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Review

Drug instrumentalization

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ABSTRACT

Psychoactive drugs with addiction potential are widely used by people of virtually all cultures in a non-addictive way. In order to understand this behaviour, its population penetrance, and its persistence, drug instrumentalization was suggested as a driving force for this consumption. Drug instrumentalization theory holds that psychoactive drugs are consumed in a very systematic way in order to make other, non-drug-related behaviours more efficient. Here, we review the evolutionary origin of this behaviour and its psychological mechanisms and explore the neurobiological and neuropharmacological mechanisms underlying them. Instrumentalization goals are discussed, for which an environmentally selective and mental state-dependent consumption of psychoactive drugs can be learned and maintained in a non-addictive way. A small percentage of people who regularly instrumentalize psychoactive drugs make a transition to addiction, which often starts with qualitative and quantitative changes in the instrumentalization goals. As such, addiction is proposed to develop from previously established long-term drug instrumentalization. Thus, preventing and treating drug addiction in an individualized medicine approach may essentially require understanding and supporting personal instrumentalization goals.

1. Introduction

Psychoactive substances can be defined as chemical compounds that change an organism's behaviour or subjective experience of itself and the external world after consuming the substance. Humans and many animal species actively consume psychoactive substances. They can accidentally consume and experience the resulting changes in behaviour and subjective experience, and they also form memories of the drug, its consumption, and resulting effects. We can readily assume that these memories give rise to regularity in that psychoactive substances are voluntarily searched out and consumed.

In a natural context, the availability of psychoactive substances is limited, but this has been overcome by humans, who have also developed behaviour that leads to the industrial production and refinement of such substances in a virtually unlimited amount. Among humans, natural availability no longer controls psychoactive drug use, but other factors do [2]. The group of psychoactive substances may comprise nutritional ingredients and pharmaceutical products, but the subgroup of addictive drugs in particular has caused major concern. These substances are defined by their ability to cause drug addiction, a major psychiatric disorder [7]. It should be noted that the classification of an 'addictive drug' describes only a potential property of the substance. It does not mean that every consumer or even the majority will develop an addiction after consumption.

When addictive drug use by humans is considered, there are two major questions that need to be answered: 1.) Why do humans consume psychoactive drugs on a scale that affects virtually all habitats and with a persistence that runs through all times of human record keeping? 2.) Why do humans become addicted to certain psychoactive drugs? Each of these questions may be answered at distinct explanatory levels in different ways. Evolutionary, psychological, and neurobiological levels address distinct aspects of the rather complex multi-level phenomenon. Ideally, all these levels of explanation provide answers that are logically coherent between explanatory levels. The aim of this review is to provide an answer to the key questions of psychoactive drug use and addiction that connects evolutionary and psychological levels of explanation and attempts to outline how this arises from a neurobiological and neuropharmacological level.

2. Drug use and addiction at evolutionary level

The consumption of addictive drugs is frequently considered to be a maladaptive behaviour as people with a genetic risk or living in certain environmental conditions may develop a drug addiction [39,213,285–287]. Many of the psychoactive drugs with addiction potential consumed by humans are plant toxins. Natural drugs, like nicotine, cocaine, or cannabis, were developed by plants as a chemical defence to prevent plant consumption. The evolutionary adaptation of

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these toxins in plant self-defence is widely accepted to deter herbivores [211]. It is still unclear why many of these plant compounds have rewarding effects, which may actually also reinforce plant consumption. On the other hand, plant eaters should not have evolved brain mechanisms that are susceptible to a reinforcing action of life-threatening toxins.

This contradiction in plant-animal coevolution is still an unresolved paradox of drug reward [95,307,308] that may be resolved at the level of neuropharmacological dose-response effects and psychological hormesis. For instance, drugs like cocaine have hedonic and euphoria-inducing effects at only low to medium doses. In high amounts that are still below a lethal level, cocaine has aversive effects. It may cause drug-induced psychosis with paranoia, hallucinations, and behavioural stereotypies [81,82,155]. As such, consumption of low to medium concentrations may benefit the consuming organism, while high amounts severely damage it and protect the original plant. This may be confirmed by addictive drugs with rather small pleasure-inducing effects, such as nicotine and caffeine, which are voluntarily consumed at only low, non-toxic doses [43].

Non-addicted individuals usually consume addictive drugs in a non-toxic dose-range [78,95]. Accordingly, the evolutionary paradox of drug reward may be resolved: in a low to medium dose range, the drug effect is not toxic in a life-threatening sense. As long as this dose range is maintained, psychoactive drug consumption may well provide a functional adaptation in evolutionary terms as it may enhance survival and reproduction of oneself or one's kin [45].

