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Drugs as instruments – a new framework for non-addictive psychoactive drug use

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Long 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 only acknowledged as a 'necessary' prerequisite for addiction, but not as a stable and wide spread behavior in its own right. The present paper 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. Specific 'instrumentalization goals' are discussed and neurobiological mechanisms of how major classes of psychoactive drugs change mental states and serve non-drug related behaviors are outlined. We argue that drug instrumentalization behavior may provide a functional adaptation to modern environments based on a historical selection for learning mechanisms which allow the dynamic modification of comsummatory 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 every day 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: drug instrumentalization, mental states, evolution, drug memory, addiction

1. Introduction

1.1. Non-addictive drug use

The use of drugs is a wide spread 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 US 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 marihuana/hashish, cocaine, heroin, hallucinogens, solvents, or prescription-type psychotherapeutics. More than 50 % of Americans aged 12 or older reported being current drinkers of alcohol and over 28.6 % of Americans aged 12 or older were users of tobacco products. European surveys revealed that in the general population of the 15-64 year olds, about 324 million people (84%) were daily drinkers of alcohol. 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 which 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. However, epidemiological data show that the majority of people who consume psychoactive drugs with an addiction potential, are not addicts and will never become addicted (Zinberg & Jacobsen 1976; Zinberg et al. 1978; Glynn et al. 1983; O'Malley & Johnston 2002). Of those people who are classified as current alcohol drinkers in the US, 14.9% are diagnosed as addicts based on the SAMHSA (2005) report. Among the 20.4 million current users (previous month use) of illicit drugs in the US, which includes marihuana, cocaine, heroin, hallucinogens, solvents, and prescription type drugs, 34.3 % have been estimated to be addicts (SAMHSA 2005). European Union estimates are similar. In the EU, 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 US National Co-morbidity Survey the cumulative risk until the age of 54 to fulfill criteria for dependence to marihuana is 10%, for cocaine up to 21% (until age 40), and for alcohol about 20% (Wagner & Anthony 2002; Chen & Anthony 2004). 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). While drug addiction is an undeniable major burden to society, considerable use of psychoactive drugs is unrelated to addiction.

1.2. Psychoactive drug use

In this review 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 and/or behavior. Whereas a 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".

2. Widening the explanatory scope for drug use

The consumption of psychoactive drugs is usually considered a maladaptation, particularly in people with genetic and/or environmental risks prone to addiction (e.g. Schumann et al. 2003, 2008; Schumann 2007; Campbell et al. 2009). Many of the drugs consumed by humans are plant toxins, such as nicotine, cocaine, or cannabis, which serve 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 developed substances that reinforce plant consumption and why any organisms should have a mechanism that reinforces the toxin consumption is therefore a puzzle. This apparent evolutionary contradiction has been termed the 'paradox of drug reward' (Sullivan & Hagan 2002; Sullivan et al. 2008; Hagen et al. 2009).

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 stereotypies (Kramer et al. 1967; Gawin & Kleber 1986; Gawin 1991). 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 psychoactive drugs are voluntarily consumed by humans and animals are usually below the acute toxic range (Gable 2004; Hagan 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).

There are a number of alternative views which seek to explain the development and persistence of psychoactive drug consumption. The behavior may, thus, either 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 be 3.) An actual improvement in success in these same motivational states.

1.) Nesse and Berridge (1997) have argued that those psychoactive drugs which 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 they 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 just relatively narrow euphoria/hedonia. While 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 man (Wilsnack 1974). While it was argued that this subjective feeling is enhanced by drugs, 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 (Hagan 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 colleges (2007) analyzed the behavioral function of methamphetamine in a population of heavy users in Atlanta (USA). They interviewed users for their perceived functions of use

and identified three main categories: 1.) enhanced function, 2.) increased productivity, and 3.) functioning normally. Importantly, this study revealed that methamphetamine users did not perceive their drug use to impair their daily functioning, but rather to enhance it (Lende et al. 2007).

Several authors 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, i.e. 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; Peele & Brodsky 2000; Molnar et al. 2009). In addition, there is evidence for beneficial effects of methamphetamine use on everyday function (Lende et al. 2007; Lende 2007).

Overall, several researchers have recognized subjectively reported beneficial effects of certain consumption patterns and review 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 results in an improvement of fitness-relevant behavior. It also suggests that humans are able to subjectively perceive and/or cognitively reflect 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 live take drugs because their effects are useful for their personal goals. Psychoactive drugs can be '*instrumentalized'*. We refer to '*drug instrumentalization*' as a two step behavioral process: A.) 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 B.) better performance of other, previously established behaviors and better goal achievement.

