bardo 1998). Currently, an involvement of many more transmitter systems and various postsynaptic mechanisms in the euphoria-inducing and reinforcing effects of psychoactive drugs is acknowledged (Everitt & Wolf 2002; Heilig & Koob 2007; Kalivas & Volkow 2005; Koob 1999; Müller et al. 2010; Nestler & Aghajanian 1997; Williams & Adinoff 2007).

Euphoria is probably the easiest to accept as an instrumentalization goal for psychoactive drugs. Nevertheless, euphoria is not the most predominant and sought-after effect during most psychoactive drug taking occasions in nonaddicts (for an evolutionary discussion, see: Hagen et al. 2009; Sullivan et al. 2008). For those drugs, which are classically associated with euphoria effects, euphoria requires a considerably higher dose than the use of the drug effects for other instrumentalization goals. Nevertheless, the mental state of a mild euphoria can be useful for many other instrumentalization goals as well; for example, for social or sexual behavior. Although an involvement of NAc DA in behavioral adaptations, in particular for the learning of stimulus-behavior-outcome associations, is beyond doubt now, it is still unclear which mechanisms code for the actual subjective feeling of euphoria. Chronic over-instrumentalization of euphoria-inducing drugs may result in tolerance to the euphoria effects and in an escalation of intake. Acute withdrawal effects are characterized by dysphoria and a depression-like mental state. In nonaddicted users, this can also facilitate drug use in order to overcome the aversive withdrawal states. Entering the "vicious circle" of an escalating consumption and withdrawal is considered to be a gateway to addiction (Heilig & Koob 2007; Koob & Le Moal 2008).

4.2.8. Improved physical appearance and attractiveness. Modern societies impose idealized concepts on males and females, respectively, which include expectations for cognitive and social performance, but also "ideal" norms for physical appearance. Given the natural variation among humans and therefore variance around idealized norms, people feel the pressure to perform behaviors that adapt their physical appearance to these norms. There are certain effects of psychoactive drugs that can be used to facilitate these behaviors and enhance their outcome. A currently predominant case in Western societies may be the pressure toward a lean appearance in females and toward a well-defined muscular appearance in males.

A popular belief is that smoking tobacco reduces body weight. Data indicate that smokers weigh less than nonsmokers. However, smokers do not eat less or consume fewer calories than nonsmokers. Several lines of evidence suggest that nicotine causes a less efficient storage of calories, most likely by its interaction with the gut (Wack & Rodin 1982). Nicotine can also reduce the weight gain usually following smoking cessation (Perkins 1992). It was shown that the activation of nicotinic ACh-receptors in the lateral hypothalamus is the most likely central mechanism by which nicotine interacts with hunger and feeding behavior toward specific food (Jo et al. 2002).

The use of cocaine and amphetamine and its derivatives for their hunger-suppressing effects has been reported as well (Boys & Marsden 2003; Boys et al. 1999; 2001; Garattini et al. 1978). The anorectic effects of amphetamine-derivatives are believed to be mediated mainly by their noradrenergic, rather than by their serotonergic or dopaminergic, effects. In particular, α1 receptor stimulation in the hypothalamus was claimed to be responsible for the reduction in food intake (Borsini et al. 1979; Samanin & Garattini 1993).

In males, a well-defined, muscular appearance is considered an ideal. Naturally, this may signal health and potency of the male to a female and increase chances of mating. Physical appearance may be enhanced by sport, exercise, or body-building. The predominant classes of drugs whose effects can be instrumentalized to facilitate exercise-dependent muscular appearance are androgenic-anabolic steroids such as testosterone or nandrolone. Their use to improve physique is especially popular among teenagers (Goldstein 1990). Anabolic-androgenic steroids increase muscle growth by a peripheral mechanism (Kochakian 1990). However, they also have direct psychoactive effects, such as an increase in self-esteem (Wood 2004; 2008). The self-perception of superior physical appearance may also feed back and increase self-confidence and, hence, affect other behaviors such as social approach or sexual behavior (Wood 2004). As such, there may be an indirect mechanism of how psychoactive drugs can be instrumentalized to first change physical appearance and as a secondary effect to change mental state and potentially all subsequent behaviors (Brower 2002). The slow-acting effects of anabolic-androgenic steroids on mental states are likely to be mediated by their slow effects on the opiate system. Chronic treatment in animals increased levels of the endogenous opioid, β-endorphin, in the limbic system and changed opiate receptor densities. This may be the base for an altered self- and social perception. The modulatory effects on the 5-HT system may account for altered levels of aggression (Kanayama et al. 2009; Quadros et al. 2010).

Several drugs are used to facilitate or inhibit behavior directed toward a change in physical appearance. Although weight reduction appears to be a predominant strategy in females, an increase in muscular appearance is an important goal in males. Both are served by different drug classes. Weight reduction can be achieved by either nicotinic-receptor stimulation or by NA activation. The facilitation of muscle growth relies on a peripheral mechanism involving androgen receptors. This effect is supported by androgen receptor–induced changes in mental states that can facilitate exercise behavior.

Altogether, the functional analysis of nonaddictive psychoactive drug consumption suggests that psychoactive drugs are consumed for their effects on mental states. Based on their ability to adapt food consumption for non-nutritional purposes, humans are able to learn that mental states can be changed by drugs in order to facilitate

other, non–drug related behaviors. Specific "instrumentalization goals" are suggested. Available evidence on the neuropharmacological effects of the used psychoactive drugs can in detail support a focused use of a great number of single drug effects for instrumentalization. We suggest that drug instrumentalization may enhance efficacy of specific fitness-relevant behaviors in modern environments. It is assumed that in order to effectively instrumentalize psychoactive drugs, the establishment of and retrieval from a drug memory is required. How this could be done is discussed in section 5.

5. The psychological mechanisms of drug instrumentalization

5.1. Drug memories

A fundamental assumption of the psychoactive drug instrumentalization concept is a memory for all drug-related issues and a systematic retrieval of these memories. In a discussion of addiction-related behaviors, Nancy Mello introduced the idea of a "memory of addiction" (Mello 1972). Norman White (1996), in summarizing later evidence, suggested that the reinforcing effects of addictive drugs may in part be brought about by their interaction with the brain's multiple memory systems. He proposed three general types of memory that are independently influenced by psychoactive drugs. These systems would be involved in conditioned incentive learning, declarative learning, and habit or stimulus-response learning (White 1996). An important role of habit learning for drug addiction was previously recognized in particular for drug self-administration behavior (White 1989; 1996). This view received important support by more recent studies demonstrating not only anatomical preconditions in the brain (Haber et al. 2000; Porrino et al. 2004), but also its functional relevance for a transfer of information between stimulus-outcome learning and stimulus-response learning systems (Belin & Everitt 2008).

Another classification of "addiction memories" suggested at least three different memory types in relation to drug consumption: a memory of a drug effect, a memory of drug use, and a memory of addiction (Boening 2001; Heyne et al. 2000). Jim Orford (2001) suggested in his "excessive appetite model of addiction" an essential involvement of Pavlovian and incentive learning mechanisms. A combination of operant reward would together with cue-induced conditioned responses drive drug consumption within a social context (Orford 2001). A more recent review distinguished brain structures involved in declarative and procedural memory and discussed how these contribute to addiction-related behaviors. Thereby, drugs are assumed to work as unconditioned reinforcers that support emotional learning, hence, encompassing Pavlovian, as well as instrumental, conditioning (Robbins et al. 2008). Overall, these concepts of drug- or addiction memory have in common the explicit focus on drug addiction, ignoring the fact that in order to establish addiction, a preceding period of nonaddicted drug use must occur. During this period, most (if not all) of the drug-related memories are established, and retrieval of these memories drives ongoing drug consumption.

Some have suggested that drug addiction is based on the vulnerabilities of natural memory systems identified for non-drug-related information (Niaura et al. 1991; Redish et al. 2008). We suggest here that nonaddictive psychoactive drug instrumentalization also involves a decision-making process that relies on an interaction of all drug-related memory systems. Parallel to non-drug-related memory systems (Milner et al. 1998; Squire et al. 1993), two major drug-memory categories are distinguished: a *declarative drug memory* and a *nondeclarative drug memory* (see Fig. 1).

The declarative drug memory contains information that is consciously accessible and can be reported verbally in humans. The declarative drug memory should comprise a *semantic memory* for drug facts and a memory for *drug episodes*. The semantic memory for a drug contains all impersonal facts, rules, and concepts involving drugs – for example, their names, where they come from, recommended doses, what others report about its effects, and the social rules of their consumption. The establishment of this type of drug memory usually starts before a person is engaged in the first episode of consumption by learning from others about the drug (Leigh & Stacy 2004; Miller et al. 1990; West 2006). An early semantic drug memory thus shapes the first expectations of drug effects, which is then constantly adapted after actual consumption started (Kidorf et al. 1995). It has been suggested that the expectation of drug effects (Del Boca

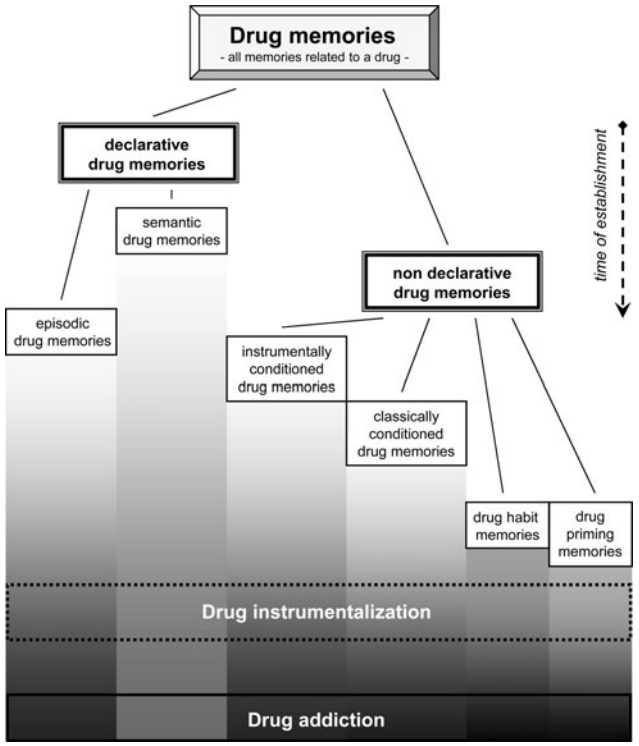

Figure 1. Drug memory systems based on normal memories that psychoactive drugs are likely to influence. A time line suggests the temporal order in which different types of drug memories are established. Drug instrumentalization relies mostly on episodic, semantic, and instrumentally conditioned drug memories. Escalating and compulsory drug use may further intensify these memories. Drug addiction is, in addition, characterized by a growing influence of drug habit and drug priming memories, as well as by classically conditioned drug memories.

et al. 2002; Leigh 1989) should be conceptualized as a retrieval process from different types of memories (Goldman et al. 1991). The expectation of drug effects have been shown to dramatically shape the physiological effects of the drug, as well as its subjective perception (Volkow et al. 2003; 2006) and, hence, influence the establishment of the episodic drug memory. We hypothesize that a person starts to establish a semantic drug memory as a precondition of psychotropic drug instrumentalization by learning from, for example, media or peer groups, long before the first encounter with the drug.

The *episodic drug memory* comprises the memories of personally experienced episodes with the drug. It is an autobiographical memory on the "what," "where," and "when" of the personal drug encounters (Dere et al. 2008). This may include memories of subjectively experienced acute drug effects – for example, the mental states the drug induced. The episodic drug memory system can also contain memories of what was done during a particular drug-induced mental state and even what effects it had in terms of the environmental feedback (Boening 2001).

Although the experience of euphoria is often the sought-after mental state, it is not the only one on the timescale of a drug episode. A single drug episode may better be considered as a sequence of several distinct mental states. Experimental studies in animals and humans have shown that it takes a few experiences of the drug effects to reliably distinguish them from placebo. Once established, however, they can be retrieved from memory and provide the base for other behavioral choices (Overton 1968; Stolerman 1992). As such, this type of memory appears to be crucial for establishing drug instrumentalization (Eissenberg & Balster 2000; Miller 2001).

The *nondeclarative drug memory*, in contrast, is not consciously accessible and can be inferred only from behavioral changes. The nondeclarative drug memories contain engrams of the classically conditioned drug memory, instrumentally conditioned drug memory, habit memory, procedural drug memories, and drug-priming memories (see also Orford 2001; Robbins et al. 2008).

Classically conditioned drug memories may contain all drug effects that refer to the process of Pavlovian conditioning (Bouton & Moody 2004). These may include, for example, the sensitization of the acute drug effects (Kalivas et al. 1993; Vanderschuren & Kalivas 2000), drug tolerance, conditioned locomotor activity, conditioned emotional and physiological responses (Foltin & Haney 2000), and conditioned withdrawal effects (Goldberg 1975; O'Brien et al. 1998; Siegel 1988).

Instrumentally conditioned drug memories comprise engrams established by instrumental conditioning. Major behaviors induced by these engrams are drug seeking and drug self-administration (Richardson & Roberts 1996; Spealman & Goldberg 1978). These memories also include drug cues that can serve as secondary reinforcers, as shown in conditioned place preference (Bardo & Bevins 2000; Childs & de Wit 2009; Tzschentke 2007), or which can reinstate drug seeking and drug self-administration (de Wit & Stewart 1981; Shaham et al. 2003; Wikler 1973). They may also include memories established by social learning, for example, by observation (Bandura 1977). A motivation to use a drug may induce a cognitive process dealing with the outcome expectancies of the drug consumption (Marlatt & George 1984). Behaviors started by this process may then be positively or negatively reinforced by the drug effects (Koob & Le Moal 1997; West 2006).

Drug habit memories refer to instrumental behavior that is no longer goal-directed but stimulus-controlled – a behavioral response that is triggered by a cue – but independent from its behavioral consequences (Robbins & Everitt 1996). This type of memory plays an important role in the transition from controlled to compulsive drug use and addiction (Belin & Everitt 2008; Porrino et al. 2004) but may already play a big role in stimulus-driven drug instrumentalization in non-addicted drug users.

Procedural drug memories comprise all memories for skills involved in handling a drug. This may range from its production (e.g., cooking up heroin; building a joint) to the actual method of self-administration (e.g., snorting cocaine; setting a needle for an IV heroin injection).

Drug priming memories refer to those engrams whose activation by a small amount of the drug, which would not induce major subjective and behavioral effects in drug naïve individuals, may in an experienced user induce drug-related behavior (e.g., reinstate drug seeking, conditioned place preference, or self-administration) and subjective effects.

5.2. A two-stage model of drug instrumentalization learning

Based on interplay of different types of drug memories, we propose a two-stage model for drug instrumentalization learning. Because the crucial function of psychoactive drug-instrumentalization is to enhance efficacy of previously learned behaviors, a precondition for this model is an already established behavior that is reflected at the level of the brain, for example in stimulus-response or stimulus-action-outcome associations. In a *drug-free state* (Fig. 2A) a stimulus (S_x) activates in a particular environmental context, a particular action and an action-outcome representation in the brain. Both facilitate a behavioral response (R_x). The behavior R_x yields an action outcome, which is perceived and processed. A comparator function weighs the expected outcome against the actually perceived outcome. The difference in expectation of outcome (ΔE_o) serves as a teaching signal to strengthen or weaken the associations of the S_x with an action representation and with an action outcome expectation. In constant environments with well-established S-R and stimulus-action-outcome associations, ΔE_o will approach zero, indicating an optimal adjustment of action expectation to action outcome. For reasons of simplicity, it will at this stage not be differentiated between approach and consummatory behavior (Ikemoto & Panksepp 1999; Robinson & Berridge 1993). Both could be considered in this model in a sequential order of approach and consumption.

During *drug instrumentalization – learning* (Fig. 2B), the organism learns how to change its mental state in a way that allows a more effective performance of an already established behavior. In *Stage I*, a specific stimulus (S_y) triggers a psychoactive drug-taking response (R_y). S_y summarizes a number of possible and well-described scenarios that lead to initial drug taking, such as peer group pressure, as well as the information on the drug itself as part of the semantic drug memory.

https://doi.org/10.1017/S0140525X11000057 Published online by Cambridge University Press

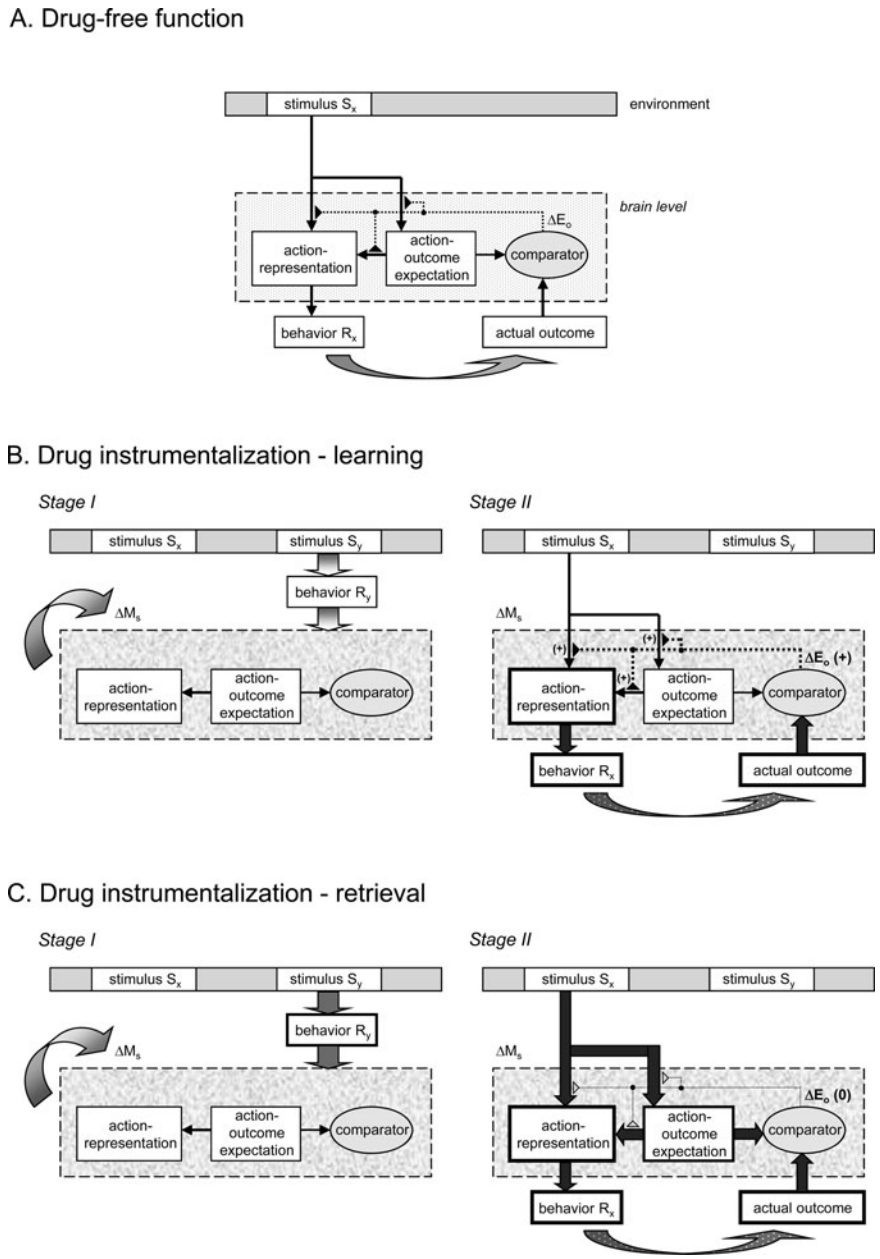

Figure 2. A two-stage model of drug instrumentalization based on the interplay of different drug memories. Drug instrumentalization is based on previously learned instrumental behavior reflected at the level of the brain in stimulus-response and stimulus-action-outcome associations.

The consequence (action outcome) of R_y is an altered mental state of the organism (ΔM_s), which is perceived by the organism. It depends in its nature on the pharmacological properties of the drug. The learning of the S_y-R_y-ΔM_s association requires procedural-, instrumental conditioned-, as well as episodic drug memories. Although R_y may initially be under control of the action outcome (ΔM_s) and semantic memories, this control can shift with excessive repetition. R_y then becomes S_y-controlled, which involves drug habit memories. During *Stage II*, the already established instrumental response based on the S_x-R_x association is performed, but under the new mental state (ΔM_s). If ΔM_s proves to facilitate the ability of S_x to activate the associated action-representation or the way in which the action-representation induces behavioral activity, the R_x will be performed more efficiently. Hence, the action outcome is enhanced when the R_x is performed under ΔM_s. The comparator detects a positive difference between the action-outcome expectation, which was generated during a nondrugged mental state, and the actual outcome achieved under ΔM_s. This difference (ΔE_o) serves as a teaching signal that not only reinforces the association of S_x with an action representation and its action-outcome expectation in *Stage II*, but also strengthens the association of S_y with R_y and its outcome ΔM_s.

During *drug instrumentalization – retrieval* (Fig. 2C), an organism is using the learned information of how a self-generated, "on purpose" mental state change can facilitate a subsequent behavior and maximize its

https://doi.org/10.1017/S0140525X11000057 Published online by Cambridge University Press

outcome. For that to occur, the presence of both stimuli, S_y and S_x, is required. In *Stage I*, S_y triggers R_y, which leads to ΔM_s with the expectation to perform the instrumental response R_x more efficiently. Once ΔM_s is achieved, S_x can now more efficiently activate the action and action-outcome representations and induce R_x. The enhanced performance of R_x under ΔM_s is generating a better action-outcome than under a drug-free mental state. If environmental circumstances and ΔM_s-enhanced action-outcome remain constant (i.e., no tolerance or sensitization develops), there will be no negative teaching signal ΔE_o generated, and the associations of S_y-R_y-ΔM_s and S_x-R_x are maintained.

6. Ontogeny of drug instrumentalization

6.1. Drug instrumentalization establishment during a lifetime

Although one can read about, and establish a factual knowledge on, the effects of drugs, more is learned during experimental consumption when a number of drug memories become established (Maloff et al. 1981). This usually starts during late childhood and early adolescence (Sher et al. 2005), when undifferentiated consumption develops into a highly specific pattern of consumption (Kuntsche et al. 2006; Spear 2000). Experimental consumption, in contrast to instrumentalization and compulsive consumption, refers to a consummatory behavior during which the consequences are initially mostly unknown to the individual. Although there are expectancies of the drug effects in drug naïve consumers (Brown 1985; Brown et al. 1980; Gustafson 1991; Miller et al. 1990; Peele & Brodsky 2000), the individual response profile after first consumption is virtually unpredictable (e.g., Jones 1971; Waskow et al. 1970). During experimental consumption, the effects of a drug are explored at usually different doses and settings (Maloff et al. 1981; Patrick & Maggs 2008). At the same time, there is also experimentation with how the drug's effects on mental states can be "used" in relation to different settings (Harding & Zinberg 1977; Simons et al. 2000; Zinberg 1984). The perceived usefulness was found to predict future use of the drug (Boys & Marsden 2003; Boys et al. 1999; Leigh & Stacy 2004).