It has been argued that the psychoactive drugs that induce positive emotions generate a mock fitness-benefit signal. This signal hijacks incentive salience mechanisms in the brain that control drug-seeking and taking behaviour [213,257,322]. Positive and negative emotions and their neurobiological mechanisms provide an unquestionable fitness benefit to an individual as they allow specific coping with advantageous and dangerous environmental conditions [213]. However, it might leave the organism with a compromised fitness when the natural function of any kind of emotion is artificially corrupted or 'hijacked' [213,228].

It has been suggested that psychoactive drugs are taken to inflate the 'self-perceived survival ability and reproduction fitness' (SPFit) [217]. Thus, the SPFit concept describes the motivation to enhance and protect survival and reproductive fitness. This was linked to feelings of personal power and sexual attractiveness. This idea is supported by findings showing that drugs like alcohol at moderate doses increase the subjective perception of power in humans. It has also been acknowledged that psychoactive drugs may well increase the subjective feeling of power and control, but evolutionary benefits of the consumption were denied [217].

Potential short- and long-term beneficial effects of psychoactive drug use have been discussed previously [95,164]. Drug use behaviour was suggested to be a potential evolutionary adaptation at the behavioural level [164,210]. It was argued that the adaptive function of drug use is to provide an individual with predictable short-term pleasure in an unsafe environment. In these circumstances, the pursuit of natural reinforcers is hard to establish. Drug addiction has been considered as a maladaptation caused by a missing regulatory function controlling salience signalling in the brain's mesolimbic dopamine (DA) system [164]. An interview analysis of the perceived behavioural function in a population of heavy methamphetamine users in Atlanta (USA) identified three main functions: 1.) enhanced functioning, 2.) increased productivity, and 3.) enabling normal functioning. Regular methamphetamine users who are not addicted did not report perceiving their drug use as impairing their daily functioning; it was perceived to enhance them overall [165]. While distinct evolutionary explanations of psychoactive drug consumption and addiction were suggested, none of them provided a coherent account of how non-addicted consumption may yield benefits, while the transition to addiction of the same drug may constitute a maladaptive and harmful behaviour.

Here, we discuss the concept of drug-instrumentalization as an evolutionary approach to non-addictive psychoactive drug consumption. Drug instrumentalization theory claims that non-addicted users consume drugs because the subsequent effects on mental states can be used to improve the performance of goal directed behaviours [2,201,202,207]. Psychoactive drugs can be 'instrumentalized'. An instrument is considered as 'something that helps to achieve a goal, which would not be achievable or require a higher workload without the use of the instrument' [201]. Drug instrumentalization consists of a two-step processes: A.) the seeking and consumption of a psychoactive drug in order to change the present mental state of a person into a previously learned mental state, and directly following the induced mental state change; and B.) improvement of the performance of another previously established behaviour [201,202,207]. An evolutionary analysis of drug instrumentalization behaviour as a mainly human cultural achievement [210,216] may need four different levels of analysis: I.) its ultimate evolution in an ancestral environment, II.) its function for reproduction and survival, III.) its proximate causation, and IV.) its ontogenetic development in the life-history of a single individual [109,214,317].

2.1. The ultimate evolution of drug instrumentalization

A major claim of evolutionary psychology is that current human behaviours are adaptations to our ancestral environment [53,54]. Thus, an adaptation should solve a problem and ultimately improve reproduction by oneself or one's kin at the genetic [53] and behavioural level [210]. Evidence for human consumption of plants and plant preparations containing psychoactive drugs has emerged in some of the oldest known human records. They suggest a systematic consumption of addictive drugs for at least ten thousand years in regions where they were naturally available [1,66,67,105,289,307]. As such, a possible evolutionary origin of psychoactive drug instrumentalization may be found in the selective ingestion of plant-derived psychoactive compounds with the hypothesized intention of mental state change and subsequent improvement of behavioural efficacy [201,202]. The selective consumption of psychoactive drugs may have an origin in the human capability of selective food seeking and consumption behaviour, as well as its flexible modification by psychological learning processes [66,171].

Psychoactive drug seeking and consumption behaviour emerges early in evolution, which suggests a strong genetic inheritance. It can be observed in fruit flies [60], rodents [12,344,355,345], dogs [251], and monkeys [73,113,128,252,341] when given access to a drug. A large number of experimental studies in animals show that they readily learn to seek and consume virtually all psychoactive drugs that are also consumed by humans [183,293,322,331]. This observation may suggest that the behavioural capacity to consume drugs—i.e. the learning mechanism—is not uniquely human, but developed early in evolution.