An *instrument* may be defined as something that helps to achieve a goal, which would not be achievable or require a higher workload without the use of the instrument. As such,

behavior itself can be an elaborate instrument (Skinner 1938; Frolov & Pavlova 2003). 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 for a place where other people are to be found and to start 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 *mental state* of the organism. 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 working modes of the brain which are held stable over longer periods of time (minutes-hours) during which they provide the functional setting for fast computational processes in the millisecond-minutes range. Mental states govern the subjective perception, memory retrieval, and the autonomic and behavioral responses of an organism (White 1996). It is suggested that mental states of the brain 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. Steriade et al. 1990; Sarter & Bruno 1997; Aston-Jones et al. 1999; Schultz 2000; Jacobs & Fornal 2010). 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 options its environment offers. These responses, in turn, determine the success of an organism in performing previously established instrumental behaviors and, thus, how effectively it can reach its goals. As such, the mental state of an organism 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 which 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', this action is best performed in an attentive mental state and less well in a tired and distracted state.

By definition, all psychoactive drugs change the mental state of an organism (e.g. Post et al. 1974; Fischman & Schuster 1982). 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 for a full appreciation of drug seeking, consumption and the resulting mental state change, the *set* of the organism, the surrounding *settings*, and the *subsequent behaviors* that follow the change in mental state are pivotal (Zinberg 1984). 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. However, after a long working day, 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', while the *B process* would be 'driving the car'. The individual instrumentalization goal would be 'driving home', which might belong to the goal class of "Improved 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 e.g. 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, i.e. its development in the life-history of a single individual (Tinbergen 1963; Hill & Newlin 2002; Nesse 2002). A distinct behavior, in order to be acknowledged as a true adaptation, needs to solve an adaptational problem which 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 between which, fast transitions must be made (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 which allows to flexibly adjusting behavioral traits according to each microenvironment (Tooby & Cosmides 1992; Cosmides & Tooby 1994). An example for this may be "social disinhibition" as a behavioral trait in humans. It is certainly appropriate and rewarded in a close social setting, but inappropriate and even punished in a professional work environment. An adaptation of flexibly shifting 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 occurred in oldest human records demonstrating consumption of natural drugs for at least ten thousand years (Abel 1980; Seefelder 1996; Dudley 2002; Heath 2000; 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 (Lozano 1998; Dudley 2000). 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 homeostasis, or failed to, this particular food will be searched out and consumed in the future, or avoided (Rozin & Kalat 1971; Johnson et al. 1975, Lozano 1998).

Ethological research in chimpanzees has shown that the choice of food may not only be guided 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 (Wrangham & Nishida 1983; Rodriguez et al. 1985; Glander 1994; Page

et al. 1992), referred to as 'zoopharmacognosis' (Rodriguez & Wrangham 1993; Huffman 2003). Zoopharmacognosis appears to be learned as much as food preference or avoidance (Lozano 1998). Self-medication can be a conditional behavior in mammals which depends on the physical state of the body, i.e. a particular food is consumed 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; Sullivan et al. 2008; Singer et al. 2009; Hagan et al. 2009). The ability to dynamically adapt food choice according to the physical state of the organism based on a learning mechanism may thus be a basic adaptive trait in mammals enhancing survival and reproduction (Clayton & Wolfe 1993; Sullivan et al. 2008; Hagen et al., 2009). 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, crucial for the understanding of 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. D9-THC in cannabis plants). Recently available purified psychoactive substances may represent a new 'niche' we have constructed which has the potential to modify the future basis of natural selection (Laland et al. 2000, 2010). Psychoactive drug consumption is now considered to be a polygenetically determined behavior (Stacy et al. 2009), influenced by environment and culture (Blomeyer et al. 2008; Clark & 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 (Yokel & Pickens 1973; Arroyo et al. 1998; Witkin et al. 1999), dogs (Risner & Jones 1980) and monkeys (Johanson et al. 1976; Ritz & Kuhar 1989; Howell & Byrd 1995; Fantegrossi et al. 2004) when given access to a drug. While the availability of purified psychoactive drugs is a new environmental feature (Nesse 2002), the behavioral

capacity to consume drugs, i.e. the learning mechanisms, developed much earlier in evolution.

2. In industrialized societies, individual work load is very high in a way that many different behaviors need to be performed 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 e.g. 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 for our pre-agricultural ancestors. This may put a selection pressure not only on single behaviors but even more on behavioral flexibility, i.e. 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 which 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 (Wakefield 1999; Cosmides & Tooby 1999), psychoactive drug use behavior may under these relatively recently occurring environmental changes have led in 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). Thus, the environment of an organism can be considered to be 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 since 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 and/or duration of a 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 e al. 1980; Maloff et al. 1981; Brown 1985; Cooper et al. 1995). 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 & 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 can be reported (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 towards one's own survival. Therefore, psychoactive drug use should be considered with regard these two life themes raised by behavioral ecologists when considering the continuous trade-off between allocations of finite human resources, like any important human behavior (Hill & Chow 2002).

In the following paragraph different proximal mechanisms of psychoactive drug use are described in terms of unique instrumentalization goals. Their general functions for reproduction and/or survival and maintenance are discussed. To substantiate these views, plausible neuropharmacological mechanisms for improved functioning are suggested.