The introduction to the drug, appropriate settings, and possible instrumentalizations are usually performed by older and more experienced members of the peer group (e.g., Eissenberg & Balster 2000; Friedman et al. 1985). However, given interindividual differences in drug pharmacokinetics and -dynamics, in personality, and in life circumstances, each person customizes his or her drug use. In fact, the individual learns about which mental states the drug can induce at different doses and how this new mental state can be used, as well as how to control consumption (Bruehl et al. 2006). For an "optimal" drug instrumentalization that yields the greatest benefits, a well-controlled consumption may be established in relation to the following parameters: goals for instrumentalization, appropriate type of drug, appropriate dose of this drug, and setting for consumption. A systematic drug use can thus become an integral part of a person's life within a socially acceptable range of behaviors (Davies 1997; Heath 2000; Waldorf et al. 1991; Zinberg et al. 1978).

6.2. Benefits versus adverse effects of psychoactive drug use

Although we argue for evolutionary benefits of non-addictive drug use here, we also must emphasize that the instrumentalization of psychoactive drugs comes at a price, which ultimately qualifies it as a risky behavior (Donovan & Richard 1985; Hill & Chow 2002). Severe damage to the brain and body peripheral organs have been documented, for example, from alcohol (Harper 2007; Parsons 1998; Ward et al. 2009), MDMA (Gouzoulis-Mayfrank & Daumann 2009; Seiden & Sabol 1996); nicotine (Ray et al. 2009), androgenic-anabolic steroids (Wood 2004), psychostimulants (Pascual-Leone et al. 1991; Volkow et al. 1992), and cannabis (Solowij 1998). Many psychoactive drugs enhance preexisting psychopathologies in vulnerable individuals (e.g., Andreasson et al. 1987; 1989; Negrete 1993).

We argue here that in the majority of nonaddicted psychoactive drug users, there are beneficial effects on self-maintenance or reproduction rate – or both – from drug use in the way that established instrumentalization may in particular at a younger age outweigh the drug-induced decline in health later in life (Crawford 2000; Lende 2007; Peele & Brodsky 2000). As such, the behavior of psychotropic drug instrumentalization may have a heritable component (Schumann 2007) that is maintained in an antagonistic pleiotropy (Williams 1957). This view is supported by life history research, which shows that risky alcohol consumption peaks at an age of 18–19 (males) and 16–17 (females) and declines thereafter (Hill & Chow 2002; Jessor 1987; Johnstone et al. 1996). The peak occurs at a stage of high reproductive efforts. In particular, *mating efforts* (locating mate, courtship) are high (Chisholm 1993). Prior to marriage and continuing thereafter, risky alcohol consumption goes down (Leonard & Das Eiden 1999; Miller-Tutzauer et al. 1991) and many pregnant women give up drinking (Nilsen et al. 2008). At that stage, *parenting efforts* usually increase (Chisholm 1993), which are not supported but rather diminished by psychoactive drug effects. We suggest that because individual resource allocations change during life history, so do instrumentalization goals and, ultimately, non-addictive psychoactive drug consumption (Heyman 1996; Hill & Chow 2002).

The major downside of drug instrumentalization, which as yet has prevented the scientific community from acknowledging any adaptational function or effect of drug taking behavior, is the risk of developing drug addiction (Nutt et al. 2007). People who use and instrumentalize drugs are at a higher risk to develop drug addiction as a psychiatric disorder (American Psychiatric Association 1994) than are drug abstainers (Kendler et al. 2003a). A striking feature of the definition of addiction is the compulsive seeking and consumption of the drug, which is no longer a controlled, goal-directed instrumentalization. Drug addiction is usually associated with an escalating consumption of large amounts of the drug. This significantly increases the impact of any toxic drug effects and directly leads every year to drug-related fatalities (e.g., EMCDDA 2009).

In this case, the adverse drug effects by far outweigh the possible use of any instrumentalization. Natural goals are devalued in the course of addiction development (Redish et al. 2008). It is highly unlikely that this form of drug consumption might have any adaptational function at all. It has been argued that even drug addiction may be an adaptation to cope with "integration failure" (Alexander 1987; 1990). This view highlights the important role of adaptation problems at the personal level for the continuation of psychoactive drug consumption. The first steps of later-stage addicts are indeed to establish non-addictive drug consumption during which they usually instrumentalize the drug effects in the above-described way. Eventually, the capacity of a drug for instrumentalization is exceeded, and no further improvement of non–drug related behavior can be achieved. Then, psychoactive drug use may not help to solve an individual adaptation problem, but, by its toxic side effects, impairs the organism. Altogether, the instrumentalization of psychotropic drugs may have adaptational effects only in non-addicts, being no longer beneficial when the individual loses control and develops drug addiction.

7. Possible implications for drug policy

Epidemiological, ethological, social, psychological, genetic, and psychiatric data on drug addiction are shaping a number of scientific theories, which often have a different focus (West 2006). A major criterion for the quality of a theory is not only how well it integrates empirical evidence and gray literature into a logical framework, but also the quality of its predictions. In terms of theories about drug use and addiction, these criteria might be rephrased as: (1) how well does the framework explain psychoactive drug use in drug addicts and in non-addicts, and (2) how effective are the predictions derived from the framework to avoid adverse effects of drug taking behavior, such as addiction, and treat these effects once they occur. The first criterion is targeted by the presented framework from an evolutionary perspective, suggesting an adaptive function of non-addictive drug use, but stressing reduced chances of survival and reproduction in drug addiction. What can be derived to serve the second criterion when dealing with drug instrumentalization? The proposed concept of non-addictive drug instrumentalization might refine the way in which to deal with psychoactive drugs. As an extension to previous prevention programs that were limited in their success (Brown & Kreft 1998), these approaches might be tailored to the different stages of the potential and actual drug user's development and a "successful" drug instrumentalization:

A. For *drug-naïve individuals*, who are usually in the adolescent to early adult age, information should be systematically provided not only on the adverse effects of addiction and accidental overdosing, but also on how drugs are instrumentalized. Although this might not prevent the initial experimentation with available drugs, it might change attitudes when it comes to the establishment of regular intake patterns. The goal should not be to prevent drug use in general, but to foster control over it by the individual from early stages of use with a better awareness of the full range of the behavioral mechanisms involved.

B. For *people who have already integrated drugs in their routines*, it is important to emphasize the need to stay in control of drug use. In particular, during periods of transition in life when new demands occur, there is an increased danger of developing new forms of drug instrumentalization. One of these periods is adolescence (NatCent/NFER 2006). Humans appear to be especially sensitive to drug effects during adolescence (Spear 2000). In this phase of life, many new demands occur that are prone to drug instrumentalization, such as sexual maturation, peer group pressure, socialization with the opposite sex, and increased cognitive demands at school and work. This is also the first time in life when several drugs become accessible and experimental consumption starts. But this is not the only transition period with an increase in demands. Later in life, when, for example, professional development settles at a high level and performance needs to be maintained at that level, stress load almost certainly increases. Periods of transition should be a major focus when prevention strategies for drug instrumentalization are considered. We argue that psychotropic drug use can have beneficial effects for an individual in modern environments. Nevertheless, one should attempt to limit the extent to which psychotropic drugs are instrumentalized. This can be done by a systematic *analysis of the personal instrumentalization pattern*, asking, for example, *which* drugs are instrumentalized, *how often*, and for *which goals*. Possibly, educational programs should aim to train young people to *self-analyze their drug instrumentalization* and seek help when coming to the conclusion that certain goals in life cannot be achieved without extensive psychotropic drug use.

The occurrence of drug instrumentalization can be seen as an indicator that particular goals are not (or are less easily) achieved by "natural means." Once these goals are identified, particular training may be sought to focus on them and to reduce the extent the drug is used for each goal. Analysis and training could be provided at a personal level or, if an instrumentalization pattern prevails in a particular group, also at family, school, or community levels. People might be trained from early age to learn how to control mental states without pharmacological means (i.e., by own mental resource management, stress-recovery management, relaxation training, controlled disinhibition and approach in social settings).

C. For people who have integrated regular drug use in their life's routines and who are *at risk of a transition to drug addiction*, over-instrumentalization of drugs and, hence, a dependence on the drug to achieve major goals in life, needs to be prevented. Also at this stage, a careful analysis of personal instrumentalization patterns and how they developed over time is required. An initial control for that should be part of a medical routine screen with the intention of preventing over-instrumentalization at an early age. It might be a useful refinement in medical interviews not only to ask for the amount of a drug consumed, but also to identify instrumentalization patterns and the degree the drug is required for achieving major personal goals in life. A more careful investigation might also

include a drug-instrumentalization biography and a detailed assessment of the types and intensity of drug memories already established (Orford 2008; Redish et al. 2008).

Based on that, alternative ways to achieve these goals may need to be identified and intensely trained. With the advent of a more individualized addiction treatment strategy (Conrod et al. 2000; 2006), factors like personality traits and genetic predictors may be useful identifying individuals who are prone to having problems achieving critical goals in life and who might be at greater risk of losing control over drug instrumentalization (Goldman et al. 2005; Kreek et al. 2005; Spanagel et al. 2005; Woicik et al. 2009). However, environmental factors and their interactions with genetic factors might also serve as biomarkers for an increased risk of drug instrumentalization and over-instrumentalization (Blomeyer et al. 2008; Kendler et al. 2003b; Sher et al. 2005).

8. Testing drug instrumentalization empirically

Whether drug instrumentalization can serve as a framework to explain large-scale, non-addictive psychoactive drug consumption in animals and humans needs to be tested empirically. Assumptions, as well as predictions, would require testing. At the level of the assumptions, testing the different types of drug memories and their establishment in the life-course is suggested. This may be done by modifying respective paradigms from non-drug memory assessment. To test predictions in humans, it would be crucial to identify instrumentalization profiles for individual drug users and evaluate the extent of drug-specific instrumentalization in the population of users. Because the full extent of the mechanisms of drug instrumentalization (e.g., non-declarative memory-based behaviors) is not consciously accessible to the user, simple self-reports may not be sufficient. Structured interviews or specifically designed questionnaires, which probe for the individual's relationship with the drugs consumed, with all potential instrumentalization goals, may be more adequate.

At the mechanistic level, animal models of drug instrumentalization may be useful for testing the origin of the behavior and its neurophysiological prerequisites. In contrast to present animal models of drug self-administration (Olmstead 2006; Sanchis-Segura & Spanagel 2006), animals should be given the chance to instrumentalize the drug self-administration behavior to enhance their performance in non–drug related behaviors. It may also be interesting to investigate in ethological studies of drug consumption in animals, whether related behaviors can be identified whose performance is enhanced in a functional way by the pharmacological effects of the psychotropic drug (e.g., Wiens et al. 2008).

9. Summary

Non-addictive psychoactive drug use appears to be much more common than drug addiction in humans around the globe. Although drug addiction as a psychiatric disease results in severe adverse effects on individuals and societies, non-addictive drug use is chosen for its positive effects. We have argued that non-addictive drug use may have a number of beneficial effects on behaviors relevant for survival and reproduction, which may explain the persistence of drug use in human societies. The basic mechanisms establishing non-addictive psychoactive drug use may have arisen in ancient environments, coming to full expression under more recent environmental changes. The key psychological argument is that drugs are used because their psychoactive effects can be instrumentalized. Drug instrumentalization is defined here as a learned behavior to change one's own mental state by consuming a psychoactive drug. Subsequently, this altered mental state allows the more effective pursuit of central survival- and reproduction-relevant goals. A better understanding of the mechanisms of psychotropic drug use in non-addicts might serve to better prevent the transition to drug addiction in the future.

ACKNOWLEDGMENTS

We thank Dr. Cathy Fernandes, Miss Alanna Easton, and the anonymous reviewers for their constructive comments on the manuscript. We also acknowledge the helpful editorial advice from Dr. Barbara Finlay. This work was supported by the UK Department of Health NIHR Biomedical Centre for Mental Health and the MRC-SGDP Centre at the Institute of Psychiatry, King's College London (UK) and funds of the University of Erlangen-Nuremberg (Germany).

Open Peer Commentary

Toward an evolutionary basis for resilience to drug addiction

doi:10.1017/S0140525X11000677

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Abstract: According to Müller & Schumann (M&S), people would have evolved adaptations for learning to use psychoactive plants and drugs as instruments that reveal particularly advantageous in modern urban environments. Here I "instrumentalize" this framework to propose an evolutionary basis for the existence of a biological resilience to drug addiction in people.

As Müller & Schumann (M&S) refreshingly remind us, most people who regularly use psychoactive drugs, even highly addictive ones such as cocaine, do not go on to develop addiction. Only a minority of regular drug users eventually become addicted (Anthony 2002). A long-standing question in addiction research, with critical consequences for prevention and policy, is how we should interpret this individual variation, particularly the high rate of non-addictive drug use. Do environmental circumstances (e.g., economic constraints, societal regulations, cultural norms) prevent people from exposing themselves sufficiently to drugs to cross the "threshold of addiction" (Benowitz & Henningfield 1994)? Or, alternatively, are most drug users somehow biologically resilient to addiction (e.g., genetically resistant to addiction regardless of drug exposure)? Epidemiology of drug addiction alone has been so far unable to resolve this apparent dilemma.

This probably explains the prevailing default view in drug prevention and policy that considers each one of us a potential addict. Given sufficient drug exposure, in this view, each one of us could be turned into a drug addict. A biological resilience to drug addiction would not exist, or such resilience would exist only in rare individuals.

Overall, the framework of M&S – which echoes, without citing it, the "mental tool" hypothesis of psychoactive drug use that Michael Pollan initially formulated in his *Botany of Desire* (Pollan 2001) – seems to support the notion of a biological resilience to drug addiction and even tentatively suggests a possible evolutionary basis for its origin. Accordingly, most people "will never become addicted" because our ancestors would have evolved psychological mechanisms to learn to counterexploit plant neurochemical defences for their own fitness benefits while avoiding their immediate costs (Hagen et al. 2009). In other words, modern humans would inherit an ancient biological constitution that would predispose them to learn to use psychoactive drugs for their indirect fitness-enhancing effects, not necessarily for their direct-rewarding effects. One striking, albeit overlooked, implication of this framework is that most of the learned motivation for psychoactive drug use would not be driven by direct pharmacological activation of the midbrain dopamine system, as it is commonly believed, but indirectly through a facilitation or enhancement of other fitness-relevant behavioral pursuits (e.g., facilitation of sexual behavior). Pushing this idea to the limit, one could even imagine designing psychoactive substances with zero pharmacological efficacy on brain dopamine signalling but whose regular consumption would still be driven by their learned fitness benefits. This prediction could be tested empirically.

Although interesting and relevant, Müller & Schumann's (M&S's) framework rests on a rather fragile biological footing. M&S convincingly show how people can advantageously instrumentalize some psychoactive drug effects to better adapt to the multiple demands of modern urban life; yet, they provide no direct evidence that these effects really increase fitness (e.g., relative to people who abstain from drug use). In addition, M&S do not explain what the selective advantages of psychoactive drug effects to our ancestors, say from the Pleistocene, could have been. The pressures of modern urban life that make psychoactive drug use advantageous are vastly different from those of ancestral environments. The hypothetical scenario for the evolution of psychoactive drug instrumentalization from food selection and self-medication of parasitic diseases lacks some crucial episodes (e.g., there is a conceptual gap between using plants as medications for physical diseases and using them as "mental tools") and, certainly, does not rule out other scenarios. For example, modern psychoactive drug use could be a relatively recent exaptation (Gould & Vrba 1982), not an ancient behavioral adaptation shaped by natural selection, or a relatively recent gene-shaping cultural innovation (Laland & Brown 2006). All these possibilities are compatible with current data on the genetics of drug addiction. Hence, the ultimate cause of psychoactive drug use remains largely uncertain, and this uncertainty weakens the foundation of the proposed framework.

The biological foundation of M&S's framework could have been made firmer by the authors better considering and integrating previous research on animal drug use in the wild (Siegel 1989) and in the laboratory (Campbell & Carroll 2000). Overall, this research suggests that psychoactive drug instrumentalization is not unique to humans and probably corresponds to an ancient behavioral trait, at least in the mammal class. For example, rats – the most frequently used animal model in the field – can learn to regulate drug use as a function of stress, pain, and hunger. Under some circumstances, hungry rats increase their consumption of cocaine (Carroll 1985) probably for its powerful anorexigenic effects. Similarly, rats can regulate opiate intake when in pain (Colpaert et al. 2001) or stressed (Shaham & Stewart 1994). Inversely, rats can reduce their intake of drugs when the resulting effects interfere with other biological goals. For example, under some circumstances, rats learn to reduce their intake of cocaine during the light resting period, probably to sleep and recover (Bass et al. 2010). Recent evidence even indicates that rats, like humans, can choose to use different drugs as a function of the demands of different environmental contexts (Caprioli et al. 2009). Hence, there is currently sufficient data for considering psychoactive drug instrumentalization as a behavioral trait common to humans and at least some other mammals.

This being said, I nevertheless concur with M&S that more research should be devoted to animal drug instrumentalization, particularly on instrumentalization of drug-induced cognitive enhancement that is perhaps unique to humans. For example, it would be interesting to determine whether increasing cognitive demands during access to certain cognitive-enhancing drugs that are normally poorly self-administered by rats (e.g., nicotine) could increase drug self-administration. Finally, and most important, most drug self-administering rats, apparently like most people, do not become addicted. Growing evidence indeed indicates that making animals addicted to drugs is harder than previously thought (Ahmed 2010). For example, we recently found that no matter how severe the cocaine exposure, most cocaine self-administering rats do not lose control over drug use, as they can readily abstain from it when another non-drug pursuit is made available. Only a minority of rats continues to take cocaine despite choice and increasing stakes (Cantin et al. 2010; Lenoir et al. 2007). These findings increase the plausibility of the hypothesis of a biological resilience to addiction to explain why most people who use psychoactive drugs do not become addicted.

ACKNOWLEDGMENTS

The author is supported by grants from the French Research Council (CNRS), Université Bordeaux Ségalen, Conseil Régional Aquitaine and Mission Interministérielle de Lutte contre la Drogue et la Toxicomaine (MILDT). I thank Eric Augier for reading a previous version of this commentary.

Drugs' rapid payoffs distort evaluation of their instrumental uses[1]

doi:10.1017/S0140525X11000689

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Abstract: Science has needed a dispassionate valuation of psychoactive drugs, but a motivational analysis should be conducted with respect to long-term reward rather than reproductive fitness. Because of hyperbolic overvaluation of short-term rewards, an individual's valuation depends on the time she forms it and the times she will revisit it, sometimes making her best long-term interest lie in total abstinence.

What seems most remarkable about Müller & Schumann's (M&S's) article is that it needed to be written at all. Uses of psychoactive drugs to improve social interaction, facilitate sexual behavior, counteract fatigue, alleviate stress, self-medicate psychiatric symptoms, expand consciousness, and just plain get high are amply familiar. To say that these are all instrumental uses is merely to say that they are behavioral operants; this we knew. And yet M&S do point out a need – to examine whether there are circumstances in which these uses may convey benefits that outweigh their obvious dangers. Such discussions could also be commonplace, except for the way that people's personal rules for self-control suborn their beliefs. Rules to avoid particular activities take on extra force if they are experienced as beliefs – for example, that those activities intrinsically will corrupt or contaminate you (Ainslie 2001, pp. 106–12). People in modern

civilization have accordingly cultivated the belief that use of psychoactive drugs regularly leads to addiction (Hammersley & Reid 2002). Science has been under pressure to support this social manipulation of belief. Witness the outcry that followed publication of a Rand study on the sixth or so of recovering alcoholics who successfully return to controlled drinking (Roizen 1987). Hence, M&S's dispassionate catalog of how psychoactive drugs are useful is actually a bold step, although they mention the social pressure on science only briefly (sect. 6.2).

Unfortunately, M&S frame their discussion in terms of evolutionary adaptive fitness and mechanisms of memory formation, neither of which is to the point. We do not choose drugs because they increase adaptive fitness; nor should we. In an age when most children survive and reproduce, that would be a powerful argument against the birth control pill. The evolved trait that is relevant to drug use is sensitivity to reward (or reinforcement, or utility), a proxy for adaptive fitness that allows individual behaviors, rather than whole organisms, to be selected. The central feature of psychotropic drug use is its dominance by the disproportionate effectiveness of imminent rewards. The hyperbolic shape by which prospective reward is discounted in all vertebrates that have been studied leads to a tendency to overvalue imminent rewards, a trait that is not maladaptive in animals for which future planning is accomplished by obedience to instincts – for example, to hoard, migrate, or build dams (Ainslie 2001, pp. 27–47). This shape is common to most forms of sensory perception (Gibbon 1977) and is probably too basic to have been altered in response to the comparatively recent evolution of superior intelligence, despite the problems it has created for evaluating rewards at disparate delays. As to what rewards us, human populations who have lived near naturally occurring psychoactive substances such as alcohol, poppy resin, and coca leaves may have undergone some inborn change of taste for these agents, but the concentrated forms that lead to widespread abuse have been common for no more than four centuries (starting with rum and gin in the seventeenth century; Austin 1978). Hence, evolutionary biology cannot assure us that any psychoactive agent increases adaptive fitness. Likewise, although some of the learning mechanisms that M&S enumerate may lead to automatisms where there is no motivational conflict, any robust pattern of consumption or abstention is based on reward (Heyman 2009).

Many people find some psychoactive agents beneficial even in the long view. That is, looking forward over more than the immediate future, we are glad of their availability; and looking backward, we are glad we consumed them. These are the cases that M&S raise for reasoned evaluation in the face of a disapproving social ethic. Hence, the question for evaluation should be how well we can separate the cases we will be glad of from those in which our preference will have proved temporary. M&S suggest that people should be taught to limit their use by "systematic analysis of the personal instrumentalization pattern" (sect. 7; italics removed); but in the light of our ingrained tendency to overvalue imminent rewards, this advice is glib.