The seeking and consumption of a particular nutrient can be very specific depending on physiological needs. Food seeking and consumption can be highly selective based on the phylogenetically old learning capability of associating sensory parameters of a nutrient, such as smell and taste, with its ingredients and subsequent effects on the organism. This is evidenced when the need for a particular nutrient can energize a focused search for and consumption of only a selected food. The consumption of psychoactive substances yields the perception of either a positive effect that maintains homeostasis or a negative effect that threatens it. Based on this, the learning of the association, and its later retrieval, this particular food will be searched out or avoided in the future [130,171,265].

Psychoactive drugs are available to animals and are widely consumed. For instance, there is a widespread occurrence of alcohol in the reproductive structures of many angiosperm plants or derived from the fermentation of nectar or ripe fruit, which is routinely consumed by primates [341]. There is also evidence for the ultimate evolution of drug instrumentalization in non-human animals. Under specific

circumstances, chimpanzees' choice of food can be directed by non-nutritional properties of plant compounds, such as secondary plant metabolites [258]. Several studies report that wild chimpanzees self-medicate for infections, gastrointestinal problems, and other physically stressful conditions with the consumption of selected plant material [84,227,260,353]. This phenomenon is known as zoopharmacognosis [114,261]. It is not genetically determined, but a learned behaviour [171], and chimpanzees already show this capability.

Self-medication can be interpreted as a behaviour that essentially depends on the physical state of the organism. In this context, a particular food is consumed only when the organism is needs to attenuate a stressful state [168,328]. Food consumption can be directed by either prophylactic/preventative self-medication, which may reduce the risk of physical distress, or therapeutic/curative self-medication, which may reduce physical distress after it has emerged [95,142,297,309]. It has been suggested that this ability to dynamically adapt the choice of food according to the actual physical state of an organism is an adaptive trait in mammals that enhances survival and reproduction [47,95,309]. Based on this, it was suggested that the adaptation of learning systems that dynamically regulate individual food choice behaviour for nutritional needs and self-medication may be the same as those involved in choosing food for changing the mental state of the organism [201,202,207].

Only in recent times, analytical chemistry has allowed for the isolation and purification of single psychoactive compounds from plant products. Thus, psychoactive drugs have become available in pure form (e.g. cocaine, amphetamine) or a highly concentrated form (e.g. alcohol). Selective breeding of drug-producing plants has increased their compound content significantly (e.g. Δ9-THC in cannabis plants). Current environments with readily accessible purified psychoactive substances may represent a new evolutionary 'niche' [160,161]. The availability of purified psychoactive substances is now part of the environment in many societies and cultures [166,210]. Thus, it may interact with an evolutionarily determined predisposition for drug use and drug addiction [18,139,140,209,287,311].

In present-day industrialized societies, the behavioural competence required is complex, and individual workloads are very high, such that many different behaviours need to be performed with great effort [210]. An increasing number of sophisticated behaviours need to be established by single individuals and performed with more effort than in the past. More complex tools need to be handled, and the expected outcomes of work are ever increasing. The modern environment of industrialized societies contains more microenvironments that are more strongly differentiated and have specific behavioural requirements. Available technical tools are increasingly specific for a single individual's microenvironments and require a growing degree of behavioural expertise in their use (e.g. software use for machine control in the work environment vs. computer gaming in a spare-time environment). Importantly, transitions between these microenvironments can also be assumed to occur at a much faster rate than for our pre-agricultural ancestors. This constitutes the growth of human culture, but also puts selection pressure on single behaviours and their outcomes [210].

2.2. Proximate mechanisms of psychoactive drug use

A number of different proximate mechanisms in the evolution of psychoactive drug consumption have been suggested, which provide unique adaptations to particular microenvironments [166,201,332]. It has been suggested that modern humans have to adapt to a multitude of distinct environments, which require specific behavioural adaptations in one organism [53,54,210]. As such, the environment of humans can be considered to be the sum of its microenvironments [33]. For each of them, behavioural adaptations are required, which may be seen as microadaptations. Furthermore, for the frequently changing microenvironments, distinct mental states may be advantageous as they allow a better expression of 'microadapted' behaviour. It has been suggested that the proximate adaptive problems that may be solved by psychoactive drug use are: i.) facilitating the transition between different mental state, and ii.) enhancing the magnitude or duration of the mental state [2,201,207].