4.2.1. Improved social interaction. The establishment and maintenance of social groups and networks is essential for many species (Hamilton 1964; Axelrod & Hamilton 1981). 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 adult people 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 coming together after school or work, are where peer groups and social networks are formed and maintained.
Interestingly, a number of drugs change mental states in a way which 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, but 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 which can facilitate social behavior under various circumstances are alcohol (Glynn et al. 1983; Bradizza et al. 1999; Kuntsche et al. 2005), marihuana (Zvolensky et al. 2007; Bonn-Miller et al. 2007), cocaine (O'Malley et al. 1985; Lende 2005), and other psychostimulants (White et al. 2006; Davey et al. 2007), when used in a low to medium dose range (Segal 1985; Cato 1992; Boys et al. 1999, 2000; Simons et al. 2000; Boys & Marsden 2003). Also some effects of nicotine and caffeine may be useful to maintain social interactions (Eissenberg & Balster 2000; Cauli & Morelli 2005).

Alcohol reduces social inhibition, the discomfort in social situations, and social anxiety, increases talkativeness, and increases the tendency to talk about private affairs (Baum-Baicker 1985; Peele & Brodsky 2000; Carrigan et al. 2008; Booth & Hasking 2009). These 'beneficial effects' are brought about by the multiple pharmacological targets of alcohol in the brain (McBride et al. 2002; Tupala & Tiihonen 2004; Harris et al. 2008; Spanagel 2009). Most important for these effects is probably the interaction of alcohol with $GABA_A$-receptors in the brain. g-Aminobutyric acid (GABA) is the most abundant inhibitory transmitter in the brain (Feldmann et al. 1997). Alcohol at low to medium doses enhances GABAergic activity, thus, 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 reward threshold of the brain (Koob et al. 1998) and, thus, may enhance the incentive value of social interaction (Ikemoto & Panksepp 1999). No claim here is made 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 2010). Social cognition, in contrast, involves also cortical networks including the medial prefrontal cortex and anterior cingulate cortex (Burnett et al. 2010). While 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 which 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 parties or club settings (Britt & McCance-Katz 2005; White et al. 2006). In addition to general arousal and increased attention, people become more talkative, disinhibited, and self-confident after consuming these drugs. In addition to that, psychostimulants suppresses fatigue, which also allows 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 NA in the CNS by their interaction with the monoamine transporters (Ritz & Kuhar 1990; Ritz et al. 1990). They block or reverse monoamine transport (Johanson & Fischman 1989; Seiden et al. 1993; Green et al. 2003; Müller et al. 2007a; Pum et al. 2007). While high NA levels may account for the suppression of fatigue (Aston-Jones et al. 1999), 5-HT may mediate the anxiolytic (Schwarting et al. 1998; Ho et al. 2004; Müller et al. 2008) 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 g-hydroxybutyrate (GHB), can at low doses stimulate social interactions. They can induce a feeling of empathy, reduce anxiety, and increase relaxation. At the same does range they are locomotor stimulants. These drugs are non-competitive glutamate N-methyl-D-aspartate (NMDA)-receptor antagonists (Jentsch & Roth 1999). Glutamate is the most abundant excitatory transmitter in the brain (Feldmann et al. 1997). Blocking NMDA receptors is considered the predominant mechanism for the observed behavioral effects (Weir 2000; Britt & McCance-Katz 2005; Wolff & Winstock 2006).

A number of psychoactive drugs can be used to change an individual's mental state in way to facilitate social interactions. A state, where conditioned and unconditioned anxiety and behavioral suppression is attenuated, can be achieved by enhancing GABAergic inhibition and reducing glutamatergic excitation. Alternatively a state in which the energetization 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/high effects, which may facilitate the transition to habitual drug use and addiction (e.g. Wagner & Anthony 2002; Chen & Anthony 2004). An

acute over dose reverses the sought effects and may even result in a schizophrenia-like psychotic state for psychostimulants or hallucinations and delirium for alcohol (e.g. Siegel 1978; Rich & Singer 1991).

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 (Taylor et al. 1999; Cooper 2006; Patrick & Maggs 2009). 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. Thus, a 'scheduled' and time dependent (e.g. Saturday night; Patrick & Maggs 2009) transition from professional to private microenvironments may 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 which 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. 2008). Certain personality traits, such as introversion, may be disadvantageous in some settings but advantageous in others. Since it is argued that mental states are changed by psychoactive drugs, one might view drug instrumentalization also as a self-induced, time-restricted personality change. For example, extraversion 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 between alcohol drinking, drunkenness and the likelihood for sexual intercourse in particular in adolescents and young adults (e.g. Sen 2002; Lavikainen et al 2009; Patrick & Maggs 2009; Wells et al. 2010). In addition to the pharmacological effects of alcohol, the expected (conditioned) disinhibitory effects mediate the higher chances of sexual intercourse (Crowe & George 1989; Cooper 2006; 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 which 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 interfering 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 and making a potential partner appear more 'attractive' (Koob et al. 1998; Ikemoto & Panksepp 1999).