If we want to undertake the controlled use of psychoactive substances, our problem is evident in M&S's own text: "Euphoria . . . is probably the greatest desire in human life" (sect. 4.2.7, para. 1), and "euphoria requires a considerably higher dose than the use of the drug effects for other instrumentalization goals" (sect. 4.2.7, para. 5). We will indeed need to know our "personal instrumentalization pattern," but a simple cost-effectiveness analysis will not suffice. We must plan strategically – game theoretically – for how our evaluation of a psychoactive substance will change as a function of time, not only because of the hyperbolic way we discount its influence, but also because of how the aroused appetite may intensify this change. Our planning will be hindered by imperfect self-knowledge, especially when we keep from rehearsing our options so as not to arouse appetite; this avoidance may lead random reminders to evoke sudden craving for the substance (this case of recursive self-prediction described in Ainslie 2010). We will need to know how our own preferences are apt to change as a function of when the substance will be available and of how much we have already consumed. For example, if we plan to stop at a lower level than euphoria, we need to take into account our likely reappraisal of this plan when we feel a lesser drug effect and take steps to forestall it.

Further complications: Euphoria per se may not lead to regret but do harm only to the extent that the urge to repeat it crowds out more sustainable sources of reward. A costly recurring urge may arise not only from euphoria, but also from a lesser instrumental level, for example, when a performer or driver feels like having drinks before starting out. And when repeated consumption is compatible with a normal lifestyle but otherwise costly, as with smoking, the intrusiveness of withdrawal symptoms becomes the dominant incentive to consume.

Many self-control methods have been described, most recently a person's interpretation of these urges as incentives in a repeated prisoner's dilemma (e.g., Hofmeyr et al. 2010). But it is hard for people to know in advance how well they will do, and after habituation has occurred, even their long-range preferences may have changed. Science does need to examine the instrumental utility of drugs, but a game-theoretic analysis with this many unknowns will often arrive at the same solution as the superstitious fear of addiction that M&S criticize: that the only bright line between abstinence and addiction is the line between abstinence and any consumption at all.

NOTE

1. This commentary is the result of work supported with resources and the use of facilities at the Department of Veterans Affairs Medical Center, Coatesville, PA. It is considered a work of the U.S. government and as such is not subject to copyright within the United States.

Drugs as instruments from a developmental child and adolescent psychiatric perspective

doi:10.1017/S0140525X11000690

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Abstract: Developmental, epidemiological, and neurobiological studies indicate that the adaptive and maladaptive functions, as well as immediate and long-term consequences of drug use, may vary by age. Early initiation seems to be associated with a reduced ability to use drugs purposely in a temporally stable, non-addictive manner. Prevention strategies should consider social environmental factors and aim to delay age at initiation.

Müller & Schumann (M&S) provide a new framework for the understanding of non-addictive substance use, acknowledging the significance of a developmental perspective. It seems important to broaden and deepen this framework theory with respect to the specific characteristics of adolescent drug use to better understand the preconditions of adult non-addictive drug instrumentalization. Adolescence is a developmental period characterized by an increase in novelty-seeking, risk-taking, and emotional reactivity. Experimental and recreational drug use usually starts during this period, with the ages 10–16 being the high-risk period for substance use onset and the subsequent three years

for transitions to regular use and abuse (Wittchen et al. 2008). However, early initiation of substance use has also consistently been shown to be associated with higher lifetime consumption, with more risky patterns of use, and with the earlier onset, longer duration, and higher severity of drug dependence later in life (Behrendt et al. 2009; Grant & Dawson 1997). Various factors may account for this association.

Adolescence is characterized by a maturational and functional imbalance between already relatively mature limbic systems, implicated in motivational and emotional processing, and functionally still relatively immature prefrontal regions, mediating top-down modulation of affective and motivational processing by cognitive control processes. This imbalance may bias adolescents, particularly in emotionally salient situations, to seek immediate, rather than long-term gains, and it may explain their increase in risky decision making, their emotional reactivity, and their heightened responsiveness to rewards (Casey & Jones 2010). Accordingly, behavioral observations indicating a higher salience of reward and increased susceptibility to the positive reinforcing properties of alcohol and other drugs are supplemented by studies demonstrating elevated neuronal responses of reward-related brain regions in anticipation of reward in adolescents compared to children and adults (van Leijenhorst et al. 2010).

Moreover, the adolescent brain appears to be more vulnerable to the neurotoxic effects of drugs, particularly in regions that mediate learning and memory processes (Brown & Tapert 2004). Repeated drug use may also more easily sensitize an already enhanced reward response, thereby inducing an increased incentive salience of drug-related stimuli (Robinson & Berridge 2008). Such probable drug-induced changes may promote a faster development of addiction in adolescent- as compared with adult-onset users. For example, in animal studies, exposure to nicotine during adolescence, but not during adulthood, leads to significant changes in nicotine receptors in rodents and to an increased reinforcement value for nicotine later in life (Adriani et al. 2003). Prospective studies also indicate that drug-induced adolescent brain changes may directly interfere with the development of mature cognitive and behavioral functioning and may impede the adaptation to developmental challenges during adolescence.

Compared with that of adults, adolescent behavior is more strongly driven by social environment, particularly during initiation and early phases of drug use (Kendler et al. 2008). During adolescence, interactions with peers become increasingly important and exert a much stronger impact on decision making than they do in adulthood (Spear 2002). The association between social influences of peers and adolescent substance use is well established. Peer effects account in particular for risky consumption patterns such as binge drinking impeding non-addictive controlled drug instrumentalization. Various studies indicate that the reward value of drugs of abuse may be affected by social context more strongly in adolescence than in adulthood (Doremus-Fitzwater et al. 2010). Because coping abilities are still poorly developed during this developmental period, adolescents are at particular risk to "over-instrumentalize" drug use to manage stress related with significant life transitions during adolescence instead of acquiring mature coping skills (DeWit et al. 2000).

Thus, experimentation with drugs may rather support the use of substances as a maladaptive coping strategy to adapt to life challenges. For example, Buchmann et al. (2010) provided evidence showing that the initiation of alcohol use in early adolescence promotes alcohol use with the objective of coping with unpleasant emotions during young adulthood. The experience of pleasant drug effects, such as relaxation and cheerfulness, may emerge as a fast-reinforcing strategy to deal with stress and to foster the continued and increased drug use, particularly when exposed to stress (Blomeyer et al. 2011) and being at genetic risk (Blomeyer et al. 2008; Laucht et al. 2009). Accordingly, adverse life events during childhood increase the likelihood for early substance involvement and subsequent addiction (Andersen & Teicher 2009).

The aforementioned restraints of a stable, goal-oriented drug instrumentalization apply particularly to adolescents with psychiatric disorders. Numerous studies have highlighted that individuals with externalizing disorders are at higher risk for both early initiation and subsequent addiction (Laucht et al. 2007; Molina & Pelham 2003). Executive function and motivational deficits resulting in increased impulsivity and emotional reactivity might interfere with non-addictive drug use. Hence, high impulsivity was found to predict the switch to more habitual and compulsive drug use in rodents (Belin et al. 2008).

Regarding implications for drug policy, prevention programs for those at younger ages or those being particularly vulnerable should aim to delay age at initiation to prevent substance use disorders, with establishing youth protection laws being particularly relevant (Buchmann et al. 2009). Programs should teach alternative and more adequate coping strategies and general life stabilization strategies. Moreover, programs should take into account the strong impact of social environmental factors on adolescent behavior. Hence, good parental monitoring associated with positive parental involvement has been found to be effective to prevent alcohol abuse (Ryan et al. 2010), particularly in genetically vulnerable subgroups (Laucht et al. 2011). In addition, the parental model of responsible drug instrumentalization has proven to be essential for the offspring's orientation. Recently, an Australian expert group developed guidelines for parents on their influence to prevent their child's drinking (Ryan et al. 2011). In the course of development, peers become increasingly important for adolescent consumption patterns, forming the reference frame for the perception of "normal" amounts of alcohol used. Most adolescents are not aware of this mechanism and tend to overestimate their friends' drinking behavior while underestimating their own. Here, campaigns establishing responsible drinking norms in the target group are promising, if located in an adequate surrounding (Scribner et al. 2011).

Drug use as consumer behavior

doi:10.1017/S0140525X11000707

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Abstract: Seeking integration of drug consumption research by a theory of memory function and emphasizing drug consumption rather than addiction, Müller & Schumann (M&S) treat drug self-administration as part of a general pattern of consumption. This insight is located within a more comprehensive framework for understanding drug use as consumer behavior that explicates the reinforcement contingencies associated with modes of drug consumption.

By associating drug consumption with emotional experience and reward, Müller & Schumann (M&S) present a specific example of the general relationship of consumer choice to reinforcement contingencies and related patterns of affect. This suggests that drug consumption, from the recreational to the addictive, can be modeled as consumer behavior.

Consumer behaviors range from routine purchasing of staples, through credit buying, environmental despoliation, and compulsive purchasing, to extreme consumption like addiction. Behaviors on this continuum (Foxall 2010) are influenced by similar genetic, neurobiological, economic, contextual, and cultural factors. Biosocial science seeks to unravel how these elements combine to

produce consumer behaviors with such disparate outcomes, and this requires a theory of consumption that integrates the contextual with the psychobiological. Positioning a behavior on the continuum reflects the degree of impulsivity/self-control it exhibits. All consumption is a choice and exhibits matching (Herrnstein 1997), which can underlie discounting; hence, behaviors at all locations on the continuum invoke temporal discounting. Occasional drug use falls within this routine category. More impulsive purchases, say of durables, lead consumers to incur expensive debt that reflects heavy discounting. Impulsivity is also apparent in environmental despoliation, whereas compulsive purchasing borders on addiction; beyond this, problem gambling, problem drinking, and overeating to the point of obesity involve delay discounting at a very high rate.

In the behavioral perspective model (BPM), consumer behaviors result from the pattern of reinforcement signaled by the consumer behavior setting (Foxall 2004). Two sources of reinforcement emerge, utilitarian (UR; functional) and informational (IR; symbolic/social), the combination of which provides a framework of four major classes of consumer behavior based on the *pattern of reinforcement* that shapes and maintains them (Fig. 1). The consumer behavior setting, primed by the consumer's learning history, predicts these outcomes contingent on the enactment of the behavior. The scope of the setting, the range of behaviors likely to be reinforced, completes the model. *Closed* settings like banks, dentists' offices, and gymnasia encourage a single pattern of behavior or at most a few; *open* settings – bars, swap meets, department stores – permit more behaviors and are thus *open*. Empirical studies (Foxall 2011) reveal these structural characteristics consistently elicit emotional responses: Utilitarian reinforcement is associated with pleasure, informational reinforcement with arousal, and setting openness with dominance (Mehrabian & Russell 1974).

Consumer behaviors that make up the continuum are defined by the pattern of reinforcement and scope of the setting maintaining them. *Routine consumption* corresponds to the operant class Maintenance, determined by low levels of both UR and IR. Closure is imposed by physiological limits to ingestion. Recreational drug use is another example. Maintenance in closed settings includes paying taxes and is also exemplified by medically supervised drug use.

For some consumers, there is a progression from this routine consumption, said to be under the control of executive brain functions, that entails delayed deleterious effects. These behaviors range from unplanned purchasing, which accounts for half of retail sales, to installment buying and credit card purchases,

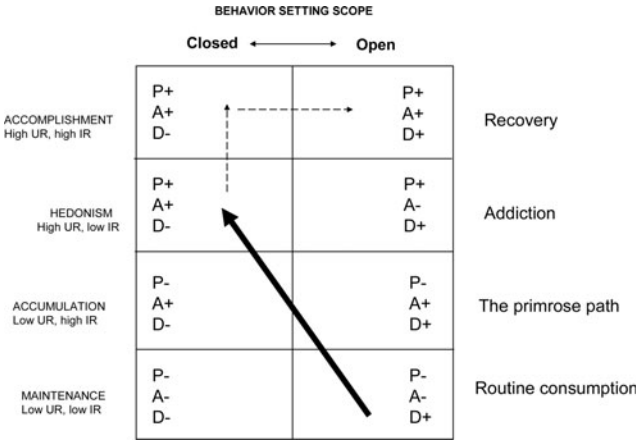

Figure 1 (Foxall & Sigurdsson). Dynamics of consumer choice. Continuous arrow shows route from self-control (low pleasure, low arousal, high dominance) to impulsivity (high pleasure, low arousal, low dominance). Broken arrows show possible route to recovery. P = pleasure; A = arousal; D = dominance; + = high; − = low.

littering, and related cases of environmental spoliation, all of which can be described in terms of melioration, the choice of whatever is more immediately advantageous. This is an insidious progression. The behavior is not halted even when its deleterious effects become apparent: rather, intertemporal choice involves preference switching, from the resolve to act for one's long-term best interests to indulgence in harmful behavior, to regret for one's deviation and desire to overcome it (Ainslie 1992). Patterns of reinforcement contingencies, explored in consumer psychology but not generally in drug use studies, control the progression.

The *primrose path* is governed by symbolic, as well as functional, results of eating and drinking, use of drugs for social leisure, and organized gambling in public places. UR is less important than the symbolic reward that inheres in IR. The primrose path begins in relatively open settings before contexts become progressively more closed as reinforcing social approval is overtaken by the addictive consequences of indulgence. Why an individual moves from routine consumption to the primrose path is apparent from embedding behavior in a network of contingencies that control the *patterns of choice* of which any particular response (say, drinking or abstaining from alcohol) is a part. The more long-term a pattern of behavior has become, the more costly it is to the individual to interrupt it.

The path from sobriety to addiction runs from Maintenance in open settings to Hedonism in closed settings; if recovery occurs, the sequence continues to Accomplishment in closed and then open settings (Fig. 1). Maintenance in open settings enables the behavior pattern of moderate consumption; moving from there into Accumulation involves entering the primrose path; the next stage, Hedonism in closed settings, involves gaining more pleasure from consumption and less by way of interpersonal reward: the path to lonely addiction (Rachlin 2000); finally, Accomplishment in closed settings involves restoration of more moderate behavior.

In line with M&S's target article, the BPM relates emotional responses to the contingencies of reinforcement that account for the continuum of consumer behavior. We propose that this model has the capacity to complement the detailed and specific analysis of drug use proposed by M&S, not by seeking to absorb or supersede it, but by providing an integrative framework. The patterns of reinforcement it embraces can be related not only to consumption behaviors, but also to their emotional concomitants; the scope of the consumer behavior setting is closely related to the physiological role of drug ingestion and processing, and the classes of consumer behavior indicate how behaviors under the control of self-regulation, impulsiveness, and compulsion are controlled and modifiable. All in all, the conceptualization of drug use as consumer behavior provides a fruitful research program that unites economic psychology and drug studies.

Nonaddictive instrumental drug use: Theoretical strengths and weaknesses

doi:10.1017/S0140525X11000719

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Abstract: The potential to instrumentalize drug use based upon the detection of very many different drug states undoubtedly exists, and

such states may play a role in psychiatric and many other drug uses. Nevertheless, nonaddictive drug use is potentially more parsimoniously explained in terms of sensation seeking/impulsivity and drug expectations. Cultural factors also play a major role in nonaddictive drug use.

Müller & Schumann's (M&S's) theory can be formulated in a weak form – that drug-induced mental states facilitate behaviour; and a strong form – that such states facilitate reproductive fitness. We believe that the weak form of the theory is easier to defend.

State memories are clearly critical for the theory. M&S suggest that such memories are based on ingestion-related phylogenetically old learning mechanisms. However, drug state/discrimination research (NIDA Research Monograph 1991) shows that animals can detect at least 40 different drug states, dose-specific states, centrally and peripherally mediated states, and states in which animals discriminate between closely related drugs (e.g., amphetamine and cocaine); and also that when animals learn about drug mixtures, the components are counter intuitively processed in parallel rather than as a novel "gestalt."

Such findings suggest that the brain detects very specifically many different types of interoceptive states. This makes sense in evolutionary terms. It allows organisms to detect different states that need regulation to maintain the constancy of the *milieu interne* and to detect different states arising from drugs that are all essentially toxins. Drug discrimination research grew out of work on ingestion, before shifting to a broader conceptualisation of interoceptive stimuli detection. We suggest that M&S's theory requires a similar conceptual shift away from ingestive behaviour.

The fact that the brain can detect many drug-induced states supports M&S's theory that many drugs may be used instrumentally. An important point, such an account of drug use parsimoniously explains reports of the use of drugs such as antipsychotics and antidepressants, which are not typically conceptualised as used drugs (e.g., Tarasoff & Osti 2007). As M&S note, because the aetiology of psychiatric disorders is little understood, it is possible that such drugs are used to induce a "less aversive mental state"; this is also suggested by radical preclinical (Colpaert & Koek 1996) and clinical (Moncrieff & Cohen 2009) theorists and supported by recent research (Mizrahi et al. 2005; Moncrieff et al. 2009).

The ability to detect many drug states is a necessary but not sufficient condition to assert that drugs are taken to facilitate fitness and/or social functioning. We are sceptical that drug use reliably enhances social functioning or reproductive success. It is a widely held belief that alcohol and drugs convey these benefits, but the evidence is unclear. Cooper (2006), reviewing research on the alcohol-sex link, suggested that several third-variable explanations could account for the association, notably expectancies and sensation seeking. Sensation seeking prospectively predicts greater alcohol/drug use, better social functioning and reproductive success, and stronger positive drug expectancies (Gullo & Dawe 2008). Sensation seeking is also highly heritable and, given its mesolimbic dopamine system basis, might provide a more parsimonious and evolutionarily plausible account of some non-addictive drug use that is consistent with Nesse and Berridge's (1997) alternative model.

In many of the instrumentalization examples discussed (e.g., facilitated social interaction and sexual behaviour), drug use is an ineffective "quick-fix" compared with long-term strategies. For example, reading the *Kama Sutra* might facilitate sexual behaviour related to reproductive success better than getting intoxicated. Similarly, exercise might be of more value, as well as improving cognitive performance, reducing fatigue, and improving physical appearance, with no risk of addiction. However, reading the *Kama Sutra* while jogging requires more time and effort than drinking. This probably reflects delay discounting, a universal highly heritable human/animal trait (Anokhin et al. 2011) believed to underlie sensation seeking/impulsivity.

Expectations concerning alcohol and drug effects have been shown to have some predictive value in determining drinking behaviour (Morawska & Oei 2005). However, the relationship between expectancy type (positive or negative) and drinking is far from clear-cut (Jones et al. 2001). Expectations of the benefits of drug use exist before a drug is first taken. However, even adolescents are aware of the negative impact of excessive use, as used in educational programs for the young about negative consequences of alcohol/drug use and ways of tackling risky situations – such as protection against peer pressure. M&S acknowledge that positive and negative expectancies prior to initial alcohol and drug use would be held as semantic memories. However, for a theory of non-addictive drug use, M&S need to consider further how competing expectancies determine which specific drug-related behaviours occur.

M&S suggest that once an individual learns that drug use can be adaptive, drugs may then be used in greater quantities which may lead to addiction. Alcohol/drug use may start as an adaptive process to facilitate interactions, but it can lead to levels of consumption that impair interactions (Rehm & Gmel 1999). This is a critical theoretical issue, but the instrumentalization theory does not consider all the likely negative consequences of heavy drug use, which should act as a warning signal to individuals before heavy usage becomes habit-like. A major issue for the theory is that it concentrates on adaptive drug use. There is little discussion of what happens in the critical transition from social to hazardous drug use, whether it be non-dependent or dependent hazardous use.

The theory does not consider cultural factors. Use is not a result of modern societal demands alone, but to such demands interacting with specific cultural contexts that determine attitudes and expectancies. The United Kingdom, Spain, France, and Germany are presumably similar societies in terms of demands on workers, although cocaine use is less prevalent in France and Germany than it is in the United Kingdom and Spain (United Nations Office on Drugs and Crime 2010), despite the fact that in evolutionary and socioeconomic terms and in cocaine supply, there is little difference between these European countries. Similarly, methamphetamine use in the United States is predominantly a "white problem," even after controlling for job status and education (Anglin et al. 2002; Cartier et al. 2006), again implicating cultural factors in use.

Our comments clearly do not imply that instrumental drug use does not occur. The challenge for the theory is to define its limits, particularly the strong fitness-related form of the theory, and to clarify the relevance of enhanced fitness or facilitated behaviour versus other factors.

Non-addictive psychoactive drug use: Implications for behavioral addiction

doi:10.1017/S0140525X11000720

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Abstract: The newly proposed framework for non-addictive psychoactive substances postulated by Müller & Schumann (M&S) provides an interesting and plausible explanation for non-addictive drug use. However, with specific reference to the relevant behavioral addiction

literature, this commentary argues that the model may unexpectedly hold utility not only for non-addictive use of drugs, but also for non-addictive use of other potentially addictive behaviors.

Müller & Schumann's (M&S's) newly proposed framework for non-addictive psychoactive substances claims the adaptive and beneficial effects of psychoactive drug use are often categorically denied. However, they make no reference to the seminal and controversial work of Bill Glasser, who was the first person to forward the notion of "positive addiction" (Glasser 1976). According to Glasser, positive addictions must be new rewarding activities (such as exercise) that produce increased feelings of self-efficacy.

Glasser argued that such activities should be (1) noncompetitive and needing about an hour a day; (2) easy, so no mental effort is required; (3) easy to be done alone, and not dependent on people; (4) having some physical, mental, or spiritual value; (5) something that, if persisted in, leads to resulting improvement; and (6) something that involves no self-criticism. However, Griffiths (1996) questioned whether the positive addictions (and the criteria for them) that Glasser outlined were "addictions" at all. Furthermore, the types of rewarding activity that M&S outlined in relation to non-addictive drug use appear to meet many of Glasser's criteria for "positive addiction."

Perhaps because of the early pioneering work of Glasser and others, there is now a growing movement suggesting a number of behaviors are potentially addictive, including many behaviors that do not involve the ingestion of a drug. These include activities as diverse as gambling, overeating, sex, exercise, video-game playing, love, Internet use, and work (Griffiths 2005a; Orford 2001; Sussman et al. 2011). In fact, there have been an increasing number of research studies over the last few decades suggesting that a wide range of substance and process addictions may serve similar functions (Griffiths 2005a; Shaffer et al. 2004). Taking a much wider conceptualization of addiction, M&S's framework also provides adaptational and functional reasons most potentially addictive behaviors do not develop beyond strong liking and healthy enthusiasm.

Griffiths (1996) also argued that an individual gained many potential benefits when engaging in potentially addictive behaviors, including: (1) reliable changes of mood and subjective experience (e.g., escape); (2) mood enhancement, including the positive experience of pleasure, excitement, relaxation, and so forth; (3) disinhibition of behavior aiding sociability (e.g., sexual behavior); (4) coping strategy (e.g., stress reduction) for vulnerabilities (e.g., insults, injuries, social anxiety, fear, tension, and so on); (5) strategy for threatening, rebelling, revenging, and so forth; and (6) source of identity and/or meaning of life. Griffiths argued that from the individual's perspective, the engagement in potentially addictive behavior served a useful purpose in her personal life. M&S incorporated much of this reasoning into their argument when developing their framework for non-addictive drug use.