Microenvironments that are prone to drug instrumentalization have been identified by questionnaire studies that ask non-addicts why and under which circumstances they have consumed psychoactive drugs and which benefits/adverse effects they have encountered. In these studies, respondents provide numerous consumption motives that can be readily translated into *instrumentalization goals* [35,36,44,51,58,105,165,173,222,231,300]. All of these instrumentalization goals serve efforts directed to one's own development, maintenance, or the genetic or cultural reproduction of oneself and one's kin [201,202,210].

3. Drug use and addiction at the psychological level

Virtually all non-addicted regular users of psychoactive drugs acknowledge subjectively perceived psychological benefits of their drug consumption [15,44,231]. Psychoactive drugs are not consumed in an arbitrary fashion, i.e. equally distributed over all microenvironments, but rather in a highly organized fashion [2]. If drug use were solely determined by the pharmacological properties of a drug, one would expect the use of a particular drug emerging under all individual predispositions (sets) and all environmental contexts (settings/microenvironments) to a comparable degree. Instead, it is rather evident that the vast majority of non-addicted human users consume psychoactive drugs as a normal part of their lives with a high degree of environmental selectivity [225,301] and to use subsequent drug effects for their personal goals in these microenvironments.

But in what way can psychoactive drugs work as an 'instrument'? The instrument in this case is the effect of the drug on the mental state. The human nervous system works in different modes of action, which can be referred to as mental states. They have also been labelled as internal or affective states. Mental states are the working modes of the brain, which are stable over periods of minutes to hours. During this time, they are the functional setting for fast neuronal signalling processes in the millisecond range. Mental states control processes like subjective perception, memory retrieval, and the autonomic and behavioural responses of an organism [340].

At the neurobiological level, there is an equivalent for this psychological concept. It is the summatory activity and the different functional states of the modulatory transmitter systems of the brain. These include the dopaminergic, serotonergic (5-HT), acetylcholinergic (ACh), noradrenergic (NA), and various neuropeptidergic and lipidergic systems [278]. They are known to control the synaptic activity of fast excitatory and inhibitory transmission and regulate information processing in diencephalic and telencephalic target regions in the brain [41,203]. Modulatory neurotransmitter systems intrinsically display different modes of basal and induced activity. However, their activity also depends on various external factors (e.g. day time, season, or environment), as well as on internal factors (e.g. glucose, oxygen, or hormone levels in the blood) [13,122,273,284,304]. Their tonic and phasic activity determines the efficacy of stimulus processing and behavioural responses in the brain. A particular mental state predisposes an organism's responses to environmental stimuli, which also determines the efficacy and success of a goal-directed behaviour. In this way, mental states have a profound influence on how effectively behavioural goals can be reached.

Whenever an organism pursues a specific goal, there is very likely one out of many mental states, which allows the organism to perform the goal-directed behaviour in the best possible way. For example, if the behavioural goal is to go from place X to place Y by using the behaviour 'car driving', the specific behaviour is performed best when being in an attentive, low-stress, and low-anxiety mental state. In contrast,

performance is probably not as good when in a tired, exhausted, stressed, anxious, or inattentive mental state [201].

When consumed, all psychoactive drugs acutely change the mental state of the consumer in a dose-dependent way [77,240]. However, for a sufficient appreciation of drug seeking and consumption and the resulting mental state change, the set of the organism, the surrounding settings/microenvironments [358], and the subsequent behaviour that follows the change in mental state need to be considered [201]. The consumption of a specific drug takes place in a particular microenvironment and by a person who is in a particular mental state. Non-drug-related behaviours are performed in this microenvironment when the drug is consumed, and a mental state change occurs. By themselves, these behaviours can be regarded as drug-independent in that they are established independently from drug use. They can also be performed without previous drug consumption.

For example, driving a car from place X to place Y is a complex behaviour. Most adults perform it without having any psychoactive drug on board. Nevertheless, in a specific situation and mental state, a performance after a drug-induced mental state change is not only possible, but often desired. For example, after a long working day with stressful and exhausting activities, having a coffee that 'refreshes' a tired mind often enables the caffeine consumer to drive home better than when being in a tired mental state. Thus, the action of caffeine on the mental state is the instrument. In psychological terms, the A-process of psychoactive drug instrumentalization would be the 'caffeine preparation and consumption behaviour'. The B-process would be the subsequent 'car driving'. The *instrumentalization goal* in this example would be 'driving home', which is part of the goal class of 'improved cognitive performance and counteracting fatigue'.