One often reported function of drugs use is to 'enhance sex'. Drugs frequently reported to be used for this purpose are alcohol, cannabis, amphetamines, ecstasy, and cocaine (Maier 1926; Boys et al. 1999, 2001; Boys & Marsden 2003). While 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 which 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. Thus, 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 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). While only 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 due to 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 improve cognitive performance in this case, both legal and illicit, in western societies.

Caffeine, a major psychoactive ingredient of coffee, tea, chocolate, and soft drinks, is a legal drug frequently used to keep people awake. During waking, the brain levels of the neurotransmitter, adenosine, steadily increase and trigger fatigue and sleepiness (Huston et al. 1996; Porkka-Heiskanen et al. 1997; Hong et al. 2005). 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 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 non-smoking humans (Rezvani & Levin 2001). In human smokers, there is a decline in cognitive abilities after smoking cessation, which can be reversed by nicotine administration (Mansvelder et al. 2005). 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 (McBride et al. 1999; Wonnacott et al. 2000; Markou 2008), 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. Amphetamine and other psychostimulants are used in the US and Australia by truck drivers to stay attentive during long driving hours (Grinspoon & Hedblom 2005; Davey et al. 2007). Prescription stimulants, such as methylphenidate, demethylphenidate, amphetamine, and methamphetamine, are used non-medically by students to promote concentration, to stay awake, to increase alertness, and to help studying (McCabe et al. 2005; Arria & Wish 2006; White et al. 2006; Sussman et al. 2006; Teter et al. 2006; Lende et al. 2007). 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 doses 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 1990; Ritz et al. 1990). This increases extracellular NA levels and causes a hyperactivation of NA receptors (Johanson & Fischman 1989; Seiden et al. 1993; Green et al. 2003), 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. While 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 the consumption and to drug addiction.

4.2.4. Facilitated recovery and coping with psychological stress. Modern societies not only request constant high cognitive and physical performance, they also allow decreasingly little time for the individual to recover from periods of intense and/or high work load (Anders 1961). This leaves the individual with the pressure of a fast recovery and finding 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, thus, increase the success of many behaviors in other microenvironments (Segal 1985; Baum-Baicker 1985; Peele & Brodsky 2000; Amendt 2003).

There are a number of pharmacologically different drugs that are instrumentalized to facilitate recovery 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 (Waldorf et al. 1991; Lende 2005), methamphetamine (Lende et al. 2007), barbiturates, benzodiazepines, and other sedative anxiolytic drugs (Boyd et al. 2009) to cope with stress (Segal 1985; Griffiths et al. 1991; Lader 1994; Boys et al. 1999, 2000; Bradizza et al. 1999; Perkins 1999; Boys & Marsden 2003; De Las Cuevas et al. 2003; Heberlein et al. 2009). 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 total abstinence (Peele & Brodsky 2000; Rodgers et al. 2000; Taylor et al. 2005; Mondaini et al. 2009; Skogen et al. 2009; but see also: Sareen et al. 2004). Moderate drinkers were also found to face less depression in the presence of stress than abstainers (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 are more likely to be involved which also contain a high number of $GABA_A$-receptors (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 wide spread illicit psychoactive drug instrumentalized to ameliorate pressure and to reduce stress is cannabis (Boys et al. 1999, 2000). The main psychoactive compound of cannabis is D9-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 non-sedating drugs, such as cocaine in animals and humans. The drug-induced increase in arousal (Haney

et al. 1995) might involve another coping mechanism which resembles more a 'fight' than a 'flight' response. Psychostimulant drugs increase aggression levels and physical strength and can suppress fatigue (Johanson & Fischman 1989; Seiden et al. 1993; Green et al. 2003), 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 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 and 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 which 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 which determine mental states. Behavioral functions and reproduction rates are significantly impaired in these disorders (Uher 2009).

In certain psychiatric disorders there appears to be an increased consumption of psychoactive drugs with a particular neurochemical profile. While 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 which do not fulfill the diagnostic criteria of a psychiatric disease (Boys et al. 2001; Boys & Marsden 2001; Boyd et al. 2006).

It is well known that psychoactive drugs are used by people suffering from negative affect to self-medicate and regain some sense of control over their mental state (Glynn et al. 1983; Khantzian 1985, 1997; Markou et al. 1998; Boys et al. 1999, 2000; 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. 2007; Zachny & 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 the use of psychostimulant drugs by non-clinically diagnosed people 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 (Wyatt et al. 1988; Maisonneuve et al. 1995). 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 Hagan (2002) suggested that at least parts 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 Hagan (2002) argued that the drug might compensate for the deficit. This might be true for some drugs. Cocaine, for example, is used by people suffering from depression 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). However, for the long term antidepressant effects, chronic drug taking is required in order to increase basal 5-HT levels and 5-HT throughput (Carr & Lucki 2010).