A recent comprehensive review by Sussman et al. (2011) examined 11 such potential chemical and behavioral addictions, including their prevalence and co-occurrence (i.e., tobacco, alcohol, illicit drugs, eating, gambling, Internet, love, sex, exercise, work, and shopping). Depending on various assumptions they made, Sussman et al. (2011) asserted that anywhere from 15% to 61% of the U.S. adult population suffers from maladaptive signs of an addictive disorder at any one time during a 12-month period. However, M&S's framework and empirical evidence not only provide additional support of the utility of non-addictive drug use, but also demonstrate it could easily be applied to other potentially addictive (non-chemical) behaviors such as gambling, exercise, and work. As M&S rightly point out, epidemiological data show that the most individuals who take drugs are not addicts and will never become addicted – this is also the case with behaviors that are potentially addictive.

M&S argue that "the general 'paradox of drug reward' may be resolved at the dose-response level: In a low- to medium-dose range, the drug effect is not toxic in the sense of being an immediate threat to life. In the range of medium to low doses, therefore, a role for drugs in functional adaptation can reasonably be considered" (sect. 2, para. 2). Here, it is worth noting the work of Larkin and Griffiths (2004), who examined "risky but rewarding behaviors" such as taking drugs like Ecstasy and participating in bungee jumping. Their aim was to illuminate from the user's perspective of what it means to take risks for pleasure in our culture. Their analysis focused on the manner in which these people made sense of their initiation and maintenance experiences and the means by which they understood and made sense of risk.

In particular, Larkin and Griffiths drew attention to the distinctions between their participants' rational and contextual reconstructions of risky decisions. These distinctions indicated that both Ecstasy users and bungee jumpers were able to draw upon a complex cultural and relational understanding of risk and pleasure and were therefore able to deal quite effectively with the contradictory experience of taking "nonvolitional" action. Most of the participants had a positive, appetitive, and willful orientation towards risk.

Much of Griffiths and colleagues' research examining a whole range of behavioral addictions such as gambling (e.g., Griffiths 2006), video game playing (Griffiths 2008), Internet use (Widyanto & Griffiths 2006), sex (Griffiths 2001), work (Griffiths 2005b), and exercise (Allegre et al. 2006) suggests that the main functional reason for engaging in potentially addictive behaviors is for their positive effects on mental mood states for those engaging in the activity.

I hope this brief commentary shows that M&S's framework for non-addictive drug use has potentially far-reaching implications outside of the chemical addictions field and perhaps provides more unifying evidence that the commonalities between chemical and behavioral addictions are more similar than different. In conclusion, I argue M&S's model may unexpectedly hold utility not only for non-addictive use of drugs, but also for non-addictive use of other potentially addictive behaviors (e.g., gambling, sex, work, exercise, video-game playing, and more).

Does drug mis-instrumentalization lead to drug abuse?

doi:10.1017/S0140525X11000859

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Abstract: Understanding the perceived benefits of using drugs to achieve specific mental states will provide novel insights into the reasons individuals seek to use drugs. However, the precision of attempts to instrumentalize drugs is unclear both across drugs and individuals. Moreover, *mis-instrumentalization*, defined as discrepancies between such endpoints, may have relevance to understanding the relation among use, abuse, and addiction.

Müller & Schumann (M&S) stress the importance of a more detailed conceptualization and study of the reasons behind drug taking, along with the notion that it can often be associated with benefits to the individual. The conceptualization and model formulization describing drug instrumentalization fills the gap left by the majority of prevailing theories of drug use that focus on drug abuse and addiction without specifically addressing the initiation of drug use and offer no account of stable, non-abusing drug intake patterns. One element that requires more consideration is the efficiency and accuracy of the employment of drug instruments to achieve specific changes in mental state, along with how a lack of precision may affect long-term patterns of drug taking.

Although it is clear that individuals take drugs to achieve a variety of goals, it is unclear how optimally an individual is able to achieve instrumentalization of a drug (i.e., desired vs. unwanted consequences of intoxication) and how these abilities may vary between substances and between individuals. In general, achieving a specific mental state will require ingestion of drug in a specific range; and variation from this range, in particular higher dosing, is likely to result in additional, potentially aversive, effects of the drug. As such drug use, with or without dependence, may involve non-optimal instrumentalization or a degree of "mis-instrumentalizaiton" (i.e., the ingestion of a pharmacological substance that fails to appropriately achieve the desired purpose determined in the drug-free state); and the deviation from the desired endpoint may be an important construct in determining the net beneficial and detrimental consequences. Given the delayed onset and enduring nature of drug effects following ingestion, it is also likely that mis-instrumentalization would tend to result from excess drug intake, a condition known to promote neuroadaptations and facilitate the addiction process (e.g., Koob et al. 2004). Below, I provide a non-exhaustive summary of drug characteristics and individual factors that will contribute to mis-instrumentalization of drugs.

Abuse liability of a specific drug is a widely employed concept in addiction research, and a reconceptualization in relation to the utility of drugs may be informative. Specifically, the impact of drug instruments on specific psychological processes may reveal which drugs are likely to be misused or "mis-instrumentalized," resulting in an increased likelihood that the individual will encounter problems when using the drugs regardless of intended purpose. Drugs that produce high levels of euphoria are likely to be abused even when initially taken for a medical purpose, which reduces the overall therapeutic utility of such drugs. Drugs that produce cognitive deficits, particularly those inducing deficits in judgment, as well as in timing and working memory (faculties that are necessary to gauge ongoing dosing), would probably produce mis-instrumentalization through either poor decisions on continuing drug intake or failure to accurately gauge cumulative intake. Further, a variety of drugs impair inhibitory control processes; and as M&S argue, such impairment may be the exact effect desired for instrumentalization (e.g., alcohol for social disinhibition). However, impairing behavioral control would also disrupt the ability to maintain intake in the desired range. Together these factors are likely to link abuse/addiction liability to the probability for mis-instrumentalization.

On the other hand, the optimal instrumentalization of drugs would be expected to vary across individuals and time. First, the ability to instrumentalize a drug for a specific effect requires intake that achieves specific dose ranges of intoxication with deviation from these levels resulting in overintoxication, adverse side effects, or both. This ability to instrumentalize drugs should not be viewed as innate but, rather like other operant behaviors, the relation between intake and achieving a desired mental state that must be learned. Inexperienced users are highly likely to fail to appropriately gauge intake for desired effect; and given that most drugs are both powerful biological instruments and promoters of adaptive processes, the acquisition of drug instrumentalization may result in high levels of abuse as well as promoting addiction. Second, responsiveness to drugs differs enormously between individuals. Individual variability is exhibited across almost all aspects of drug responsiveness and forms of learning and, hence, the ability to appropriately instrumentalize drugs for specific effects most likely varies between individuals. Conceivably, poor "learners" will fail to appropriately regulate intake to achieve the desired state and avoid excess intake. Individuals responding in such a fashion are at risk for repeatedly abusing drugs and are likely transitioning into addictive behavior. Third, responsiveness to drugs also differs within an individual across time. For example, it is widely reported that the subjective effects of psychostimulant drugs vary across women's reproductive cycles (Evans & Foltin 2010). Hence, if women, relative to men, attempt to instrumentalize cocaine intake for a desired level of euphoria, they would be expected to make more errors in determining the desired level of drug intake (i.e., more likely to take excessive amounts of drug), which could mediate sex differences in addiction vulnerability (Becker & Hu 2008). Analogous elevations in the potential for misinstrumentalization would be expected for changes in stress levels, energetic states, age, and so forth. Accordingly, it may be that an inability, whether enduring or transient, to appropriately gauge necessary levels of drug intake for drug instrumentalization would put an individual at risk for aversive consequences, including induction of neuroadaptations mediating the development of addictive behaviors.

Further, in addition to the proximate mechanism that M&S discuss, drugs are used to "fit in" or to indicate maturity. The impacts of "peer pressure" and mimicry of parents/role models on drug taking should not be overlooked as these factors are likely to contribute to the motivation to use a drug, as well as the desired drug effect to be achieved. Accordingly, the role of semantic knowledge of or perceived knowledge of drug use by others, as well as the social context of that semantic knowledge, may explain the high impact of environment on early drug use (e.g., Kendler et al. 2008), a time when the user is relatively inexperienced with the drug and the pathways to beneficial drug use or detrimental drug abuse are largely undetermined.

Drug instrumentalization and evolution: Going even further

doi:10.1017/S0140525X11000744

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Abstract: Müller & Schumann (M&S) deserve applause for their interdisciplinary examination of drug use, evolution, and learning. Further steps can deepen their evolutionary analysis: a focus on adaptive benefits, a distinction between approach and consummatory behaviors, an examination of how drugs can create adaptive lag through changing human niche construction, the importance of other neurobehavioral mechanisms in drug use besides instrumentalization, and the importance of sociocultural dynamics and neural plasticity in both human evolution and drug use.

Müller & Schumann (M&S) approach substance use through a broad interdisciplinary approach that spans evolutionary theory, neuroscience, and psychology. They focus on the idea of "drugs as instruments" as a concept that both illuminates substance use and can unite these different areas of research. This dual approach – broad integration and specific concepts – should be applauded and emulated.

Their use of evolutionary theory to analyze drug use and understand the links between use behavior, neurobiological impacts, and mental states represents an important step forward in evolutionary analysis of substance use and abuse. Like neurobiological and psychological research, evolutionary approaches have largely focused on trying to explain addiction, rather than on the more widespread behavior of substance use. M&S show the importance of focusing on drug use itself and help move the evolutionary debate forward by going much further than the simplistic argument that people use drugs because they "create fitness benefits."

With drug instrumentalization, M&S focus on mental states, which then help in achieving behavioral goals. As they put it,

drinking coffee can help with driving a car better. The combination of mental effects and behavioral goals can lead to a variety of benefits, ranging from improved social interactions to coping with stress and euphoria. This focus on functional use is important because it opens research up to a range of uses and meanings for drugs that better reflect reality, rather than simply reducing drug use to either self-medication or getting high (Lende et al. 2007).

Drugs can provide concrete adaptive benefits, however, not simply changes in mental states. For example, moderate alcohol use is associated with improved cardiovascular benefits over the life span. Steroid use can improve competitive ability, often with negative mental benefits. Adaptive benefits can also play an important role in reinforcement of drug use. Survey research among adolescent drug users in Bogotá, Colombia, examined how many times respondents had been involved in agreeable sexual situations and had won competitions or fights as a result of substance use. Using a summary variable of evolutionary benefits (the sum of both sexual and competitive benefits), addicted individuals reported 2.76 total benefits versus 0.98 benefits for non-addicted individuals ($p < 0.001$, two-tailed t-test) (Lende 2007). Evolutionary theory focuses on competition and reproduction, and drug use can provide adaptive benefits.

In future work, M&S can improve their overall evolutionary analysis in other ways. When considering the evolution of the adaptive mechanisms underlying substance use, a basic distinction can be drawn between approach behaviors and consummatory behaviors (Lende & Smith 2002). Both foraging and sexual reproduction involve the basic adaptive problem of finding food or mates and then eating the food or engaging in mating. Different neural and bodily mechanisms underlie these two dimensions of the basic adaptive problem. Instrumentalization folds these two dimensions into one learning process. However, the structure of the adaptive problem indicates that evolution has probably produced a more complex learning architecture, and substance use will differently relate to seeking and consumption behaviors and effects.

M&S's focus on niches and flexible responding is useful, and it can be augmented by closer consideration of adaptive scenarios and changes over evolutionary time. For humans, niche construction has been argued as a way to buffer humans against selection pressures. The drug instrumentalization view represents one major way humans might be able to create a cultural niche that lowers selection pressures, thus creating adaptive lag (Laland & Brown 2006).

Evolutionary medicine often focuses on evolutionary discordance, the difference between modern environments and the environments in which we evolved, for example, taste buds that evolved to taste sweetness in low-sugar environments and are now faced with an abundance of sugar. M&S propose that today in industrial societies we face many different microenvironments, often requiring large shifts in behavioral strategies with short transition times. Given the time lag in initial drug effects and the length of time many drugs remain in the system, it is not clear that drugs can fulfill the proposed function. Moreover, it is also not clear that there is an environmental mismatch. Decades of research on hunter-gatherer societies have continually emphasized their social and linguistic complexity and the enormous variation in their foraging strategies.

The importance of social and cultural forces in human evolution dates back at least 2 million years, and most likely longer, given strong evidence for chimpanzee cultural/behavioral traditions. New research on neural plasticity, including evidence that culture directly shapes neural function, indicates that a compartmentalized and isolated view of mental function is also biologically inaccurate. Flexible local responding, directly shaped by local sociocultural dynamics, looks like a key to understanding human evolutionary history. This makes an approach that locates instrumentalization solely at the psychological and internal level at odds with evolutionary and neurobiological research.

Drug use takes place in specific social contexts and is shaped by cultural meanings and social expectations. A full account of instrumentalization cannot rely solely on a psychological process of changing internal states; drugs are often used for external social reasons, and social learning mediates the specific effects drugs have. Neuroanthropology, which integrates the insights of neuroscience and psychology with social and cultural anthropology, offers an enriched way to understand how people engage in drug use (Lende 2005).

Neuroanthropology can also be used to examine specific neural mechanisms that play a role in involvement with drugs. Alongside instrumentalization, processes of attention and incentive salience ("wanting drugs") mediate how people use drugs and offer ideas about how individuals move from use to abuse (Lende 2005). Individuals might have an instrumental idea about substance use, for example, using alcohol to relax. However, social dynamics can oblige use irrespective of an individual's goal – the toast at a start of a meal to celebrate coming together. Even with instrumentalization, involvement matters in shaping the actual behavior pattern: say, seeking out alcohol to relax and hence kicking off the start of a family meal with its celebratory toast.

Optimal drug use and rational drug policy

doi:10.1017/S0140525X11000756

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Abstract: The Müller & Schumann (M&S) view of drug use is courageous and compelling, with radical implications for drug policy and research. It implies that most nations prohibit most drugs that could promote happiness, social capital, and economic growth; that most individuals underuse rather than overuse drugs; and that behavioral scientists could use drugs more effectively in generating hypotheses and collaborating empathically.

Bravo to Müller & Schumann (M&S) for their gutsy rethinking of drug use as a normal part of human behavior. Their notion of drug instrumentalization suggests that drug use is a major way that people try to overcome the mismatch between evolved human nature and the peculiar demands of modern society. In this view, our ancestors for millennia had been evolving endogenous psychoactive chemicals such as hormones and neurotransmitters to cope with the behavioral demands of prehistoric life. With the rise of agriculture, cities, divisions of labor, and legal monogamy, human life became more complex and frustrating faster than genetic evolution could track, so people turned to exogenous drugs to cope with civilization's loneliness, monotony, oppression, anxiety, and chronic stress. Eventually, far-future humanoids may genetically engineer their brains to include drug-glands that secrete a much wider array of useful psychoactives on demand, as depicted in the science-fiction "Culture" novels by Iain M. Banks (2010). Until that future utopia, we do the best we can with the few good drugs available at the moment and the flagrantly irrational drug policies that constrain their use.

So far, three approaches have dominated the drug policy debates:

1. Criminal justice model: punitive prohibition, the drug user as criminal, harm elimination, abstinence as the goal, the War on Drugs, zero tolerance, 12-step programs, moral panic (see Reuter 2009);

2. Public health model: decriminalization, the drug user as patient, harm reduction (Sullivan & Wu 2007; Tammi & Hurme 2007), moderation as the goal, cost/benefit analysis, the Vienna Declaration for evidence-based drug policy (Wood et al. 2010);

3. Libertarian model: legalization, the drug user as normal citizen, benefit maximization (Tupper 2008), happiness as the goal, and – to reduce any negative externalities of drug use – a combination of light regulation (Pudney 2010), optimal "sin taxes" (O'Donoghue & Rabin 2006), and libertarian paternalism (Sunstein & Thaler 2003) to promote responsible social norms for drug use.

M&S sympathize with both the public health and the libertarian models. By highlighting the benefits of drugs as used by most people most of the time, they imply that drug policy should try to maximize the benefit/cost ratio of drug use in society. Whereas the criminal justice aimed to eliminate the harm caused by the small proportion of people who use some drugs too much, a benefit-maximization paradigm suggests that most people have not tried enough drugs, do not use enough drugs, and do not manage their drug use as optimally as they might. That is, we are generally underdrugged and misdrugged, not overdrugged.

Many of us are not happy that the three most boring drugs in history – alcohol, nicotine, and caffeine – are the only ones legally available in most of the developed world. M&S offer good reasons that legalizing a much more varied drug-menu could promote not just individual happiness (see Moore 2008; O'Malley & Valverde 2004), but also social capital from drug-induced friendliness and neighborliness. For example, group happiness from collective ecstatic rituals (Haidt et al. 2008) may be promoted by empathogens such as Ecstasy or GHB (Bedi et al. 2010; Dumont et al. 2009). Likewise, educational achievement and economic growth might be promoted by legalizing not just caffeine and nicotine, but a wider array of smart drugs such as Ritalin and Provigil (Husain & Mehta 2011; Repantis et al. 2010; Sahakian & Morein-Zamir 2007). If the social and economic benefits of drug use are real, then nations that legalize more good drugs should attract more investment and skilled workers and should produce more knowledge, wealth, and influence, driving a virtuous cycle of cross-national competition to liberalize drug policies.

Psychoactive drugs may play special roles in the lives of behavioral scientists in generating hypotheses, conducting thought experiments, collaborating sympathetically, and empathizing across ages, sexes, personality traits, mental illnesses, and species. Rumors suggest that some of the best ideas in evolutionary biology and evolutionary psychology since the 1960s were inspired by drug experiences, but researchers rarely credit particular drugs in the acknowledgments sections of their papers. It seems absurd that many psychologists try to understand perception and consciousness without having any personal experience of hallucinogens (Nichols 2004) such as LSD, salvia (Gonzalez et al. 2006), psilocybin (Griffiths et al. 2006), or ayahuasca (Kjellgren et al. 2009). Timothy Leary rightly understood that psychology could learn some important lessons from hallucinogens (Leary 1967; Leary et al. 1963). I do not expect APA accreditation programs to start requiring LSD trips and Ecstasy raves as part of the doctorate psychology curricula any time soon – but it is worth contemplating how such experiences might instill useful insights, epistemic humility, and clinical empathy in young researchers. In any case, tenured researchers could show more guts by coming out of the closet more often about the role of drug experiences in our scientific lives.

A rational drug policy could include the following elements. Citizens have a basic human right to use psychoactive drugs (as argued by the Center for Cognitive Liberty and Ethics) – except when such use imposes a clear and present danger on others, as when driving or being pregnant. Every drug should be legal for adults unless its benefit/cost ratio is demonstrably close to zero. Learning how to use drugs effectively and safely should be an important part of education from adolescence onward, with opportunities for exploring their various subjective effects, domain-specific benefits, and potential risks. Research should prioritize the discovery of new psychoactive drugs that yield new benefits or reduced side effects. Most urgent, scientists positioned to influence research funding – such as those on NIDA panels – should favor grant proposals that study the benefits, and not just the costs, of psychoactive drugs. Given the heartbreaking mismatch between evolved human nature and the demands of modern society, we need all the help we can get from psychoactive drugs that allow us to learn, work, socialize, mate, parent, enjoy life, and study human consciousness more effectively.

Sacramental and spiritual use of hallucinogenic drugs

doi:10.1017/S0140525X11000768

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Abstract: Arguably, the religious use of hallucinogenic drugs stems from a human search of metaphysical insight rather than from a direct need for cognitive, emotional, social, physical, or sexual improvement. Therefore, the sacramental and spiritual intake of hallucinogenic drugs goes so far beyond other biopsychosocial functions that it deserves its own category in the drug instrumentalization list.

Müller & Schumann (M&S) deserve to be hailed for their bravery for addressing the socially sensitive issue of non-addictive psychoactive drug consumption from a scholarly perspective. In discussing drug instrumentalization, M&S list an eight-item classification of the proximate mechanisms of psychoactive drug use. From these items, our commentary concerns the category labeled as "sensory curiosity – expanded perception horizon" (sect. 4.2.6), which includes hallucinogens, entactogenic drugs, dissociative anesthetics, and cannabis. Although hallucinogenic drugs are generally associated with changes in perception and cognition, we challenge the idea that these drugs would be consumed primarily for their sensory perception–changing properties. Within hallucinogenic drugs, we leave aside dissociatives and deliriants and focus on the third subclass: the so-called psychedelics. From a neuropharmacological point of view, this subclass includes serotonergic psychoactive phenethylamines and tryptamines, such as mescaline, psilocybin, LSD, and DMT. However, by using the term "psychedelic" in its original meaning (i.e., "mind-manifesting"), we could also include other drugs with different neuropharmacological mechanisms but similar use purposes, such as *Salvia divinorum*. In this commentary, we argue that in the particular case of sacramental and spiritual drug intake, the purpose of psychedelic drug use goes so far beyond sensory perception that it deserves its own category in the drug instrumentalization list.

Unlike the other listed drug instruments, hallucinogens can induce unique kinds of subjective experiences with a rich phenomenology, which, from the experiencer's point of view, may have much deeper functions than merely gaining insight by restructuring prior knowledge. These experiences include increased apperception, dissolution of ego boundaries, feelings of unity and insight, presence of or encounters with nonhuman entities or beings, and, generally, perceiving all of these as independent from one's own mind. In culturally predefined contexts, the purpose of these hallucinatory experiences is not merely to increase self-understanding and self-discovery, but also to address ultimate questions that shape or shake the fundamental worldview. We argue that for humans, gaining such metaphysical insight can be a major motivating factor in seeking these extraordinary hallucinatory experiences. In religious or spiritual sets and settings, psychedelic drugs that are used for sacramental

purposes could be more properly termed as "entheogens," translatable into "becoming divine within" (Ruck et al. 1979).

In support of our view, a vast amount of archeological evidence and historical documentation suggests that hallucinogenic psychoactive drugs have been used for ritual and ceremonial purposes around the world and across the ages (Roberts 2001). Traces of ritualistic hallucinogen use were found in many belief systems in ancient cults and cultures: The sacred *Soma* drink is mentioned in the Indian Vedas, *Teonanácatl* (literally, "divine mushroom"), morning glory seeds were consumed in Meso-American cultures, the ancient Greek Eleusinian mysteries used the enigmatic *Kykeon* drink, Siberian shamans became inebriated with the fly agaric mushroom (*Amanita muscaria*), and so on (Schultes & Hofmann 1979). There are also numerous examples of contemporary sacramental drug use, such as the Native American Church using *peyote* cacti legally, and several *ayahuasca*-based religious groups spreading out from South America. It is even hypothesized that the common root of many ancient religions could be found in Paleolithic supernatural and animistic beliefs that were perhaps based on hallucinogen-induced thoughts and visions of shamanic practices (La Barre 1979).