Psychiatric disorders are characterized by an altered mental state and inadequate behavioral responses. Several psychotropic drugs were found to be useful by individuals to temporarily ameliorate at least parts of their disease related mental or/and cognitive disturbances. Since 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 co-morbid 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 which 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 loose 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 and/or quantitatively altered cognitive performance (Stillman et al. 1993; Lende et al. 2007) may also count as an example of

novelty. While 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 which then are interlinked. Novelty and new sensations can be considered as primary reinforcers in humans and animals (Zuckerman 1990; Weil 1998). 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 which enhances survival chances and reproduction of an organism. 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 the discriminative stimulus properties of a drug (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 are not novel anymore and something other than the novelty effects are needed to motivate continuation of drug use. If there are no other motives or instrumentalization goals arising, the 'experimental' consumption of the drug may cease. This is supported by drug consumption surveys which collectively show considerably higher rates for trying a particular drug once in a life time versus regular consumption, measured e.g. as 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 the mental state of an organism in a way that present stimuli and/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, thus, drive psychotropic drug consumption only for a relatively short period of time, i.e. 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 the self-administration studies in animal, which showed that those drugs that are consumed primarily for their sensory perception changing properties by humans, like hallucinogens, are not regularly self-administered by animals (Nichols 2004).

A particular group of psychoactive drugs used to change sensation and perception of the external world and to increase self-understanding and self-discovery are hallucinogenic drugs (Cato 1992; Boys et al. 1999, 2000; Boys & Marsden 2003; Nichols 2004). These

drugs include natural compounds, like mescaline and psilocybin, as well as semi-synthetic drugs, like lysergic acid diethylamide (LSD). They induce a mental state which is 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 (Nichols 2004; Geyer & Vollenweider 2008). In this state, environmental stimuli can be perceived in a new way which 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 (Gonzales-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 interneurons (Sheldon & Aghajanian 1990; Aghajanian & Marek 1997). 5-HT and 5-HT_2 receptors play an important role in sensory stimulus processing (Pum et al. 2008a; Quednow et al. 2008, 2009; Jacobs & Fornal 2010). 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 (McMahon et al. 2001; Müller & Carey 2006; Adell et al. 2010), 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 enactogenic drug, MDMA (Boys et al. 1999, 2000), 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 its use beyond the sensory curiosity.

Phencyclidine, ketamine and gammahydroxybutyrate (GHB) are drugs used in the club and rave scene. 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 (Weir 2000; Britt & McCance-Katz 2005; 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 in a way 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, and 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 (Tatarkiewicz 1976; Marcuse 1984). Human brains work towards linking this subjective feeling with either the receipt of a primary or secondary reward, or with the change in reward contingencies, i.e. when a formerly meaningless stimulus now predicts reward availability or a formerly useless behavior now yields a reward. While 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 (Peele & Brodsky 2000; Lende & Smith 2002). An enhanced mood by itself, i.e. 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 instance of a mental state change, which may allow more efficient performance of many other goal-directed behaviors and, thus, enhance chances for survival and reproduction.

Psychoactive drugs like heroin, morphine, cocaine, amphetamine, methamphetamine, methylphenidate, and MDMA can induce a potent feeling of euphoria and an emotional 'high' (e.g. Resnick et al. 1977; Javaid et al. 1978) and are used for this reason by non-addicts (Boyd et al. 2006; Teter et al. 2006; McCabe et al. 2007; Zacny & Lichtor 2008). A certain degree of euphoria can also be induced by other drugs of abuse, such as alcohol, cannabis, LSD, benziodiazepines, and nicotine (e.g. Boys et al. 1999, 2000; Boys & Marsden 2003; Sher et al. 2005). However, the later 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) supported by the hugely influential finding that drugs of abuse increase DA levels in the Nac in vivo, while non-abused drugs do not (Di Chiara & Imperato 1989; Di Chiara 1995). It is now well understood how pharmacologically different classes of drugs converge in their acute neurophysiologic effects of increasing mesolimbic DA activity (Koob 1992; Di Chiara & North 1992; Ameri 1999; 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 hyper-activated during acute drug exposure. In humans, drug-induced euphoria is usually more intense than naturally occurring euphoria. However, there subsequently appeared to be several conceptual problems with the DA hypothesis (Salamone et al. 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 (Young et al. 1993; Brischoux et al. 2009; Matsumoto & Hikosaka 2009). While these findings may have preserved an outstanding role for DA in reinforcement learning and addiction (Robbins &

Everitt 1996; Ikemoto & Panksepp 1999), 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, they 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 (Robinson & Berridge 2003). 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 (Nestler & Aghajanian 1997; Koob 1999; Everitt & Wolf 2002; Kalivas & Volkow 2005; Williams & Adinoff 2007; Heilig & Koob 2007; Müller et al. 2010).

Euphoria is probably the easiest to accept instrumentalization goal for psychoactive drugs. Nevertheless, euphoria is not the most predominant and sought after effect during most psychoactive drug taking occasions in non-addicts (for an evolutionary discussion see: Sullivan et al. 2008; Hagen et al. 2009). 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, e.g. 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 non-addicted 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 & LeMoal 2008).

4.2.8. Improved physical appearance and attractiveness. Modern societies impose idealized concepts on males and females respectively, which not only include expectations for cognitive and social performance, but also include 'ideal' norms for physical appearance. Given the natural variation among humans and therefore variance around idealized norms, people feel the pressure to perform behaviors which 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 towards a lean appearance in females and towards 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 non-smokers. 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 behaviour towards specific food (Jo et al. 2002).