Arguably, the use of psychedelics would be indeed difficult to link with direct physical, emotional, social, or sexual advantages leading to evolutionary benefits. Rather, these drugs are generally associated with the perceptual, cognitive, stress-coping, and self-medication dimensions that may only indirectly advance survival and/or reproduction. Nevertheless, several hypotheses exist in the literature on how exceptional human experiences – hallucinogenic alterations of mind in particular, but other altered states of consciousness as well – may increase the fitness of the individual. Findings in cultural anthropology support the idea of psychedelics being used as "problem-solving devices" (Baker 1994), or as "psychointegrator plants" (Winkelman 1995). Resembling the Threat Simulation Theory (Revonsuo 2000), which argues for a virtual training function of dreaming, a similar "training situation" hypothesis could be suggested to hold also for psychedelics: Deliberately provoked hallucinogenic experiences may increase self-knowledge by rehearsing and developing coping strategies that might be utilized later in life. Along with these theories and hypotheses for the instrumentalization of hallucinatory phenomena and hallucinogenic drugs, M&S seem to offer only cognitive explanations, such as "coincident activation of previously unrelated representations that are then interlinked" (sect. 4.2.6, para.2). Instead, we argue that cognitive and psychosocial explanations for hallucinatory phenomena are likely to cloud more appealing causes, which seem to be deeply embedded in human culture: sacramental (when a psychedelic drug itself is treated as a part of a religious rite) and spiritual (when psychedelic experiences, rather than a drug itself, form or lead to transcendent experiences) purposes.

Besides admittedly serving sociocultural functions as well, the ritual and ceremonial use of hallucinogenic drugs seems to originate from a separate "higher" need for mystical experiences full of significance and importance. This view is supported by concepts in humanistic psychology, such as Maslow's theory of human motivation with the later added transpersonal level in the hierarchy, relating to self-transcendence and peak experiences (Maslow 1969). As the above examples show, hallucinogenic drugs are used as specific drug instruments for a very particular form of human enhancement: experience of transcendence. Thus, hallucinogenic drug instruments may be used for purposes that exceed biological, psychological, or social explanations, and the very human-specific thriving on these forms of use deserves to be addressed in its own drug instrumentalization category. While discussing medical issues, the benefit of adding a fourth spiritual level into the biopsychosocial model of human functioning has been suggested recently (Bishop 2009). In our opinion, an extended multilevel biopsychosocio-spiritual framework could also explain more comprehensively the functions of non-addictive psychoactive drug use.

The instrumental rationality of addiction

doi:10.1017/S0140525X1100077X

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Abstract: The claim that non-addictive drug use is instrumental must be distinguished from the claim that its desired ends are evolutionarily adaptive or easy to comprehend. Use can be instrumental without being adaptive or comprehensible. This clarification, together with additional data, suggests that Müller & Schumann's (M&S's) instrumental framework may explain addictive, as well as non-addictive consumption.

"Drugs are bad." "Addiction is a disease." These claims can polarize popular thinking about drug consumption and tacitly influence research. Against this background, Müller & Schumann's (M&S's) proposal should be welcomed for its good sense. Most drug use never meets diagnostic criteria for addiction. M&S offer an instrumental framework underpinned by an information-processing model for explaining non-addictive consumption. They argue that drugs alter mental states – a fact that once learnt can be instrumentalized. Given that altered mental states may help to achieve desired ends, drugs can be purposively consumed because they are reliable means to those ends. M&S suggest eight ends served by consumption: (1) improved social interaction; (2) facilitated sexual behaviour; (3) improved cognitive performance; (4) coping with stress; (5) alleviating psychiatric symptoms; (6) novel perceptual and sensory experiences; (7) hedonia or euphoria; and (8) improved physical and sexual appearance. Finally, M&S argue that non-addictive drug consumption is both an adaptation and adaptive in modern society. Despite the risk of consumption becoming addictive and so plausibly maladaptive, non-addictive drug use potentially enhances survival and reproduction in virtue of its instrumental effects.

It is crucial to distinguish three claims. First, that non-addictive drug use is instrumental; second, that it is evolutionarily adaptive; and third, that its desired ends are easy to comprehend. Use can be instrumental without being adaptive or even easily comprehensible. The philosopher G. E. M. Anscombe (1957) famously wondered whether we can ever make sense of someone wanting a saucer of mud. Wanting a saucer of mud is unlikely to be adaptive. Without further explanation, it is not easy to comprehend. But if a saucer of mud is what you want, you display instrumental rationality if you mix dirt with water and dump it in a saucer: That behaviour is an instrumental means to the desired end.

Facilitated sexual behaviour may strike us as evidently adaptive. The adaptive case for hedonia may prove to be harder to establish. But evolutionary considerations aside, all of the ends M&S identify are intelligible human goods: sex, social interaction, cognitive capacity, new experiences, pleasure, and relief from stress and distressing symptoms. On the whole, it is natural for people to use available means, including drugs, to achieve these ends. Moreover, as with all instrumentally learned behaviour, we should expect there to be an account of the information-processing, learning, and memory underpinning it. Hence, the heart of M&S's framework boils down to this: non-addicts consume drugs for good reasons, that is, in order to achieve desired ends that are intelligible human goods, and, given this, we need an information-processing account of how knowledge of the effects of drugs is acquired, stored, and used to drive context- and end-specific consuming behaviour. This is indeed good sense. But we should wonder why research on drug consumption is such that it needs to be said.

Aside from the polarization of popular thinking, one likely reason is that much research on drug consumption focuses on addiction: where use seems maladaptive, and where it is hard to

comprehend how anyone could desire such ends. Alongside tolerance and withdrawal, diagnostic criteria for addiction include increasing focus on use at the expense of other goods, continued use despite desire for control and efforts to achieve it, and use-consequent physical and psychological harm (APA 2000). M&S suggest that their framework may help to develop clinical interventions that reduce the likelihood of instrumental use becoming addictive, by suggesting the need for education, identification of high-risk individuals, and understanding of an individual's pattern of instrumentalization so that alternative means to the ends served by drugs can be learned. These clinical interventions are already routine (Petersen & Mcbride 2002). The bolder question that M&S's framework invites, but which they do not pursue, is whether addictive consumption is also instrumental behaviour. It may not be adaptive, and it may seem from the outside no more comprehensible than wanting a saucer of mud, but it may yet be an instrumental means to desired ends.

To deflect this question, M&S gesture at research showing that as use escalates, control devolves from the prefrontal cortex to the striatum, in line with a shift from action-outcome to stimulus-response learning (Everitt & Robbins 2005). In rats, drug use that is initially goal-directed and sensitive to devaluation of outcome becomes increasingly habitual: triggered automatically and insensitive to mild devaluation. But, in humans, behaviourally complicated and temporally extended habits that have developed out of action-outcome learning are typically still subject to some executive control, through the formation of decisions and the exercise of will. Habits make control hard, but they do not extinguish it.

As Heyman (2009) emphasises, large-scale survey data suggest that addiction peaks in adolescence and early adulthood but, in the majority of cases, has resolved permanently, without clinical intervention, by the early thirties (Anthony & Helzer 1991; Kessler et al. 2005a; 2005b; Stinson et al. 2005; Warner et al. 1995). Addicts tend to "mature out." The exceptions are addicts who suffer from additional psychiatric disorders: Chronic, relapsing addiction is associated with psychiatric comorbidity (Regier et al. 1990). These data, in combination with M&S's good sense, suggest a reason for thinking that even the worst cases of addiction are instrumental. Such drug consumption is a habitual means to desired ends (4) and (5), namely, coping with high levels of stress and alleviating psychiatric symptoms (Pickard & Pearce, forthcoming/anticipated 2012). Until these underlying problems are addressed and/or alternative but equally effective means of achieving these ends secured, addicts may have little incentive to resolve to control their drug habit, despite consequent harm. M&S are plainly right that non-addictive use is instrumental. The harder question is whether addiction is as well.

Drug addiction finds its own niche

doi:10.1017/S0140525X11000781

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Abstract: The evolutionary framework suggested by Müller & Schumann (M&S) can be extended further by considering drug-taking in terms of Niche Construction Theory (NCT). It is suggested here that genetic and environmental components of addiction are modified by cultural acceptance of the advantages of non-addicted drug taking and the legitimate supply of performance-enhancing drugs. This may then reduce the prevalence of addiction.

The article by Muller & Schumann (M&S) is both relevant and timely, given recent debates around the use of so-called smart drugs to boost cognitive performance and what the role of the medical profession should be in prescribing drugs such as methylphenidate and modafanil for this purpose.

My main comments relate to the evolutionary aspects of the article and the relationship between drug use and drug addiction. The following comments will help to strengthen the link between drug use and addiction within the framework that M&S outline. This is important because drug addiction is a significant problem in terms of morbidity and mortality – and also because, in a non-trivial sense, drug addiction is what makes drugs interesting. It also needs to be remembered that all drug-taking is harmful or problematic at the level of society and that a significant component of this social harm arises from the high criminality around the production and supply of drugs.

Although M&S briefly acknowledge that the existence of modern drugs may represent a new evolutionary niche, I think this point should be expanded, with particular reference to the cultural aspects of drug taking. Niche Construction Theory (NCT) (Kendal et al. 2011) states that changes in the environment are functions of both the organism and the environment and also that changes in the organism are (different) functions of the organism and the environment.

According to NCT, the influence of the organism – humankind in this case – on the environment has led to the construction of a niche where modern drugs and drug-culture are part of the environment. This is an important note; drugs can then be seen as part of the fitness landscape over which selection pressures operate and for which adaptive advantage is gained. In this context, the process of taking drugs constitutes the interaction between the organism and the environment, and through natural selection those organisms that are "better" at taking drugs will survive. This accords with M&S's suggestions for a number of adaptive advantages that accrue from taking drugs.

There are two important consequences of this scenario. One is that social influences on drug taking will be very strong; for example, a drug-culture will exist. This will be an important part of the process of niche construction – according to NCT, the organism and its genetic determinants will have an effect on changes in the environment. The second consequence is that the trait of "drug liking" will have a strong role to play, and this helps to make more explicit the link between drug taking and addiction. To be specific, if adaptive advantage accrues through drug taking and natural selection will favour those who use drugs, then the trait of drug-liking and its genetic underpinning will be promoted. Any predisposition for liking drugs will be perpetuated. A by-product of this will be the perpetuation of addiction in those who have a strong liking for drugs but are unable to cope with the consequences of drug use. A possible pharmacological mechanism for this is a reduction in the number of postsynaptic dopamine D_2 receptors, which is seen in those who have a stronger liking for drugs and also in those who have been addicted to various substances including alcohol, cocaine, and heroin (Lingford-Hughes et al. 2010).

We may then suggest that addiction is a gene × environment problem – there is both a cultural influence and a genetic predisposition – in other words, that it is a problem of the niche. In order to reduce the persistence of addiction, the niche needs to continue to develop or a new niche needs to be constructed. One possibility here may be the cultural acknowledgement and acceptance of the proximal mechanisms of psychoactive drug use that M&S outline and the advantages these give. If this were the case, a new niche, or further development of the current niche, by the legitimate manufacture and administration of performance-enhancing, but relatively safe, drugs, such as methylphenidate, MDMA, modafanil, or even ketamine, may allow for an alteration in drug culture such that drug-liking and its genetic underpinning is no longer necessary to drive the selection process.

In other words, drug-taking is much less driven by drug-liking. This may then allow for the diminution in representation of these genes in the population and an alteration in the cultural environment of drug-taking. Both the genetic and environmental

underpinnings of addiction will be modified, and a reduction in the prevalence of addiction may occur. One issue with this suggestion is the time frame over which this might happen. Although operations on both the genetic expression and the cultural environment itself may massively speed up the change in phenotype – that is, addictive behaviour – it may still be a very slow process. Mathematical modelling may help in verifying the validity of this hypothesis.

Why do we take drugs? From the drug-reinforcement theory to a novel concept of drug instrumentalization

doi:10.1017/S0140525X11000847

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Abstract: The drug-reinforcement theory explains why humans get engaged in drug taking behavior. This theory posits that drugs of abuse serve as biological rewards by activating the reinforcement system. Although from a psychological and neurobiological perspective this theory is extremely helpful, it does not tell us about the drug-taking motives and motivation of an individual. The definition of drug instrumentalization goals will improve our understanding of individual drug-taking profiles.

Can one imagine how Yemenis would feel without having a daily khat chewing (80% of Yemenis chew khat containing the alkaloid called cathinone, an amphetamine-like stimulant)? Can one imagine how a Dutch person would feel without having her caffeine in the morning (90% of the Dutch drink coffee)? Can one imagine how a French person would feel without having a glass of wine along with his meal? I could go on with numerous examples of accepted drug-taking behaviors, most of them deeply, culturally embedded into our societies. Pondering these examples, one might easily realize the more philosophical question: Why do we take drugs? Roy Wise and other neuroscientists have formulated the drug reinforcement theory (Wise & Rompre 1989). This theory posits that all drugs of abuse activate the brain reinforcement system and thereby act as biological rewards. This drug-induced reinforcement process increases the rate or probability of further drug-taking behavior. The drug-reinforcement theory is extremely helpful for understanding the biological substrates of a drug-taking behavior in general (Sanchis-Segura & Spanagel 2006), but does not explain why person A likes to drink coffee in the morning and several glasses of beer when coming home from work, whereas person B might smoke a cigarette after each meal but not consume any other drug.

Müller & Schumann (M&S) have attempted to construct a new psychological/neurobiological framework – namely, drug instrumentalization – to provide an answer for individual non-addictive psychoactive drug use. Drug instrumentalization is a learned behavior designed to change the mental state and thereby improve the current quality of life by taking a psychoactive drug. M&S define an extensive list of drug instrumentalization goals, such as improved social interaction, the feeling of well-being, and many others. The definition and validation of drug instrumentalization goals will help to understand individual drug-taking profiles, which may change over the life course of an individual. However, at least three important drug instrumentalization goals are missing in M&S's target article:

1. **Positive taste perception:** Sometimes a self-reflection is very helpful. For example, without disclosing my lifetime drug-taking profile in full detail, at present I have a big cup of tea in the morning, drink different alcoholic beverages regularly in the evenings, and smoke a cigarette from time to time. Why do I consume these three different drugs on a regular basis? The first reason that comes to my mind is that I enjoy the taste. Although there are no systematic population-based studies on whether positive taste perception can be considered as a drug instrumentalization goal, there are millions of coffee/tea shops around the world, millions of wine-tasting sessions, and cigarette advertisements have historically focused on the pleasing taste of tobacco. Positive taste perception as an instrumentalization goal may be limited to alcoholic beverages, coffee/tea, and tobacco, but these are the primary semi-luxury consumables on which money is spent. Positive taste perception may also play a role in betel nut and Khat drug chewing and to a certain extent even cannabis smoking.

2. **Adaptation to peer pressure:** Very commonly, we consume drugs as a result of peer pressure. Especially during adolescence, peer pressure is an intense motivator and might even be the most important driving force behind taking drugs at a younger age (Borsari & Carey 2001; Faggiano et al. 2008). Only by taking the drug does one adapt to this peer pressure and become rewarded as being a member of a particular group.

3. **Cultural and religious rituals:** Cultural and religious traditions can be considered drug instrumentalization goals. Many indigenous populations still consume drugs only in ritual settings; for example, Voodoo is a religion that originates in Haiti and involves a zombie creation ritual where a number of psychoactive compounds, such as tetrodotoxin, are ingested and lead to the mental and physical experience of a death-like state (Davis et al. 1983). However, Western societies also have several cultural rituals, such as champagne drinking on New Year's Eve. The purposes of these cultural and religious rituals can be diverse, but most of them are used to intensify spiritual beliefs or group affiliations.

It will be critical for the drug instrumentalization theory to provide a full list of goals that have to be integrated into a questionnaire for future validation in different ethnicities. I am really looking forward to a well-developed and validated questionnaire that will allow M&S to rigorously test their fascinating new theory!

Despite my great enthusiasm for this well-conceived novel theory that, in fact, does provide a new framework on non-addictive psychoactive drug use, I have to note one important point of criticism. M&S mention the use of methamphetamine to enhance daily performance as a drug instrumentalization goal (Lende et al. 2007). From my perspective, this is not a true instrumentalization goal as acute methamphetamine use carries immediate drawbacks and causes harm to the individual and its environment. In this context, it is important to recall a recent case of Tik (methamphetamine) use in Cape Town, South Africa, where a mother killed her own son because she could not endure his methamphetamine-induced personality changes (Maroldt 2011). By no means is there a beneficial effect of methamphetamine on overall functioning, as stated in the paper by Lende et al. (2007), to which M&S refer. Methamphetamine or crack smoking is too dangerous and too addictive, and the boundaries between a controlled drug-taking behavior and a highly compulsive one can vanish within hours.

But is it evolution. . .?

doi:10.1017/S0140525X11000823

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Abstract: We applaud Müller & Schumann (M&S) for bringing needed attention to the problem of motivation for common non-addictive drug

use, as opposed to the usual focus on exotic drugs and addiction. Unfortunately, their target article has many underdeveloped and sometimes contradictory ideas. Here, we will focus on three key issues.

First, it is unclear that Müller & Schumann's (M&S's) model of drug instrumentalization is necessarily an evolutionary argument. In their rationale for drug use as an adaptation, M&S state that "non-addictive psychoactive drug instrumentalization helps to solve an adaptational problem, employing species-general learning mechanisms that dynamically adapt the search for and consumption of plants and plant compounds" (sect. 4.1, para. 4). However, a domain-general cognitive model, which is what M&S are invoking here, does not require an evolutionary argument for a specific suite of behaviors like drug use – such a mechanism can putatively "solve" contextual problems based on trial-and-error learning. Note that similar arguments supported by empirical data have been made for functional situational exploitation of psychoactive drugs, without invoking adaptationist theory (e.g., Sahakian & Morein-Zamir 2007).

Other aspects of M&S's adaptationist hypothesis strike us as implausible. Psychoactive drugs have their effects because they alter neural signaling, often by mimicking neurotransmitters such as acetylcholine or dopamine, or by interfering with their metabolism or reuptake. Consider two evolutionary scenarios: (1) the evolution of a complex neurobiological mechanism to manipulate the central nervous system via untargeted systemic administration of environmental neurotoxins, which then accurately evaluates the social consequences of the resulting behavioral consequences, as M&S propose; or (2) the evolution of pathways to directly modulate endogenous neurotransmitter signaling systems in the CNS in response to social cues in the environment. We find (2) more plausible because it provides the same benefits as (1) but avoids its manifold costs.

To be clear, we believe that there might be adaptations to manipulate one's own CNS with plant neurotoxins, but only in circumstances, such as mental illness or nutritional deficiency, in which the brain would be unable to adequately modulate endogenous neurotransmitter signaling (Sullivan & Hagen 2002). We and others have also argued that plant neurotoxins could provide non-cognitive benefits, such as combating rapidly co-evolving pathogens (Hagen et al. 2009; Sorensen-Forbey et al. 2009; Sullivan et al. 2008).

Second, M&S have proposed a range of *new* or novel adaptive behaviors associated with drug use without considering how they might negatively affect *existing* cognitive mechanisms. For example, M&S propose that people may use drugs for "improved social interaction" (sect. 4.2.1). Primates are characteristically "social" and can be assumed to have cognitive adaptations to facilitate sociality and attention. One must assume that natural selection has "shaped" those adaptations to perform well on average. Any drug that affects the nervous system is also going to interfere with the existing primate mechanisms for sociality. How do we, or M&S, know that this interfering with the primate nervous system is going to improve or impair the existing mechanisms for sociality? M&S seem to have given this little thought, and their account is somewhat naïve in that no reference is made to the possibility of drugs causing impairment in social cognition. After all, there is overwhelming evidence that drugs such as alcohol interfere with other cognitive mechanisms, such as those involved with motor control.

M&S reiterate this theme in their proposal that drug use increases sensory curiosity and expands perceptual horizon. Given that all mammals have evolved senses, perception, and attention to survive and reproduce in their various environments, how is interfering with these existing mechanisms an adaptation? M&S do not address the possibility of impairing existing sensory adaptations. Again, their accounts seem somewhat hopeful at best.

Third, we disagree with M&S's characterization of our notion of "the paradox of drug reward." Our idea is that there is a conflict between the evolutionary biological view that plant toxins evolved to *deter* animal herbivores, and current proximate neurobiological models that argue that commonly used drugs (which are also plant toxins or their close chemical analogs) are *rewarding* in animal nervous systems. M&S propose that the "'paradox of drug reward' may be resolved at the dose-response level: In a low- to medium-dose range, the drug effect is not toxic in the sense of being an immediate threat to life. In the range of medium to low doses, therefore, a role for drugs in functional adaptation can reasonably be considered" (sect. 2, para. 2). We do not disagree with the latter part of M&S's statement, at least, but we are unclear what it has to do with the paradox. M&S seem to be saying that the "goal" of the toxin-bearing plant is to kill the herbivore, whereas functional benefits may occur at the sub-lethal dosage. Here M&S appear to have made the Spencerian "survival of the fittest" error with the presumption that evolution requires lethal selection. In reality, chemical defenses in plants are more likely to interfere with herbivore feeding and reproduction, not to kill them, and the dosage that will achieve this is different for insects and mammal herbivores in their respective ecological niches. The possible range of chemical defense dosages from wild plants indeed allows the possibility of functional benefits for invertebrates and vertebrates, as we have previously argued and outlined in great detail in the papers that M&S cite.

Finally, M&S include a section on the implications of their model for drug policy (sect. 7). In our view, M&S's ideas need development, and it is premature to make policy recommendations.

Flaws of drug instrumentalization

doi:10.1017/S0140525X11000732

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Abstract: The adaptive use of drugs, or "drug instrumentalization," is presented as a reality that the scientific literature has largely ignored. In this commentary, we demonstrate why this concept has limited value from the standpoint of nosology, why it should not be viewed as "adaptive," and why it has dangerous implications for policy and public health efforts.

In their target article, Müller and Schumann (M&S) propose a "new neurobiological framework" for non-addictive drug use whereby people use psychoactive drugs to better perform specific behaviors that are relevant for their own "fitness." This concept, referred to as *drug instrumentalization*, is viewed as adaptive; and M&S present it as a reality that the scientific literature and policy makers have largely ignored because of their fears of promoting addiction. The vast majority of M&S's article is composed of a review of the literature of already well-documented facts. Unfortunately, M&S accord very little effort in: (1) defending the validity of this concept as a stable difference between "adaptive" drug users and those who develop addiction; and (2) demonstrating the benefits of promoting "successful" drug instrumentalization among potential or actual drug users. It is these two points alone that constitute the novel contributions of this target article. We contest both points based on the arguments presented below.

Drug instrumentalization: An unrecognized and "adaptive" class of drug users? Drug instrumentalization is a state phenomenon that refers to *momentary reasons* for using a drug. It is not indicative of the problems that the individual may or may not have relative to drug use and therefore cannot be used to separate "adaptive" from "non-adaptive" substance users. For example, even an individual with severe alcohol dependence may have a

drink just before giving an important presentation at work to calm severe anxiety; an individual with cocaine dependence may use this drug to acquire the necessary energy to complete an important task. Drug instrumentalization exists across all stages of drug use, abuse, and dependence and therefore has no intrinsic value in characterizing a distinct class of drug users.

A second error concerns the use of the term "adaptive," which has been used almost as a synonym of drug instrumentalization. There are numerous momentary reasons for drug use that promote the attainment of specific goals, but by no means do these elements justify the label "adaptive" (even among non-dependent individuals). To use M&S's own example, alcohol may be used to increase extroversion and therefore improve the likelihood of contact with the opposite sex. Extroversion may be increased, but what about the increased probability of aggression, sexual assault, or at-risk sexual behaviors? In addition to momentary negative consequences, the non-adaptive nature of drug instrumentalization should also be visible in the long term. Through such instrumentalization and based on the same learning and memory mechanisms that M&S cite, would it not be reasonable to assume the individual would increasingly rely on alcohol as a social vehicle, as well as to become increasingly inhibited with the opposite sex in alcohol-free contexts?

Our conclusion is that drug instrumentalization is not useful for a classification of drug users, and it is certainly not windicative of adaptive behavior.

Can we (and should we) promote "successful drug instrumentalization"? The take-home message of the target article is that drug use is not necessarily problematic in itself and may even be useful for a large segment of the population. A logical consequence of embracing such a viewpoint would be the normalization of drug use or even its encouragement. Although it may be true that increasing the acceptability (and hence availability) of substances may not change the *relative* proportion of persons who develop addiction among users, it would almost certainly increase the *absolute* prevalence of addiction because it would increase the base prevalence of use.

Moreover, M&S pay little attention to the very extensive literature documenting diverse biological (e.g., Crabbe 2002; Goldman et al. 2005; Koob & Le Moal 2006), psychological (e.g., Belin et al. 2008; Caspi et al. 1997; Piazza et al. 1989), and environmental (e.g., Grant et al. 2004; Swendsen et al. 2009) vulnerabilities to addiction. These risk factors explain why a large portion of regular drug users will develop harmful use behaviors or addiction (Swendsen & Le Moal 2011). The authors insist that this percentage is small, probably because they refer to epidemiologic estimates of addiction among individuals who have ever used drugs. However, these lifetime estimates are largely influenced by single-episode experimentation, and they are by no means comparable to rates of addiction among regular or frequent drug users (i.e., the very population conceptualized as drug "instrumentalizers"). For example, although "only" 40% of individuals who have ever smoked will develop nicotine dependence (Dierker et al. 2008), the majority of individuals who smoke at least once a week will indeed become dependent. It would be a similar error to believe that most individuals can use heroin, cocaine, or methamphetamine frequently in their daily lives with purely adaptive results and without high rates of addiction.

Finally, there is a flagrant contradiction in the propositions that M&S make for the promotion of "successful" drug instrumentalization. Whether for drug-naïve individuals or for regular drug users, M&S insist on the need for providing education and help in the *control* of drug use. Why would this be necessary? The response is obvious: The pharmacological qualities of addictive drugs have the capacity to transform drug users, whatever the reason or nature of instrumentalization, into drug addicts. M&S's tacit recognition of this point is in stark contrast to their far bolder message that addictive drug use can have a safe, prolonged, and "adaptive" place in the everyday lives of large sections of the population. It would be a serious mistake to accept this latter framework over the former reality. The price to pay for society in helping individuals find other ways to function other than by using drugs cannot be compared to the price that would be paid by conceptualizing drug use as being a normal and adaptive part of daily life.

In summary, we have argued for why the concept of drug instrumentalization has limited value from the standpoint of nosology, for why it should not be universally viewed as "adaptive," and for why it has dangerous implications for drug policy and public health efforts.

Psychoactive drug use: Expand the scope of outcome assessment

doi:10.1017/S0140525X11000793

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Abstract: The "hijacking" and "drug instrumentalization" models of psychoactive drug use predict opposite outcomes in terms of adaptive behavior and fitness benefits. Which is the range of applicability of each model? To answer this question, we need more data than those reported by studies focusing on medical, psychiatric, and legal problems in addicted users. An evolutionary analysis requires a much wider focus.

An evolutionary analysis of psychoactive drug use needs to focus on the relationship between mental state and adaptive behavior. To analyze the complexity of such a relationship, it may be useful to classify mental states and behaviors into dichotomous categories: positive and negative. Pleasurable mental states and adaptive behaviors fall into the positive category; aversive mental states and maladaptive behaviors fall into the negative category.

Applying such a classification, there are four possible combinations (Table 1). Three of these combinations (#1, 3, 4) were common throughout our evolutionary history and are easily explained by the adaptive functions of emotions. Emotions have evolved to provide information about costs and benefits of past, present, and future behavior. The capacity to experience mental pleasure and mental pain helped the individual to pursue goals relevant to biological adaptation and to avoid maladaptive situations (Nesse 1990).

Combination # 1 reflects the strict association between mental pleasure and adaptive behavior. The neuroscientist Jaak Panksepp (1998) has succinctly expressed this concept with these words: "Pleasure is nature's way of telling the brain that it is experiencing stimuli that are useful." Under natural conditions, brain reward systems were activated when (and only when) the individual was pursuing or achieving a goal relevant to biological adaptation. Conversely, under minimally adaptive circumstances, an individual experienced mental suffering (e.g., anxiety and depression) that functioned in part as a warning system that

Table 1 (Troisi). *Possible combinations of mental states and adaptive behaviors*

# 1. Mental pleasure/Adaptive behavior	# 2. Mental pleasure/ Maladaptive behavior
# 3. Mental pain/Adaptive behavior	# 4. Mental pain/Maladaptive behavior

one's goal-seeking efforts were failing (combination #4) and in part as a motivational drive activating counter-strategies that were likely to redirect toward the achievement of adaptive goals (combination #3 as a transient state preceding return to combination #1) (McGuire & Troisi 1998). Finally, the experience of a pleasurable mental state in absence of potential or actual fitness benefits (combination #2) was extremely rare if not impossible under natural conditions.

Psychoactive drug use substantially modifies the relationship between mental state and adaptive behavior. Each of the four possible combinations needs to be reanalyzed from a different perspective. Nesse and Berridge (1997) first described combination #2 in their "hijacking" hypothesis of psychoactive drug use. The hijacking hypothesis suggests that a key factor causing the maladaptive consequences of psychoactive drug use is the inhibition of the incentive systems that normally motivate the individual to explore and investigate the social environment in order to get natural rewards. Through the availability of drugs, the individual no longer needs to vigorously pursue courses of action to experience the entire range of positive emotions that may derive, for example, from the establishment of intimate relationships or the achievement of competitive success (Troisi 2001). Müller & Schumann (M&S) propose an alternative evolutionary model. Psychoactive drugs can be consumed in order to change the present mental state into a previously learned mental state, which then allows for better performance of other, previously established behaviors and better goal achievement. M&S apply their model to situations that include both combination #1 (e.g., enhancing pleasure during sexual behavior) and #3 (e.g., self-medication for mental distress facilitating transition to combination #1). Combination #4 is not contemplated by either evolutionary or conventional models: No one takes drugs to self-induce aversive mental states.

The hijacking and drug instrumentalization models predict opposite outcomes in terms of adaptive behavior and fitness benefits. This does not necessarily mean that the two models are incompatible. They could apply to different situations involving individuals with different neurobiological profiles and personality traits. Yet, the question remains: Which is the range of applicability of each model? M&S make a sharp distinction between non-addicted and addicted users and apply the hijacking model to the latter group only. Because the prevalence of addiction is relatively low, drug instrumentalization would apply to the majority of cases of psychoactive drug use. Such a conclusion is premature for two different reasons.

First, we do not have reliable data on the impact of psychoactive drug use on adaptive behavior. Most studies assessing the harmful potential of drug use limit their analysis to medical, psychiatric, and legal problems in addicted users. An evolutionary analysis requires a much wider focus. For example, the use of social network software is increasing sharply. In the next few decades, virtual reality is likely to progress to the point that users will be able to interact with virtual partners through the concomitant stimulation of all sensorial channels. In terms of medical and legal risks, virtual reality is a "clean" instrument for manipulating mental state. However, its potential capacity of alienating the individual from the natural sources of satisfaction and joy in the real world could have a major disrupting impact on social functioning.

Second, the use of psychoactive drugs to alleviate aversive mental states may have maladaptive consequences. Not all mental symptoms are the same: Many manifestations of psychological distress are sophisticated adaptations, and their suppression (the so-called symptomatic or palliative therapy) may lead to unfavorable outcomes (blocking the transition from combination #3 to combination #1.) For example, prospective studies (e.g., Mellman et al. 2002) have shown that there may be an increased incidence of post-traumatic stress disorder in individuals treated with anxiolytics immediately after exposure to trauma. The deleterious effects of acute phase treatments are likely to be caused by their interference with the acute stress response, a set of physiological and psychological mechanisms that evolved to cope with traumatic events in the natural environment. In healthy volunteers, exposure to antidepressants increases the recognition of positive face emotions and decreases recognition of negative emotions (Harmer 2010). When given to individuals who are showing a physiological response to adverse circumstances, might antidepressants interfere with a correct reading of social interactions in everyday life?

If the impact of psychoactive drug use on adaptive behavior is a relevant issue (and probably it is not for most drug users and mental health practitioners), future studies inspired by evolutionary models should expand the scope of outcome assessment.

Drugs, mental instruments, and self-control

doi:10.1017/S0140525X1100080X

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Abstract: The instrumental model offered by Müller & Schumann (M&S) is broadened to apply not only to drugs, but also to other methods of self-control, including the use of mental constructs to produce adaptive changes in behavior with the possibility of synergistic interactions between various instruments.

On the plausible assumption that the mind is instantiated in the physical structures and processes of the brain, mental changes can be realized only through physical alterations of the brain. Even if one takes into account embodied cognition and the extended mind hypothesis (Clark 1997), the brain remains the core substrate of the mental; and any ability to control or modify the mental must rely on the capacity to physically alter the brain. This is no less true from the first-person, internal perspective than from the external, third-person point of view. However, the nature of the causal interface can vary enormously. An equivalent change in mind or behavior might be produced by a conscious act of will, an environment of conditioning reinforcers, or a therapeutic drug. Despite the similarity of result, the practical means by which the change is produced and the nature of the causal affordance on which that change relies may differ greatly. It is therefore important to get clear about the range of possible processes, as well as the ways in which multiple mechanisms might interact.

In that regard, the theory of Müller & Schumann (M&S) can be quite helpful. M&S propose that we view at least some nonaddictive drug use from an instrumental perspective – that is, that we view drugs as instruments that enable the user to produce adaptive changes in mind and behavior by altering relevant underlying brain states. This perspective seems apt not only for many cases of drug use, but also for a far wider range of processes by which we control our minds and behaviors, including many cases that involve mental constructs. Ideas and patterns of thought, like drugs, can be usefully viewed as instruments by which we exercise adaptive control over our minds and behaviors. Moreover, there are probably many instances in which various instruments, including drugs and ideas, synergistically combine in mutually supporting ways.

Consider a representative example. M&S note that alcohol use can facilitate social interaction and reduce social anxiety, which can have obvious utility and perhaps even enhance sexual and reproductive success. Alcohol has the relevant effects in part through its direct and indirect actions on $GABA_A$ and dopamine receptor systems. Hence, nonabusing alcohol users may well

learn to use alcohol as an instrument in social interactions; and in doing so, they are also learning to use alcohol to modulate the relevant receptor systems, even though they typically have no conscious knowledge of those systems.

One might also decrease social anxiety through mental constructs or environmental manipulations. For example, one might use relaxation techniques or positive mental imagery to reduce social anxiety. Alternatively, one could try to reshape one's responses to social settings by exposing oneself to a carefully selected sequence of social environments whose initial members were nonthreatening and provided a lot of positive reinforcement. In each case, the relevant means serves in an instrumental way as a lever by which the person can change the underlying physical bases of her emotional and behavioral responses to social interactions. As with the use of drugs, the person need have no knowledge of the underlying physical bases in the brain through which the relevant instruments produce their effects.

Moreover, one could combine the instrumental use of drugs such as alcohol with the use of other instruments of change. The overall effect might be interactive rather than merely additive. For example, one could use alcohol to help produce positively reinforcing outcomes in selected social environments and then subsequently use conditioned associations with specific features related to alcohol consumption in those contexts to enhance the future anxiety reducing effect of alcohol. The successful outcomes produced by alcohol might also provide experiences that could be used as positive imagery or even to rationally persuade oneself to be less fearful of social situations. The non-addictive consumption of alcohol might thus be used in a dynamic mutual interplay with mental and environmental instruments where each enhances the overall adaptive value of the other.

The instrumental use of psychoactive lifestyle drugs M&S describe is similar in these respects to the use of psychotherapeutic drugs, especially with regard to the possibilities for positive interactions with other means of instrumental control. Consider, for example, the utility of combining drug therapy typically involving SSRIs with cognitive behavioral therapy in the treatment of obsessive compulsive disorder (OCD). Each mode of therapy can be viewed instrumentally in M&S's sense and provides a means by which the OCD patient can gain some control over the physical brain systems that underlie her anxiety, compulsive behaviors, and lack of control over repetitive and intrusive thoughts. The two therapies involve different modes of intervention, and the causal interface that each provides is quite unlike the other. Nonetheless, the net results are similar not only at the behavioral level, but also in terms of the brain changes that underlie successful treatment (Baxter et al. 1992). The drug-based direct modulation of serotonin activity, the conditioning effect of exposure and response prevention therapy, and the frontally mediated first-person cognitive reinterpretation of obsessive thoughts all converge on a similar set of brain changes in successfully treated OCD patients. Moreover, many patients obtain the best results from a combination of therapies, which is likely to involve interaction effects. The SSRIs, like the drugs discussed by M&S, alter the underlying base state in ways that facilitate the use of more cognitive constructs to modulate the relevant brain systems.

Hopefully, M&S's instrumental model will encourage a more positive social attitude toward non-addictive drug use. Drug use is too often stigmatized on the basis of the small percentage of users who develop harmful addictions. Moreover, even non-addictive users are typically viewed as having lost some measure of control through the supposed capture by drugs of biological reward systems. M&S's alternative view of drugs as adaptive instruments has the potential not only to explain non-addictive drug use, but also to legitimize such use as among the tools that may enhance our self-control, rather than diminishing it.

Aspects of nicotine utilization

doi:10.1017/S0140525X11000811

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Abstract: This commentary reviews the effects of nicotine on mood and cognition in support of the drug utilization concept of Müller & Schumann (M&S). Specifically, it amplifies the concept with the nicotine utilization hypothesis (NUH), which opposes the nicotine withdrawal hypothesis (NWH). Evidence against NWH comes from changes in mood after abstinence and the performance effects of nicotine supporting drug utilization.

Surveys find that 80% of smokers claim they smoke more when worried, 75% say they light up when angry, and 60% feel that smoking cheers them up (e.g., Russell et al. 1974; reviewed Warburton 1990). As the Surgeon General's Report stated:

> The conclusion from this literature is that in the general population, persons perceive that smoking has functions that are relevant for mood regulation. Persons report that they smoke more in situations involving negative mood, and they perceive that smoking makes them feel better in such situations (US DHHS 1988; p. 399).

In other words, smokers are using nicotine as a form of drug utilization as described by M&S.

Nevertheless, it has been argued that these mood effects represent only relief of withdrawal symptoms (NWH) and not a motive for smoking as in the NUH (functional model, Warburton 1987). Both NWH and NUH predict that abstaining smokers will experience dysphoria after abstinence, but NWH predicts that there will be a stereotyped syndrome, so that ex-smokers will eventually return to their non-smoking state.

Numerous studies do not show a stereotyped syndrome, or an invariable cluster of symptoms for every quitter. For example, Hughes et al. (1991) found that anxiety was the commonest sign after two days (49%) then restlessness (46%). Irritability was 38% whereas depression was 31%. As well as over half of quitters having no mood changes, the percentage of participants having a specific sign vary remarkably across studies. This is not what one would expect from the NWH.

NWH also predicts that ex-smokers will not differ in mental health from non-smokers after prolonged abstinence. Warburton (1994) examined the incidence of depression or nervous illness in smokers. Women, current and ex-smokers, were more likely to have experienced depression or nervous illness than those who had never been smokers. But, male ex-smokers were intermediate between never-smokers and current smokers and not significantly different from either group.

Ex-smokers were subdivided into number of years since quitting. Those who had quit 20 or more years or fewer than 10 years before had a significantly greater incidence than those who had stopped 10 to 19 years before, but the latter did not differ significantly from never-smokers. Clearly, there was no simple relationship between duration of abstinence and mental health, unless nicotine exposure had damaged the brain permanently.

A comparison of cigar smokers, pipe smokers, and never-smokers was made because they absorb significant doses of nicotine. There was no relation between nicotine exposure and the incidence of depression or nervous illness in these groups and so no support for the idea that exposure to nicotine has adverse effects on mental health and that ex-smokers return to "normalcy" after cessation.

More evidence for NUH is factors that predict initiation, and so predate nicotine exposure – for example, personality. Gilbert (1995) found an association of smoking with neuroticism and depression. Twin designs have evaluated whether the association between smoking and depression was causal or non-causal

(Kendler et al. 1993). The best-fitting model suggested that the relationship between smoking and depression resulted solely from genes that predispose to both smoking and major depression.

These data fit the hypothesis that genes predispose to anxiety and depression. In the teenage years, susceptible individuals find that smoking enhances their mood. Consequently, some adopt smoking as a form of nicotine utilization, and not surprisingly, ex-smokers miss these effects when they quit.

A second result from smoking surveys is that smokers claim that smoking helps them think and concentrate (Russell et al. 1974). Despite many studies (see Warburton 1990), the NWH doubts whether nicotine influences cognition. But, nicotine improved attentional performance in animals not in withdrawal (see M&S). Positive effects of nicotine on the performance of non-smokers have been found (Wesnes & Warburton 1984), and smoking improves minimally deprived smokers (e.g., Warburton & Arnall 1994). Other studies (e.g., Warburton & Mancuso 1998; Mancuso et al. 1999) have applied a transdermal nicotine patch for 6 hours so testing is done after any tolerance would have developed. In these studies, attentional performance was improved over the baseline in comparison with placebo at 3 hours and at 6 hours, indicating clearly that nicotine deprivation is not necessary for enhancing performance, contradicting the NWH.

Mancuso et al. (1999) found that transdermal nicotine patches improved speed of verbally producing a sequence of 100 letters in a random fashion (random letter generation) but did not affect the occurrence of stereotypical errors significantly, which is consistent with nicotine modulating an intensity system. Hence, for tasks requiring mental effort, nicotine "locks" the brain in the attentional mode.

It has been claimed that only simple tasks are improved and certainly not creativity. However, nicotine improved performance of non-smokers in a flight simulator (Mumenthaler et al. 1998). And the fallacy of the creativity statement can be demonstrated by looking at a list of creative people. Notable smokers were Charles Darwin, Albert Einstein, Isaac Newton, James Watson, Bertrand Russell, Jean-Paul Sartre, Ludwig Wittgenstein, Vincent van Gogh, and Pablo Picasso.

Early evidence on memory improvements in humans and animals was summarized in Warburton (1990). Later studies confirmed that attentional resources are important for the associative processing and demonstrated that nicotine improves verbal memory only for the semantically processed information (Rusted et al. 1995; Warburton et al. 1992; 2001). Semantic processing requires more effort and produces a more richly encoded memory trace with more associations. Nicotine facilitates these associations and enhanced storage, which raises the possibility that nicotine facilitates the formation of the drug memories, described by M&S.

These data support the NUH, the functional model (Warburton 1987), which is a version of M&S's drug utilization hypothesis. The NUH views nicotine use as a purposive activity by which the smoker improves mood and performance. It can be seen as adopted for coping with problems, as well as for enhancing function. Motives are both exogenous (situational) and endogenous (genetic). The NUH predicts that abstinence experiences will vary, because functions differ for the individual. Hence, cessation programs must be individually tailored.

Governing drug use through neurobiological subject construction: The sad loss of the sociocultural

doi:10.1017/S0140525X11000835

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Abstract: Based on their "drugs as instruments" framework, Müller & Schumann (M&S) propose a staged drug policy that matches well the neoliberal governance scheme. To mend the sad loss of the sociocultural dimension in their model, I propose three such considerations: first, sociocultural interactions with the brain; second, sociocultural context and justice of drug use; and third, sociocultural preparedness for implementing their drug policy.

In a very simplified version of the history of human psychoactive drug use, we have observed that in the past those who used psychoactive drugs were once taken as examples of individual moral failure and beastliness (O'Malley & Valverde 2004). Then, in the welfare states, drug users were pictured as the outcome of mind pathology ("disease of the will") by a variety of psy-experts (O'Malley & Valverde 2004; Valverde 1998). As the war on drugs advanced, the political economy of neuroscientific studies of addiction also boomed; and the discourse of addiction as the "chronic, relapsing brain disease" gradually anchored in public imagination (Campbell 2010). With the development of a variety of neuroscientific molecular and imaging technologies, the so-called "neuromolecular gaze" emerged as a way to construct identities and selves by the language of molecular neurobiology (Abi-Rached & Rose 2010). Meanwhile, as practices of harm reduction gained momentum, drug users have been construed as entrepreneurs of life who conduct their lives by making choices based on drug use risk information (O'Malley 2004).

On the one hand, from the perspective of public health, whether drugs are legal or illicit is no longer an important distinction for assessing drug harm (Jonas 2005). On the other hand, scholars have been finding that the pleasure and benefit of drug use have been downplayed to serve the purpose of moderating drug use (Moore 2008; O'Malley & Valverde 2004). In their article, Müller & Schumann (M&S) propose that psychoactive drugs are instruments used by individuals to adapt to modern environments. Their model almost merges seamlessly with the above trend as M&S emphasize controlling all drug use through individual education, training, screening, biographing, biomarking, and even treatment. The hope is to make neoliberal drug users both neuromolecularly knowledgeable and freely self-governed. Although M&S mention environment from time to time in their article, there is a sad loss of sociocultural visions in their discussion of drug policy implications. In the following, I argue for the supplementation of such considerations to their individualized neoliberal drug misuse prevention model.