Also the use of cocaine and amphetamine and its derivatives for their hunger suppressing effects has been reported (Garattini et al. 1978; Boys et al. 1999, 2000; Boys & Marsden 2003). 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 a1 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 increases chances of mating. Physical appearance may be enhanced by sport, exercise, or body building. The predominant class 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, thus, affect other behaviors such as e.g. 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, b-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).

There are several drugs that are used to facilitate or inhibit behavior directed towards a change in physical appearance. While 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 behaviour.

Altogether, the functional analysis of non-addictive 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 the subsequent section.

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. The idea of a 'memory of addiction' was introduced by Nancy Mellow in a discussion of addiction related behaviors (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 multiple memory systems of the brain. 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 (Heyne et al. 2000; Boening 2001). 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 which support emotional learning, thus, encompassing Pavlovian as well as instrumental conditioning (Robbins et al. 2008). Overall, these concepts of drug- or addiction memory have in common that they focused explicitly on drug addiction, ignoring the fact that in order to establish addiction, a preceding period of non-addicted 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.

It was 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). It is suggested here that non-addictive psychoactive drug instrumentalization also involves a decision-making process which relies on an interaction of all drug-related memory systems. Parallel to non-drug related memory systems (Squire et al. 1993; Milner et al. 1998), two major drug-memory categories are distinguished: a *declarative drug memory* and a *non-declarative drug memory* (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, e.g. 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 (Miller et al. 1990; Leigh & Stacy 2004; 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 was suggested that the expectation of drug effects (Leigh 1989; Del Boca et al. 2002) should be conceptualized as a retrieval process from different types of memories (Goldman et al. 1991). The expectation of the 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 thus, influence the establishment of the episodic drug memory. It is hypothesized that humans start to establish a semantic drug memory as a precondition of psychotropic drug instrumentalization by learning from e.g. media or peer group, long before 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, e.g. 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).

While the experience of euphoria is often the sought after mental state, it is not the only one on the time scale 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. However, once established 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 drug instrumentalization establishment (Miller 2001; Eissenberg & Balster 2000).

The *non-declarative drug memory*, in contrast, is not consciously accessible and can only be inferred from behavioral changes. The non-declarative 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 e.g. 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; Siegel 1988; O'Brian et al. 1998).

Instrumentally conditioned drug memories comprise engrams established by instrumental conditioning. Major behaviors induced by these engrams are drug seeking and drug self-administration (Spealman & Goldberg 1978; Richardson & Roberts 1996). These memories also include drug-cues which can serve as secondary reinforcers, as shown in conditioned place preference (Bardo & Bevins 2000; Tzschentke 2007; Childs & de Wit 2009), or which can re-instate drug seeking and drug self-administration (Wikler 1973; de Wit & Stewart 1981; Shaham et al. 2003). They may also include memories established by social learning, e.g. by observation (Bandura et al. 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, i.e. 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 (Porrino et al. 2004; Belin & Everitt 2008), 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 i.v. 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.