In recent decades, in addition to research into brain representations of sociality and morality, we have witnessed the exploration of brain plasticity in cultural neuroscience. According to the major theme and preliminary evidence in the field, brains have complex interactions with socioculture and could change through accumulated sociocultural experiences (Kitayama & Uskul 2011). Our brains are not hard-wired and could evolve and adapt with the requirement of sociocultural practices. Also, we explore our brains and interpret neuroscientific data via the concepts and frames we adopt in our current sociocultures (Gergen 2010). Therefore, it is no surprise that, as shown in M&S's drug policy model, the discourse of individual brain plasticity matches well the neoliberal individual self-governance; and concurrently, the neuroscientific description of the brain reflects the neoliberal thought paradigm (Malabou 2008; Pitts-Taylor 2010). M&S could make their model more reflexive and dynamic by incorporating this sociocultural dimension. Henceforth, we could have a richer explanation of how drug-related memory and learning may unfold in different sociocultural contexts.

A bigger drawback in M&S's model is the omission of sociocultural contexts that facilitate or inhibit excessive psychoactive substance consumptions. In the typical neoliberal regulation regime, such as the one suggested by M&S, it is informed individuals who should take responsibility and blame for drug misuses. However, historical studies have shown that the adverse effects of drug misuses have not hit everyone or every group equally (Acker 2010; Singer 2008) The neoliberal model of drug policy carries

the risk of neglecting the sociocultural backgrounds that make the prudent choices of drug use difficult. For example, in a poor and distressed community, even equipped with all the personal technology of moderated drug use, adolescents might start misusing drugs after they finally succumb to peer pressure, volatile family atmospheres, and/or doomed images of their future. Also, under the active promotion of drugs, it is doubtful that informed consumers could always make rational choices.

As both legal and illegal drugs are making their way into people's lives, the poor seem to be the most drugged group (Singer 2008). Therefore, as observed in the complex causal networks of drug misuses that are also multileveled (from molecular through individual to the sociocultural) (Windle 2010), the individuals might not be the best intervention targets as M&S indicate. Abundant literature has shown the impacts of neighborhood and social determinants on health (Kawachi & Berkman 2003; Marmot & Wilkinson 2006). We should analyze along the multilevel sociocultural dimensions to address social justice issues not only about equality of what, but also about equality of whom (Young 2001).

Furthermore, according to a WHO analysis, in the developed countries, tobacco is the number one risk factor of mortality, with alcohol ranking as number three (Lopez et al. 2006). Not all the negative impacts came from addictive uses. If all the other legal and illicit drugs joined the neoliberal market, although many people would benefit from drug uses, the absolute number of those who suffer would also escalate. The worst scenario would be the other drugs joining tobacco and alcohol to become the strong risk factors of morbidity and mortality. Before implementing their drug policy, M&S should have examined what kind of sociocultural structures and institutions could stand the abovementioned impact. Through deliberative democracy we might be able to add agreed communitarian measures into the neoliberal governance scheme to achieve the common good. For example, we could enable the sociocultural environment and resources to facilitate the positive and avoid the negative drug uses (Duff 2010). Besides, it might be favorable to make the drug companies or dealers take social responsibility seriously by requiring them to internalize the externality of social costs by paying a premium for each sale of drugs earmarked for social welfare use. Hence, we might begin to map a more comprehensive drug policy based on the neurobiological framework offered by M&S.

Authors' Response

To use or not to use: Expanding the view on non-addictive psychoactive drug consumption and its implications

doi:10.1017/S0140525X1100135X

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Abstract: Proposing a change to the view on psychoactive drug use in non-addicts touches a sensitive issue because of its potential implications to addiction prevention, therapeutic practice, and drug policy. Commentators raised nine questions that ranged from clarifications, suggested extensions of the model to supporting data previously not regarded, to assumptions on the implications of the model. Here, we take up the suggestions of the commentators to expand the model to behavioral addictions, discuss additional instrumentalization goals, and review the evidence from laboratory animal studies on drug instrumentalization. We consider further the role of sociocultural factors and individual development in the establishment in drug instrumentalization and addiction. Finally, we clarify which implications we think this model may have. We conclude that drug instrumentalization theory can be further applied to other behaviors but will require a sensitive debate when used for drug and addiction policy that directly affects prevention and treatment.

In our response, we first address the relationship of drug instrumentalization with drug addiction and how this may translate on the relationship of behavioral instrumentalization and behavioral dominance to behavioral addiction. Subsequent responses then focus on extending and clarifying the idea of drug instrumentalization.

R1. From drug instrumentalization to behavioral addictions and back

Griffiths suggests the proposed model of non-addicted drug use may also hold utility for non-addictive use of other potentially addictive behaviors. We agree with this notion and would like to probe our model in relation to behavioral addictions. We argued that drug instrumentalization is a precursor of drug addiction. Although drug instrumentalization may provide a behavioral benefit, drug addiction does not, and it represents a pathological condition. In analogy to drug instrumentalization, we hypothesize that in certain situations behavioral dominance (a precursor of behavioral addiction) may be advantageous for the integrity of an individual and its chances for reproduction.

A behavioral addiction has as its core a naturally occurring behavior that becomes dominant (Shaffer et al. 2004). For example, gambling addiction can be seen as the dominance of playing behavior; sex addiction, as the dominance of behaviors directed towards sexual intercourse. As such, the occurrence of the behavior itself may have an unquestionable evolutionary origin. We suggest that both a balanced as well as a focused behavioral strategy, can serve well to maximize the reward of an individual depending on actual environment and personality. Thereby, the establishment of one dominant behavior at the cost of all others may be an adaptive behavioral strategy in environments with restricted access to primary or secondary rewards. For example, it may be acceptable if a gold miner who seeks for gold as a secondary reward and who has no access to social communities, displays a strong bias toward the mining work rather than attempting to balance the reward. Physical and/or mental characteristics of a person may also restrict the access to rewards at any time during life. They are usually accepted as the source of a behavioral dominance when acknowledging the exploitation of "talent." In this case, other than the obtained type of reward may become very hard to access, so that a balance in the reward is virtually not possible. Altogether, we suggest, human capability to establish

a behavioral dominance is based on an ancestral adaptation to uncertain environments and/or to individual characteristics.

We argued in the target article that non-addicts consume psychoactive drugs because such consumption can change their mental state. A mental state change can then allow a more effective performance of certain behaviors and a better reaching of particular goals. Although we defined these goals on empirical and psychopharmacological grounds, they may translate easily to concepts of primary and secondary natural rewards. The suggested goals of drug instrumentalization essentially involve goal-directed behaviors as they also occur in behavioral dominance and behavioral addiction. The goals of drug instrumentalization are, thus, only a part of the goals that can potentially be served by goal-directed behavior in general and by a behavioral dominance in particular. This was noted by **Griffiths** in his comment and in previous work (Griffiths 1996).

Social interaction may serve as an incentive by itself for social animals and humans (Matthews et al. 2005; Panksepp & Lahvis 2007). In the absence of alternative rewards, there may develop a behavioral dominance for this behavior, for example, when people spend excessive time in interaction with friends, but neglect the partner, children, or work. This behavioral dominance may develop into a behavioral addiction, as it is seen, for example, in excessive Internet chat room use as a kind of Internet addiction (Shaw & Black 2008; Weinstein & Lejoyeux 2010), which may help to overcome a shortage in peer group access or problems with social behavior and self-esteem in the "real world" (Niemz et al. 2005).

Sexual behavior and the resulting experience of an orgasm may serve as a strong primary reward. As secondary rewards, sexual cues may drive approach, as well as consummatory (copulatory or masturbating) behavior. Naturally given physical appearance and acquired social skills may have a strong influence on access to this particular reward. In contrast to sexual behavior involving a partner, one can assume equal access to autosexual behavior (masturbation). This behavior, however, appears driven by sexual cues. Accessibility to these cues may therefore have a major influence on the expression of the behavior and the "natural reward" obtained by it. There may possibly be two ways in which sexual behavior can be subject of a behavioral dominance. One may be related to sexual cue driven autosexual behavior. This can be observed as obsessive masturbation (Black et al. 1997). The Internet provides an easy access to sexual cues now. In connection with autosexual behavior, this may result in excessive cue-seeking and hence time spent "consuming" images and virtual sexual contact on the Internet (Griffiths 2001; Kalman 2008). Another type of behavioral dominance related to sexual behavior may manifest in excessive seeking of sexual partners and sexual behavior (Garcia & Thibaut 2010; Goodman 1992). However, this behavior requires considerably more effort than the first pattern and may be restricted to those people with a privileged access due to, for example, physical parameters, specific social skills, or high exposure to sex partners.

A high cognitive performance is required in many work-related activities in industrialized societies. Thereby, "work" may summarize all behaviors that yield a secondary reward reserve, usually in the shape of money. Money can in principle be exchanged for virtually all natural rewards; but in contrast to them, money can be stored more efficiently and accumulated as well. Although cognitive performance may by itself not constitute a behavioral dominance, "work" in general may well do. This can result in a behavioral addiction of wealth acquisition (Slater 1980) and workaholism (Burke 2004; Spence & Robbins 1992). The driving force may be a secondary reward accumulation, which uses cognitive performance only as one behavioral subcomponent.

The end of a negative stimulus or situation works as a "negative reinforcer" for the ante-ceding behavior. There are several behavioral activities that may serve this function in particular, and these activities are related to psychological stress. All have in common that they require little effort and are easy to learn; and some may involve highly automatic behavioral components that require little cognitive activity (Marks 1990). Overall, they provide relieve from psychological stress and mood alterations by involving the individual in low-effort motor activities and/or distracting attention from mental preoccupation with real problems (Griffiths 2005). Given a lack of behavioral alternatives that may lead to a controlled (and predictable) stress relief, a behavioral dominance for these behaviors may develop and can progress to a behavioral addiction. This can be seen in excessive gambling with various types of card, machine, computer, and Internet role-playing games (Griffiths 1996; Rehbein et al. 2010). In particular, excessive "fruit machine" gambling involves easily accessible and highly automatized behaviors (Griffiths 1993). Gambling addicts reported that a major driving force into the gambling was not only the chance of an effortless win, but also relief from psychological stress in situations with few behavioral alternatives. Other activities that were reported to provide relief from psychological stress and that are prone for behavioral dominance and addiction are physical exercise (Allegre et al. 2006) and eating behaviors (Grilo et al. 2011).

In drug instrumentalization, the pharmacological effects of a drug on the brain may account for the drug's beneficial effects toward ameliorating mental problems. However, there are also certain behaviors that were shown to provide at least temporary relief from persisting mental problems. These behaviors can become dominant and even develop into a behavioral addiction. There is evidence that physical activity and sport can have a significant antidepressant action (Martinsen 1990; Paluska & Schwenk 2000). However, excessive sport may result in an exercise addiction (Allegre et al. 2006). In particular, drug-addiction may be effectively medicated or self-medicated by the establishment of a non-drug-related behavior (e.g., Roessler 2010; Ussher et al. 2008). This may eventually result in the replacement of a drug addiction by a behavioral addiction (Hatcher 1989).

Physical appearance and attractiveness for the opposite sex is believed to facilitate sexual behavior. There are behavioral patterns that may be seen primarily directed toward enhancing physical appearance, like exercise and body building in males (Hale et al. 2010) and the suppression of eating behavior in females. Both can result in a behavioral dominance and addiction, such as, for example, exercise addiction (Allegre et al.

2006; Hausenblas & Downs 2002) or anorexia nervosa (Gucciardi et al. 2004).

R2. Extending the list of instrumentalization goals

We suggested an initial list with drug instrumentalization goals and drugs that may serve these goals. As we have learned from the comments, this list may be seen as a start rather than an end. Several commentators have suggested additional instrumentalization goals that we'd like to discuss here. **Móró & Noreika,** as well as **Spanagel,** suggested considering the use of psychoactive drugs in spiritual activity and religious rituals. Moro & Noreika argued that in particular sacramental and spiritual drug intake, which is famously associated with psychedelic drugs, may go far beyond a simple expansion of the perception horizon. We fully agree with this suggestion and add this as ninth instrumentalization goal to the list as: *Facilitating spiritual and religious activities*.

Móró & Noreika and **Spanagel** delivered a number of arguments and a mechanistic description that we want to adopt and expand here. Religion seems to be a unique human phenomenon. It provides a metaphysical base to explain the world beyond purely experience-driven cognitive constructs. Religion may provide the final reference for an individual's structure of sensory perception and thinking and in that way can give normative advice on behavior. Most important from a biological point of view may be that it provides a shared cognitive framework to explain the environment of individuals and groups. This may effectively "synchronize" perception style, thinking patterns, and behavior of social groups and foster altruism within the group. Altogether, religion provides health and well-being benefits, which make it seem an adaptive advantage (for a critical discussion see Atran & Norenzayan 2004).

How could psychoactive drugs benefit maintenance of a religion? In mono- as well as polytheistic religions, there is a god or gods with a higher understanding of the world and more-or-less universal power to influence environment and the fate of living creatures. All these religions have in common restricted contact with the supreme deity; that is, under normal circumstances and in a normal mental state, a normal human being may not have access to the "divine." Learning from it/them or influencing the "divine will" and its ways of action is very limited. However, both are considered desirable. Many, if not all, religions have established a mediating mechanism that assures some kind of contact, that is felt to allow either enhanced insight into the divine or a perceived way to influence its action and solve problems of the individual or the group. Having a direct or indirect contact to the divine can be assumed to reinforce religious practice in the individual and strengthen the religion within the group. **Móró & Noreika** argue that "in culturally predefined contexts, the purpose of these [psychedelic drug induced] hallucinatory experiences is not merely to increase self-understanding and self-discovery, but also to address ultimate questions that shape or shake the fundamental worldview." Changing the mental state can be achieved by meditation and particular thinking patterns (**Van Gulick**). A more powerful way, however, is by using psychoactive drugs. This practice was abandoned with the arrival of the monotheistic religions of, for example, Judaism, Christianity, and Islam in most parts of the world's population and exchanged for meditation. However, it is still in place in some natural religions, for example, in the Amazonian basin (Jay 2010).

Why is this drug use different from the goal *sensory curiosity – expanding the perception horizon*? We suggest that while similar types of drugs are used, an exploratory use may be seen as undirected. Using it as part of spiritual and religious activities, in contrast, facilitates these activities in a directed way. People have clear intentions what they use the drug for and what mental state they wish to achieve.

Drugs that were and are used for this purpose include THC (Abel 1980), cocaine (Streatfeild 2001), and nicotine (Jay 2010). Hallucinogenic drugs used include mescaline and psilocybin that can be found in the peyote cactus and in mushrooms, respectively, in south and central Americas. In South America, dimethyltryptamine (DMT) is used as a hallucinogenic compound (Geyer & Vollenweider 2008; Nichols 2004) in preparations from tropical plants (Jay 2010). The latter were termed "entheogens," acknowledging their application for religious purposes (Ruck et al. 1979). **Móró & Noreika** suggested placing sacramental and spiritual drug use in the center of drug instrumentalization because of its deep embedding in human culture. However, in Western societies, most non-addictive drug use is predominantly nonreligious and has no sacramental or spiritual embedding any more. In another comment, **Ahmed** asked what the selective advantage of psychoactive drug use might have been in an ancestral environment. We speculate that an instrumentalization to facilitate spiritual and religious practice might actually have been among the first documented examples of drug instrumentalization in humans (Abel 1980; Heath 2000).

Another instrumentalization goal proposed for consideration by **Spanagel** and **Kippin** is drug use to adapt to peer group pressure and, as one may add, as a peer group defining behavior. We agree there is evidence that the use of drugs of particular types may form an entrance criterion for peer groups in adolescence and early adulthood and, thus, exert a social pressure to the individual. The consummatory behavior is then rewarded by becoming a member of this group. Here the opposition to adult norms, which suggest abstaining from illicit drugs and limiting intake of the legal ones, may play a larger role than the drug effect on mental state itself. Furthermore, there is no particular mental state that facilitates peer group bonding beyond that of perceived improved social interaction. Consuming psychoactive drugs may therefore be one among many other "risk behaviors" (Donovan & Richard 1985; Hill & Chow 2002). As such, we do not see a clear relationship between the pharmacological effects of a particular drug and peer group formation/maintenance yet. Accordingly, we suggest to classify the choice and consumption of psychoactive drugs related to peer group formation not as an independent primary drug instrumentalization goal.

Spanagel also suggested considering the taste of a drug preparation and the seeking of sensory pleasure that it may provide as an instrumentalization goal. However, the psychoactive drug is usually not tasty itself, but rather the additional components of the preparation are (Peynauld 1995). This would suggest two implications: (1) the

preparation is consumed for the reinforcing effects of the pleasantness of the taste, and (2) the psychoactive effects of the drugs would play no essential role in the reinforcing effects and maintenance of the consummatory behavior. These points may be refused at the point of observation. For example, there is nonalcoholic beer and wine, which in its taste comes at least close to the alcohol-containing product. However, its consumption is not nearly that of the alcohol-containing preparation. Though it may trigger a cue-induced relapse in alcohol-dependent patients in withdrawal, it could so far not replace the alcoholic drink in non-addicts or addicts just by its taste. Similarly, decaffeinated coffee achieves similar taste as the caffeine-containing original preparation. Also, this approach did not replace the psychoactive drug–containing preparation. Accordingly, we rather argue that the taste (and other sensory parameters) of a psychoactive drug preparation may well play a role at the sociocultural level to foster and control drug consumption. However, its reinforcing effects may be too subtle and in many drugs not being present at all in order to serve as a unique goal for drug instrumentalization. Even when appreciating the taste and cultivating the social paraphernalia of legal drug consumption, we may still ask ourselves which of the named instrumentalization goals we are after when "liking the taste."

R3. Further support for drug instrumentalization

Several authors have highlighted previously published evidence and concepts that further support drug instrumentalization theory. A very important set of evidence was highlighted by **Ahmed,** who discussed the evidence from animal research. Experimental animal research has shown that various species learn to self-administer psychoactive drugs when given access to them. These experiments usually use the paradigm of intravenous self-administration as a consequence of an operant behavior in a very minimal setting. In these settings (e.g., a Skinner box), animals can normally not perform goal-directed behaviors other than the one leading to drug delivery (or an activity control behavior with no consequences). As such, they cannot instrumentalize their drug seeking and consumption. Ahmed pointed out, however, that for animals in an experimental setting, drug instrumentalization also may be established when other behaviors are allowed that can be served by previous psychoactive drug consumption.

Further support for this view comes from alcohol-drinking studies in rats, which were meant to model a "bar like" situation in humans. Tomie and colleges showed in a series of experiments that single-housed male rats learn to drink alcohol before a "social opportunity" occurs in the shape of access to a conspecific animal (Tomie et al. 2004a; 2004b; 2005). One can interpret these data as using the alcohol when expecting a social interaction opportunity to enhance behavior or perception of it. This effect was even more pronounced when males were allowed access to females rather than to males (Tomie et al. 2006). Although same-gender interaction may support the instrumentalization goal of *improved social interaction*, alcohol drinking before opposite gender access may support the goal of *facilitated sexual behavior* in animals. However, drinking studies in rats also showed that not all human instrumentalization goals may be served in rodents alike. The exposure to social stress rather reduced alcohol drinking in rats before and after stress exposure (van Erp & Miczek 2001; van Erp et al. 2001), which suggests that the instrumentalization goal of *facilitated recovery and coping with psychological stress* may not be served by alcohol in rodents. These findings may also provide support for the suggestion that drug instrumentalization developed as an ancient adaptive trait. Hence, the behavior may have been established at least in some mammals, but being limited in its expression by the availability of and the access to psychoactive drugs. It also suggests that the ultimate cause for drug instrumentalization behavior may be different between instrumentalization goals.

These findings may have wide-ranging implications for basic research on neuronal mechanisms of drug addiction. Until recently (Ahmed 2010), it was considered that self-administration is the most effective model to study drug addiction (Richardson & Roberts 1996; Spealman & Goldberg 1978). However, it has been known for a considerable time that the characteristic escalation of consumption and loss of control by adverse consequences is observed only in a minority of drug-consuming animals (Deroche Gamonet et al. 2004; Vanderschuren & Everitt 2004). Based on this and other evidence (Cantin et al. 2010; Lenoir et al. 2007), **Ahmed** suggested a biological resilience to addiction, which may protect most of the rodents and humans from becoming addicts and which may allow them to control their consumption of psychoactive drugs when using them in a systematic way. Overall, we agree with Ahmed's conclusion that "this research suggests that psychoactive drug instrumentalization is not unique to humans and probably corresponds to an ancient behavioral trait, at least in the mammal class." At that point it can be only speculated that there may have been a parallel selection for psychoactive drug instrumentalization and the resilience to addiction. Given the abundance of animal studies in very restricted environments, we call for more research in understanding the mechanisms of operant and non-operant drug self-administration in relation to drug-facilitated behaviors in more realistic environments.

Considering the adaptive advantage of drug instrumentalization, **Reid** suggested better consideration of Niche Construction Theory (Kendal et al. 2011; Laland et al. 2000; 2010), which was only mentioned as a potential factor when the drug instrumentalization theory was initially laid out. Reid argued that the "influence of the organism, humankind in this case, on the environment has led to the construction of a niche where modern drugs and drug-culture are part of the environment." We fully agree with this view. We also agree with Reid's notion that "drugs can then be seen as part of the fitness landscape over which selection pressures operate." Reid further argued that "natural selection will favour those who use drugs, then the trait of drug liking and its genetic underpinning will be promoted." We have argued that a controlled use of now widely available psychoactive drugs may be beneficial for the individual in this niche. Selection pressure may, hence, operate toward drug instrumentalization – that is, toward the most effective use of available psychoactive tools. At that point we disagree with Reid in that we believe that not the trait of "drug liking" may be promoted but the trait

of "drug instrumentalization," which may include efficacy of the drug memory and its interplay with non-drug memories. The manifestation of this niche and the pressure for drug instrumentalization may be recognized in the search of individuals and pharmaceutical companies for cognitive enhancers (Husain & Mehta 2011). The principle of instrumentalization of these drugs may be the same as we proposed it for potentially addictive drugs. Accepting this, one might further expand this thinking and suggest to search for pharmaceutically engineered and non-addictive "little helper" (Hesse 2010; Sahakian & Morein-Zamir 2007) for all of the proposed instrumentalization goals that are currently served by addictive drugs.

At the conceptual level, **Warburton** suggested that the proposed drug instrumentalization model may have its special application in the nicotine utilization hypothesis (NUH), which was proposed earlier (for review, see Warburton). We agree with this view, which is supported by self-reports of smokers who claim that smoking helps them concentrate and think (Russell et al. 1974), as well as from experimental evidence on cognitive performance (Mumenthaler et al. 1998).