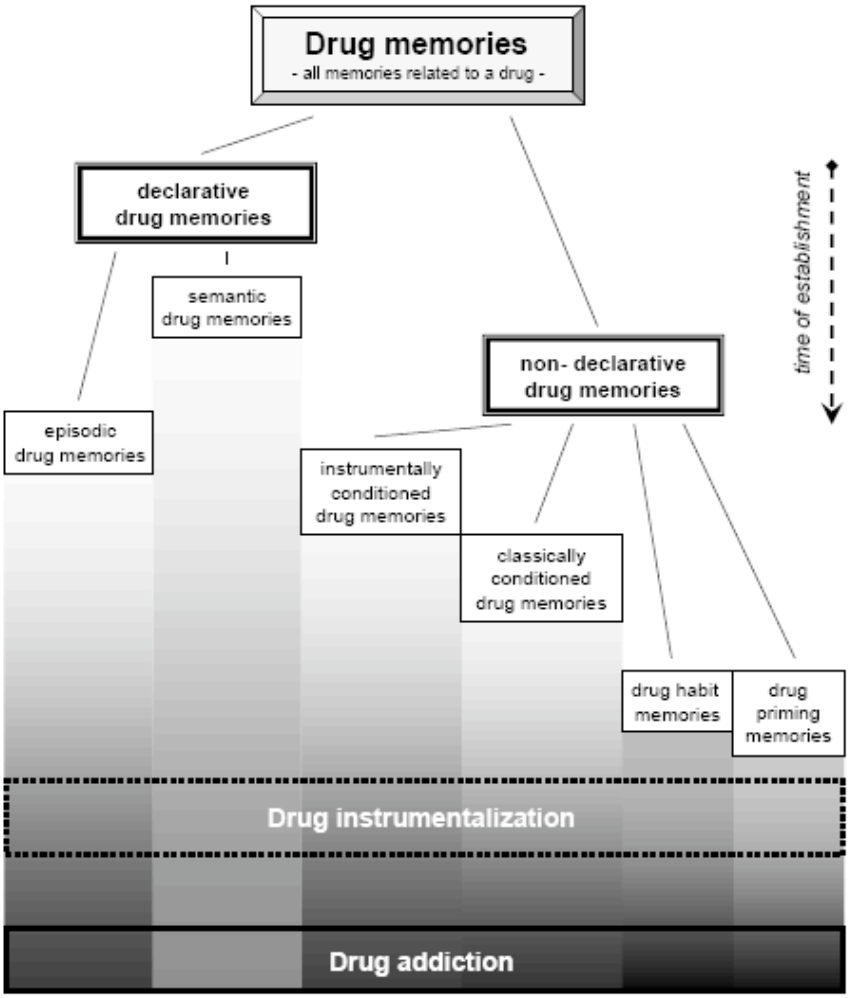

Fig. 1

Figure 1: *Drug memory systems based on normal memories that are likely to be influenced by psychoactive drugs. 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 (for a detailed description: see main text).*

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. Since 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 which is reflected at the level of the brain e.g. 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 (DE_o) serves as a teaching signal to strengthen or weaken the associations of the S_x with an action representation and with action outcome expectation. In constant environments with well established S-R and stimulus-action-outcome associations, DE_o will approach zero, thus, 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 (Robinson & Berridge 1993; Ikemoto & Panksepp 1999). 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. The consequence (action outcome) of R_y is an altered mental state of the organism (DM_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-DM_s association requires procedural-, instrumental conditioned- as well as episodic drug memories. While R_y may initially be under control of the action outcome (DM_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 (DM_s). If DM_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. Thus, the action outcome is enhanced when the R_x is performed

under DM_s. The comparator detects a positive difference between the action-outcome expectation, which was generated during a non-drugged mental state, and the actual outcome achieved under DM_s. This difference (DE_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 DM_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 outcome. In order 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 DM_s with the expectation to perform the instrumental response R_x more efficiently. Once DM_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 DM_s is generating a better action-outcome than under a drug free mental state. If environmental circumstances and DM_s-enhanced action-outcome remain constant (i.e. no tolerance or sensitization develops), there will be no negative teaching signal DE_o generated, and the associations of S_y-R_y-DM_s and S_x-R_x are maintained.