R4. From interoceptive drug discrimination to drug instrumentalization

The ability to discriminate the effects of psychoactive drugs is an essential prerequisite for drug instrumentalization. **Goudie, Gullo, Rose, Christiansen, Cole, Field, & Sumnall (Goudie et al.)** noted that "drug discrimination research grew out of work on ingestion, before shifting to a broader conceptualisation of interoceptive stimuli detection." They suggest that for a better understanding of drug instrumentalization, a conceptual shift away from ingestive behavior may be required. We agree. Although ingestion of plant preparations containing psychoactive drugs was historically the behavior that led to the bioavailability of the drug and to subsequent changes of the mental state, other ways of preparation and application became available for a number of psychoactive drugs. These include, for example, smoking/inhaling, snorting, and injecting. Although some of them circumvent ingestion and lead to direct availability of the drug to the bloodstream or nervous system, it may still represent a consummatory behavior.

We have focused in our assessment of the discriminative drug effects on the mental state, which reflects the mode of action of the brain function. Expanding this view, one should certainly acknowledge that the discriminative stimulus properties of virtually all psychoactive drugs have a peripheral component, which may interact with mental state changes. Most psychoactive drugs affect not only molecular targets in the CNS, but also often – with even higher sensitivity – ones in the body periphery. Not only the expected effects of the drug on mental state, but also its side effects on peripheral state, are part of the semantic memory about a psychoactive drugs. As such, the peripheral drug effects and their interoceptive detection may be an important part of judging the drug effects and self-titrating the dose for potential instrumentalization.

Goudie et al. further noted that the ability to detect different drug states may not be sufficient to facilitate other behaviors. We agree with this point and like to point out further mechanisms. A systematic drug instrumentalization requires a memory for mental states. This ability was demonstrated experimentally in humans and rats by testing the discriminative stimulus properties of a drug. This can at least in part be dissociated from its rewarding effects and may occur without any euphoria at all. Animals and humans were shown to be capable of recognizing the unique discriminative stimulus properties of psychoactive drugs and to use this information to guide goal-directed behavior (e.g., Hodge et al. 2006; Preston & Bigelow 1991). Drug instrumentalization also needs a comparator function that determines whether the one or other mental state is preferable in a particular set and setting (Zinberg 1984). This may involve not only comparing mental states, but also assigning them an emotional significance and value. Thereby, significance and value are dynamic – context-specific. For example, behavioral disinhibition and reduced anxiety is a valuable mental state in a social context, but not in a professional work environment. Based on this, we propose that mental states may have a value and that humans are able to assign it to the representation of this state and retrieve it later on.

Finally, it requires a mechanism of transition, something that brings the organism from one acknowledged mental state into another in a somewhat predictable way. A behavioral sequence that can result in such a transition in humans and animals is the self-administration of psychoactive drugs (Skog 2000; Wiens et al. 2008). As **Van Gulick** pointed out in his comment, psychoactive drugs are not the only way to change the mental state. In fact, the mental state of human beings changes constantly in a "natural way" by intrinsic mental activity or as a consequence of the individual's interaction with the environment (e.g., by sensory perception). There are memories of the different mental states as part of the autobiographic memory. However, there are only limited ways to change these mental states *on purpose* along the three axes of (a) *quality* of change (i.e., into a particular direction), (b) *quantity* of change (i.e., the magnitude of change) and (c) *time* (i.e., with predictable times of onset and duration). In particular, under adverse conditions, such as a depressed mood, it may appear difficult to find any way to do it "naturally" (Snaith 1993). In that, the systematic seeking and consumption of psychoactive drugs might have appeared as a unique instrument to change mental states on purpose.

R5. Drug instrumentalization establishment during lifetime

An important aspect of how psychoactive drugs are instrumentalized is the age at which people establish drug consumption and possibly instrumentalization. **Banaschewski, Blomeyer, Buchmann, Poustka, Rothenberger, & Laucht (Banaschewski et al.)** have pointed out that an early initiation of psychoactive drug consumption, which starts now in early adolescence, appears to be associated with a reduced ability to use drugs purposely in a temporally stable, non-addictive manner later in life. It seems that the earlier in

adolescence consumption starts, the higher is the lifetime consumption and risk of developing addiction (Behrendt et al. 2009; Grant & Dawson 1997). A necessary conclusion from this would be to tailor prevention strategies that aim to delay age of consumption onset. We fully agree with this suggestion and like to expand this view from drug use to drug instrumentalization. We suggest asking people, in surveys, not only when they started to experiment with a drug, but also when and how they first established a systematic and effective drug instrumentalization. Experimenting with psychoactive drugs is dangerous. Based on some semantic knowledge, novices try to explore different drugs at different doses with unpredictable individual responses. Because of this, self-titration almost necessarily involves occasional overdosing. Establishing an early drug instrumentalization, however, derives its hazards still from other sources. First, the brain is still in an important developmental period. Repeated exposure to the drug during this period may have significantly more irreversibly damaging effects on brain function leading to behavioral impairments than when drug exposure hits a fully matured adult brain. Second, in adolescence, salience of natural rewards is more highly reflected by enhanced activation of the brain's reward system (van Leijenhorst et al. 2010). At the same time, puberty imposes a lot of new demands and goals on the individual, which may result in considerable stress (Banaschewski et al.). Getting access and establishing a position in the peer group, approaching the opposite sex, increasing cognitive efforts in school, expanding the perception horizon and building/maintaining an "attractive" physique are just some of the tasks at that age. All of these can potentially be served by drug instrumentalization. In addition, there appears a perception/memory bias toward the positive effects of drugs.

Although predominantly positive expectancies of drug effects at younger ages predict future drug use, in adults, negative expectancies shape future consumption as well (Boys & Marsden 2003; Boys et al. 1999; Leigh & Stacy 2004). We have argued that drug instrumentalization is essentially a reinforcement-driven behavioral sequence. Given the enhanced reward sensitivity, this would make adolescents particularly vulnerable to the establishment of drug instrumentalization. We suggest that an early onset of drug consumption, may, thus, especially in socially and/or genetically "at risk" adolescents (Blomeyer et al. 2008; Laucht et al. 2009) lead to early onset of drug instrumentalization to help solving adolescent developmental tasks. This may be further facilitated by additional adverse life events during childhood (Andersen & Teicher 2009). Once drug instrumentalization is established to enhance performance of one particular behavior (e.g., disinhibition and peer group bonding by alcohol), a behavioral strategy may be derived. This strategy may be drug instrumentalization – that is, the knowledge that psychoactive drugs may be a ready means to address any problem in life. Therefore, we suggest introducing a systematic monitoring of drug instrumentalization as early as monitoring experimental consumption. Both need to be, if not avoided, then delayed in their onset. There may be a chance to address both separately in prevention and support programs.

Kippin noted that achieving efficiency and accuracy of mental state changes during the establishment of drug instrumentalization may be a crucial problem during experimental consumption, which might strongly affect later drug taking. We agree with Kippin's suggestion that during this learning process, people experiment in a trial-and-error way with toxic drugs. To find an optimal dose range for a desired mental state change can be achieved in a "bottom up" and "top down" self-dosing approach. This does indeed result in a considerable number of overdosing episodes. It may become obvious, for example, in weekend binge drinking in young adults in Western societies. Overdosing usually results in a highly aversive episode, which is usually remembered well; and the type of drug or the high dose is avoided in the future. Experimentation with new psychoactive drugs, as well as dose self-titration for the desired effects, matures into knowing the preferred drugs and optimal doses in most people when reaching adulthood and facing a new life episode (Leonard & Das Eiden 1999; Miller-Tutzauer et al. 1991; Nilsen et al. 2008).

R6. Drug instrumentalization in addictive and non-addictive drug use

Pickard asked whether drug instrumentalization is limited to a non-addictive drug use or whether there may be also one in diagnosed drug addicts. Pickard suggested that "it may not be adaptive. . .but it may yet be an instrumental means to desired ends." This would imply that addicts are not only passive victims of a disease, but may also within an overall negative health benefit still maintain "islands" of subjectively perceived benefits. There have been several attempts to recognize potential benefits of addictive drug consumption, mostly derived from subjective reports. Alexander (1987; 1990) has argued that an addictive drug use may be beneficial to cope with "integration failure." Davies (1997) argued that also in classified addicts, people chose drug taking not because there is a compulsive drive to do so, but because there are personal benefits. Considering single behaviors, we agree that in drug addiction, there may also be some subjective benefits derived from the drug use. Who can deny that, for example, addicted alcoholics may forget their severe problems, which they did not find other ways to resolve, during binge drinking episodes? However, we strongly argue the importance of considering the overall situation and perspectives of the individual.

Almost all psychoactive drugs can cause severe damage to the brain and body periphery. Chronic alcohol consumption can, for example, cause cognitive deficits and neuronal loss (Harper 2007; Parsons 1998; Ward et al. 2009); chronic ecstasy consumption can destroy serotonergic terminals in the brain and induce cognitive deficits (Gouzoulis-Mayfrank & Daumann 2009; Seiden & Sabol 1996); nicotine consumption can cause various forms of cancer (Ray et al. 2009), and high doses of androgenic–anabolic steroids may cause myocardial infarction (Wood 2004). Chronic consumption of psychostimulants can lead to cardiovascular problems, cerebral atrophy, and a decline in cognitive performance (Pascual-Leone et al. 1991; Volkow et al. 1992). Many psychoactive drugs enhance pre-existing psychopathologies in vulnerable individuals (Robbins & Everitt 1999; Wood 2004). Chronic consumption of cannabis/marijuana may

not only cause cognitive deficits (Solowij 1998), but also induce schizophrenia (e.g., Andreasson et al. 1987; 1989; Negrete 1993). Accordingly, the effects of the high drug exposure on personal health, social environment, private economy, and the public are usually so severe that an overall beneficial effect or an adaptation must be denied.

We have argued that drug addiction is preceded by drug instrumentalization, or at least the attempt of it. A crucial mechanism for the transition from controlled drug instrumentalization to drug addiction is the "over-instrumentalization" of psychoactive drugs. We suggest that over-instrumentalization should describe the attempt of a person who "successfully" instrumentalized one or more psychoactive drugs to meet increasing demands for goal achievement by increasing the frequency and/or dose of the consumed drug. Although drug instrumentalization can be seen as a dynamic process with respect to changing goals and drugs used for it, we assume that there is generally a sigmoid dose/frequency-efficacy function in drug instrumentalization. There may actually be quite a small dose window for the optimal mental state for each drug serving a particular instrumentalization goal. If this dose window is left by increasing the dose of the drug, no instrumentalization may be possible any more. For example, overdosing oneself with alcohol at a social occasion may have sedating effects. The mental state change with a too high dose may then be less supportive for the goal of social interaction than no drug-induced mental state change. In that, the attempted over-instrumentalization is actually a mis-instrumentalization, as **Kippin** suggested. Kippin discussed a number of consequences of mis-instrumentalization with which we fully agree. One of the most adverse effects is the increased risk of losing control over drug consumption beyond any utility for instrumentalization and to develop a drug addiction. As such, drug instrumentalization requires a fine-tuned learning process to get established and works only when the window of psychoactive drug doses is carefully self-titrated.

R7. Sociocultural determinants of drug instrumentalization

Goudie et al. noted that, in its initial shape, drug instrumentalization theory did not consider cultural factors. They argued that drug use is not a result of modern societal demands alone, but to such demands interacting with specific cultural contexts that determine attitudes and expectancies. We fully agree with this view and would like to expand the theory by a cultural dimension. Drug instrumentalization is a dynamic process over time, across and within cultures, groups, and individuals. We would argue that cultural factors essentially determine which drugs are available for legal or illicit consumption, approved dosage ranges and corresponding behavioral effects, and finally for which goals the available drugs are allowed to be used.

Depending on the respective culture, only a subset of the known psychoactive drugs is permitted for legal use (Heath 2000). Some cultures have explicit rules that determine *which* drugs may be used and how (Harding & Zinberg 1977; Maloff et al. 1981; Moreira et al. 2009). Western societies do, for example, allow for alcohol, nicotine, and caffeine, but prohibit cocaine and opiates. Islamic societies disallow alcohol but are less restrictive with psychostimulants like khat (Rehm et al. 2003). There are specific occasions and places where drug use is explicitly allowed and encouraged, often to a programmed excess (Heath 2000). These social rules can be fixed in religious and secular law terms with sanctions and punishment threatened. The rules on *how* to use the drugs are established in social rules of use, which are passed by social learning mechanisms from parents, peers, and media (Harding & Zinberg 1977; Zinberg et al. 1978).

There is also evidence for measures to prevent toxic doses. This can be found by the thresholds that, for example, European countries have fixed in laws on alcohol use. Although small amounts of alcohol in the blood are tolerated for taking part in public activities and work, there is a certain threshold (associated with an amount of drug to be consumed) at which legal punishment is threatened. Besides that, there are culture-specific, often mutually agreed and unwritten rules on consumption of allowed drugs, which also prevent lethal overdosing. These rules are defined by approval and disapproval of the behavioral consequences of the drug, rather than on absolute amounts consumed (Harding & Zinberg 1977; Maloff et al. 1981). At some occasions (e.g., at a restaurant visit), alcohol drinking is accepted and encouraged to a level of increased social interaction and moderate behavioral disinhibition (correlative to a low dose of the drug); it is disapproved when inducing aggression and overtly intrusive behavior (reflecting high levels of drug intake). At other occasions (e.g., at the Munich Oktoberfest), excessive alcohol consumption may be encouraged, but is also disapproved of when the consumer drinks up to a level that endangers consciousness and vital functions. Disobedience of these rules may result in social punishment. These rules also exist for illicit drugs but are clearly less easy to encounter in their application. What they have in common is that they attempt to control the dose-range of potentially toxic substances and to prevent drug abuse and addiction (Harding & Zinberg 1977; Zinberg et al. 1978).

Wu has noted that because social considerations play an important role in drug addiction, so they may do in non-addictive drug instrumentalization. Given the "peer pressure, volatile family atmospheres, and/or doomed images of their future" people from poor socioeconomic background lose control over drug instrumentalization more easily than people from higher social classes (Wu). On the opposite end, drugs may be instrumentalized to enhance well-being and happiness of individuals and within social groups (**Miller**). By conceptualizing drugs as "exogenous neurotransmitters" and proposing the use of drugs to actively shape individual perception, Miller described the apotheosis of an individualistic and "neoliberal" approach criticized by Wu, who emphasized drug instrumentalization as a reactive coping strategy to compensate for socioeconomic disadvantages. This made for interesting tension in the debate. Miller, however, also stressed the use of drugs in a social context and provided some interesting and noteworthy examples of drug instrumentalization in scientific thinking. Taken together, it is undisputed that drug instrumentalization has a strong social component with many dimensions, such as the goals and behaviors drugs are used for or the type of drugs available in microenvironments.

There may be also significant differences in alternative ways to change the mental state (see **Van Gulick**). One may argue that people with poorer socioeconomic backgrounds may attempt to instrumentalize drugs partially to overcome consequences of this situation. We have argued that there are clearly limits to the extent psychoactive drugs can be instrumentalized. They can certainly not equalize "natural" (e.g., genetic or early developmental) or social (e.g., born in a poor environment) disadvantages. As such, there may appear more instrumentalization goals in socially unprivileged people than in privileged ones. At the same time, there are fewer alternative "tools" (see Van Gulick) and less rational control established by families and the educational system. This may explain why poorer people use more psychoactive drugs and generate a higher proportion of addicts, who may have driven drug instrumentalization to its utmost ends and beyond.

R8. The claims of the drug instrumentalization theory

Several authors suggested that the major claims of the drug instrumentalization theory may be dissected, which may help to define the limits of the theory. **Goudie et al.** and **Pickard** distinguished two essential and independent claims. The first one is that drug instrumentalization theory suggests "drug use is instrumental" (Pickard) and "that drug-induced mental states facilitate behavior" (Goudie et al.). The second and wider-ranging claim refers to the evolutionary origin and role of drug instrumentalization as an adaptation, suggesting that the behavior has a fitness-related evolutionary origin and enhances reproductive fitness. In addition, Pickard identified a third claim that says "the desired ends [of drug instrumentalization] are easy to comprehend." Although most commentators appeared to agree with the first claim, they were skeptical about the second one (Goudie et al., Pickard, **Troisi, Ahmed, Ainslie, Sullivan & Hagan**). Several authors have suggested that the second claim may not even be necessary to hold the first one.

The most important critique was that there is as yet no clear evidence for an increase in reproductive fitness by non-addictive drug instrumentalization. We think that distinguishing different claims is useful in order to separately address the supporting evidence. We believe that there is good evidence in support of the first claim as outlined in the main text. When scanning the available evidence on psychoactive drug consumption, we noted that non-addicted drug use is a rather persistent phenomenon across several species. In humans, it is evident over long periods of time for different psychoactive drugs in virtually all habitats. In an attempt to explain this persistence, we considered whether it may have provided an evolutionary advantage. We think this claim is supported by the available evidence – though we have to admit that an explicit testing of this hypothesis and more empirical evidence are required.

The idea that psychoactive drug consumption may represent an adaptation in certain circumstances is not new, as some commentators allude to. **Lende** discussed evidence from interviews of Colombian adolescent drug users from which he constructed a summary variable of evolutionary benefits out of sexual and competitive benefits. We hope that this neuroanthropological approach may also guide future field research on non-addicted psychoactive drug use in humans. **Ainslie** suggested that there is an evolved trait that controls psychoactive drug consumption, but that it is one controlling the sensitivity to "reward, reinforcement or utility". We disagree that sensitivity to reward alone would be able to explain the rather sophisticated and highly organized non-addicted drug use we currently observe. However, sensitivity to the "utility" of drug use may be a relevant trait for selection, which may well favor non-addictive drug instrumentalization. Accordingly, those individuals with a high sensitivity for the use of psychoactive drug effects for certain purposes and at the same time resilience for compulsive use and addiction (**Ahmed**) may face an advantage. **Sullivan & Hagen** suggested earlier that the manipulation of one's own CNS with psychoactive plant compounds may actually be an adaptation, but one restricted to circumstances of mental illness or nutritional deficiencies (Sullivan & Hagen 2002).

True adaptations that have enhanced reproductive fitness may only become obvious over long periods of time. Most animals that do self-administer and instrumentalize psychoactive drugs under laboratory conditions, have only irregular access to psychoactive drugs in their natural habitats. Judging adaptive effects on fitness may therefore be difficult. On the other hand, recorded human history may be a too short time to allow for a longitudinal analysis. In addition, early human records may not provide sufficient information on drug use (types of drugs, content of psychoactive compounds, and frequency and occasion of use) and possibly supported behaviors. It may also be hard to judge whether a known drug instrumentalization has actually increased the reproductive fitness to a measurable extent.

Acknowledging these difficulties and also possible alternative explanations (**Ahmed**), we understand our discussion for an ultimate cause of the behavior rather as a suggestion and directive for future research than as a proven claim. However, we and others (**Lende;** Lende et al. 2007) have provided a number of arguments that do – at least from our point of view – suggest that drug instrumentalization is adaptive and has an ancient origin instead of being a most recent behavior. We took this suggestion further and expanded the list of potential circumstances, assuming indeed what **Pickard** called the third claim that we may at least grossly comprehend what is finally good for us. Regarding drug use as a consumer behavior with distinct reinforcement mechanisms as suggested by **Foxall & Sigurdsson** may further enhance insight. Based on these suggestions, we would like to call for a more thorough investigation of the potential beneficial and adaptive effects of drug instrumentalization at the levels of single individuals, groups, and the population, which should go beyond self-reports or counting babies.

R9. Implications of the drug instrumentalization theory

Here, we wish to clarify that drug instrumentalization theory was primarily suggested in order to better explain the present situation, incorporating a wide range of evidence from different disciplines. In doing so, we did not

https://doi.org/10.1017/S0140525X11000057 Published online by Cambridge University Press

intend to judge whether it is good or bad that human beings consume psychoactive drugs. If one accepts the second claim of the theory (see sect. R8) that the ultimate cause of the behavior is related to an increase in reproductive fitness, it may be hard to reject the behavior as purely maladaptive. However, because this claim still needs to be sufficiently supported with evidence (or disproved), it remains open for debate whether non-addictive drug instrumentalization may be rejected by its implications, as **Swendsen & Le Moal** do, or actively encouraged, as **Miller** suggests.

On that point, we should note that at least Western society has already made its decision on non-addictive drug instrumentalization, but under another label. Though ethical debate on cognitive enhancers is ongoing (e.g., Hesse 2010; Sahakian & Morein-Zamir 2007), systematic search and use of psychoactive drugs for healthy individuals is already well underway. Also, pharmacological help to achieve other instrumentalization goals, such as *improved physical appearance and attractiveness* has long been pursued, for example, by the development and use of anorectic drugs (Bray 2000; Ryan 2000). At this point, we welcome a debate on the implications but agree with **Sullivan & Hagen**'s precautionary view that it is still too early for political suggestions regarding known drugs with an abuse potential based on drug instrumentalization theory.

We argued that drugs are used to systematically alter one's own mental state in order to better perform non-drug-related behaviors. **Van Gulick** pointed out in his commentary that there are other ways to change the mental state that may not rely on psychoactive drugs, such as by "ideas and patterns of thought." We fully agree that certain types of mental activity may change general mental state. For example, a focused consideration of the positive elements in life may yield a more pleasant mood/mental state than a thinking pattern focusing on negative elements. This change in mental state may in turn determine whether and how other behaviors are performed. It is tempting to conclude that health policy should try to replace psychoactive drug use by enabling individuals to use their mental capabilities. The problems with this simplistic advice may be that efficacy of the mental activity-induced state changes can depend considerably, for example, on intelligence and training. Psychoactive drugs, in contrast, "work" in virtually all individuals no matter how privileged one person is. Regarding the relatively wide spectrum of mental state changes (e.g., behavioral disinhibition vs. cognitive enhancement), one might also question whether cognitive activity may work in all those directions. If psychoactive drugs cannot be removed from modern life, one may at least aim toward reduction and controlled consumption. In that we think **Van Gulick**'s suggestion of a combination of pharmacological and mental tools for instrumentalization may provide a valuable approach in health and disease.

ACKNOWLEDGMENTS

We would like to thank the many commentators who provided many thoughtful comments and a lively discussion. This work was supported by funds of the University of Erlangen-Nuremberg (Germany), the UK Department of Health NIHR Biomedical Centre for Mental Health, and the MRC-SGDP Centre at the Institute of Psychiatry, King's College London (UK).

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[The letters "a" and "r" before author's initials stand for target article and response references, respectively]

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