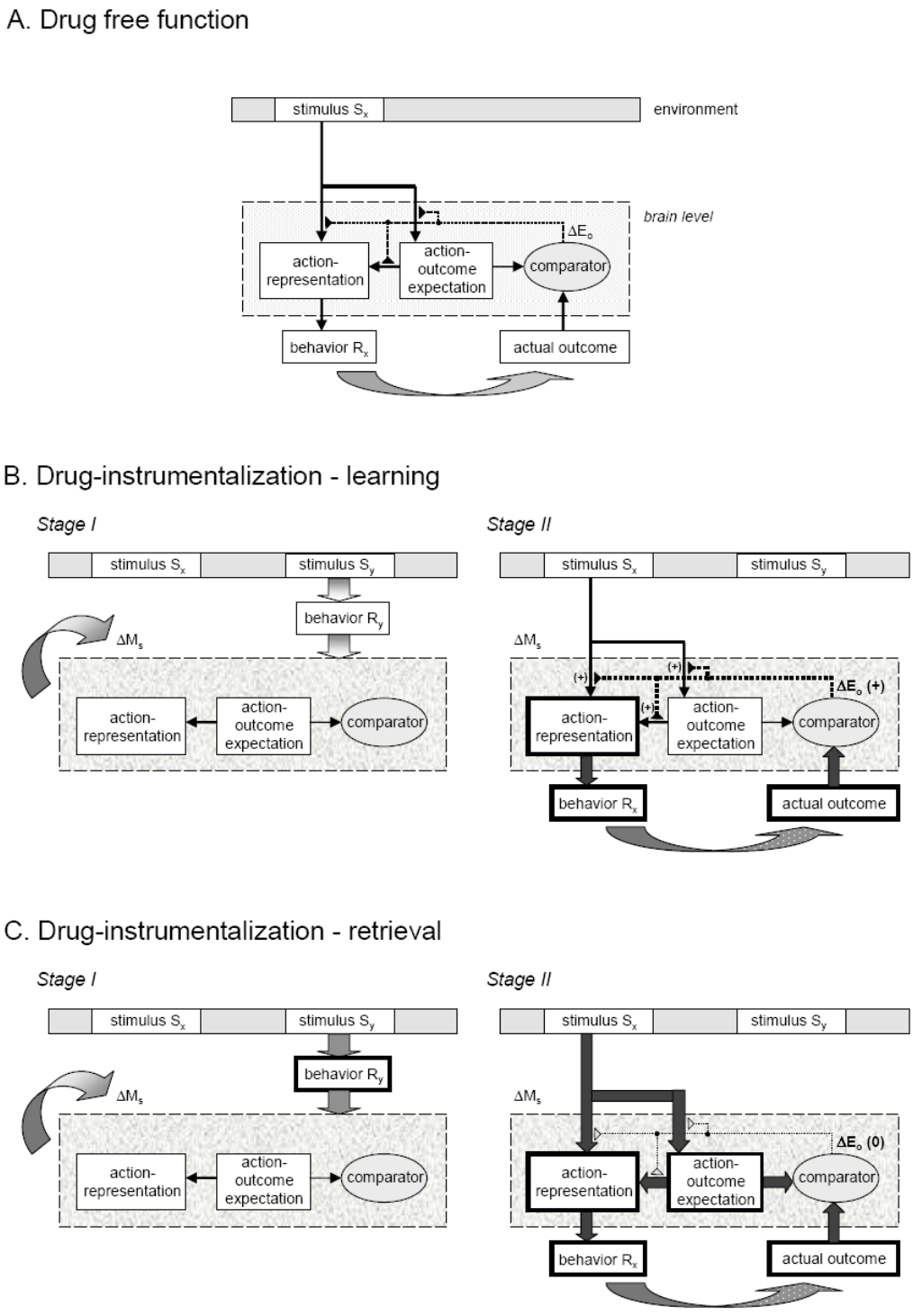

Fig. 2

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 (for a detailed description: see main text).*

6. Ontogeny of drug instrumentalization

6.1 Drug instrumentalization establishment during a life-time

While one can read about, and establish a factual knowledge on, the effects of drugs more is learnt 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 (Spear 2000; Kuntsche et al. 2006). Experimental consumption, in contrast to instrumentalization and compulsive consumption, refers to a consumatory 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 et al. 1980; Brown 1985; Miller et al. 1990; Gustafson 1991; Peele & Brodsky 2000), the individual response profile after first consumption is virtually unpredictable (e.g. Waskow et al. 1970; Jones 1971). 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; Zinberg 1984; Simons et al. 2000). The perceived usefulness was found to predict future use of the drug (Boys et al. 1999; Boys & Marsden 2003; Leigh & Stacy 2004).

The introduction to the drug, appropriate settings and possible instrumentalizations are usually performed by older and/or more experienced members of the peer group (e.g. Friedman et al. 1985; Eissenberg & Balster 2000). However, given inter-individual differences in drug pharmacokinetics and -dynamics, in personality, and in life circumstances, each person customizes its 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. They also learn 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 indeed an integral part of a person's life within a socially acceptable range of behaviors (Zinberg et al. 1978; Waldorf et al. 1991, Davies 1997, Heath 2000).

6.2. Benefits vs. adverse effects of psychoactive drug use

Although it is argued for evolutionary benefits of non-addictive drug use here, it has to be emphasized 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/or body peripheral organs have been documented for e.g. alcohol (Parsons 1998; Harper 2007; Ward et al. 2009), MDMA (Seiden & Sabol 1996; Gouzoulis-Mayfrank & Daumann 2009); 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).

It is argued here that in the majority of non-addictive psychoactive drug users, there are beneficial effects on self-maintenance and/or reproduction rate 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; Peele & Brodsky 2000; Lende 2007). As such, the behavior of psychotropic drug instrumentalization may have a heritable component (Schumann 2007) which 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 (Jessor 1987; Johnstone et al. 1996; Hill & Chow 2002). 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 (Miller-Tutzauer et al. 1991, Leonard & Das Eiden 1999) 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. It is suggested that since 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 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 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 leads every year to directly 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 was argued that even drug addiction may be an adaptation in order to cope with 'integration failure' (Alexander 1987, 1990). This view highlighted the important role of adaptation problems at the personal level for the continuation of psychoactive drug consumption. Importantly, the first steps of later 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 only have adaptational effects in non-addicts, but is 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 plethora 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 grey 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 which 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 not only on the adverse effects of addiction and accidental overdosing but also on how drugs are instrumentalized should be systematically provided. While 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 life's 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 which are prone to drug instrumentalization, such as sexual maturation, peer group pressure, socializing with the opposite sex, and increasing 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 e.g. 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 e.g. *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 can not be achieved without extensive psychotropic drug use.

The occurrence of drug instrumentalization can be seen as an indicator that particular goals are not (or less easily) achieved by 'natural means'. Once identified, particular training may be sought to focus on these goals and to reduce the extent the drug is used for this goal. Analysis and training could be provided at personal level or, if an instrumentalization pattern prevails in a particular group, also at family-, school-, or community level. 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, thus, 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 (Kendler et al. 2003b; Sher et al. 2005; Blomeyer et al. 2008).

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. Since the full extent of the mechanisms of drug instrumentalization are not consciously accessible to the user (e.g. non-declarative memory-based behaviors), 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 in order to test the origin of the behavior and its neurophysiological prerequisits. In contrast to present animal models of drug self-administration (Sanchis-Segura & Spanagel 2006; Olmstead 2006), animals should be given the chance to instrumentalize the drug self-administration behavior in order to enhance their performance in non-drug related behaviors. It may also be interesting 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. While 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.

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