4. Instrumentalization goals and their neuropsychopharmacology

While classical reinforcement theory would assume that pharmacological drug action in the brain is basically the same under all circumstances, recent findings suggest that quite distinct pharmacological actions and brain pathways may serve different drug instrumentalization goals in specific microenvironments [2]. We discuss the current progress in the understanding of drug instrumentalization and examine the underlying neurobiological and neuropharmacological mechanisms that have started to emerge [206]. For human instrumentalization goals where no neurobiological evidence is available, plausible mechanisms derived from neuropharmacological profiles of the drugs used are discussed.

4.1. Improved social interaction

Human beings are social individuals. Social interactions comprise numerous goal directed behaviours that have innate rewarding effects [182,229]. There are several known psychoactive drugs that can change a present mental state into one that facilitates effective social interactions among humans [331]. These substances include alcohol [28,85,159], marihuana [19,101,359], cocaine [166,224], other psychostimulants [57,102,339], nicotine, and caffeine [43,69]. All of these drugs have an effective dose window for this goal that is well below toxic levels in a low to medium range [25–27,42,196,290,296].

In humans, alcohol can attenuate social inhibition, the discomfort in social situations, and social anxiety. At the same time, it increases social approach behaviour [15,20,40,231]. These effects occur specifically at a relatively low dose of alcohol. An important mediator of these effects is the interaction of alcohol with the γ-butyric acid (GABA) type A ($GABA_A$) receptor in the brain. GABA is the most abundant inhibitory transmitter in the brain and is essential for the natural or conditioned suppression of behaviour [99,184,303,319].

The activity of GABA at the $GABA_A$-receptor is enhanced by alcohol. This effect is considered to be causally responsible for the reduction of natural and acquired anxiety. It may directly lead to a disinhibition of behaviour. Alcohol has also been shown to increase monoaminergic modulatory neurotransmitter activity at the synapses of the mesolimbic system of the brain [61,204,302]. These neurochemical effects may lower the reward threshold of the brain [149] and enhance social reward [121,263]. In this dose range, however, alcohol can also have negative effects, particularly on social cognition. These effects are most likely mediated by alcohol's action in higher cortical areas [38,323].

Humans also use psychostimulant drugs in a social context, such as in clubs or at parties. This use includes drugs like cocaine, amphetamine, methylphenidate, methamphetamine, and methylenedioxymethamphetamine (MDMA/ecstasy) [32,339]. When consumed in a low to medium dose range, psychostimulant drugs may increase attention and enhance general arousal levels. During social interaction, they suppress fatigue [76]. However, they may also increase social aggression [70]. Animal studies showed that rats increase their intake of cocaine after exposure to an aggressive dominant resident animal that they cannot avoid or escape from [190]. This may be seen as an experimental demonstration of an attempt to instrumentalize some of the psychopharmacological effects of cocaine in order to better cope with the negative psychological experience of an uncontrollable social stressor.

Psychostimulant drugs are well known for their pronounced neurochemical effects on modulatory neurotransmitter activity in the brain. They dose-dependently enhance the extracellular levels of DA, serotonin (5-HT), and noradrenaline (NA) in the mesolimbic system [252,253]. This is mediated by either blocking the corresponding monoamine transporters or by acting as a competitive substrate for transport [89,129,199,221,244,291]. In particular, the noradrenergic effects may account for the effects on attention [13]. Serotonergic action may mediate the anxiolytic [110,200,288] and aggression-enhancing effects of these drugs [167,245]. Furthermore, the dopaminergic action may enhance the rewarding effects of social stimuli and social interaction [16]. Overall, several classes of psychoactive drugs are currently used by non-addicts to facilitate social behaviour. However, exaggerated drug use for this instrumentalization goal may also facilitate the transition to habitual drug use and addiction [207,333].

4.2. Facilitation of sexual behaviour

Mating behaviour is a goal-directed behaviour that naturally has highly rewarding properties [230]. Mating behaviour in humans ranges from behaviours such as partner seeking and approach behaviour to actual sexual intercourse. Virtually all drugs that are instrumentalized to improve social interactions are also used to facilitate mating behaviours in distinct microenvironments. These drugs include alcohol, cannabis, amphetamines, ecstasy, and cocaine [25–27,172]. For alcohol in particular, a strong association has been reported between drinking, a mental state change towards drunkenness, and the perceived chances for sexual intercourse among adolescents and young adults [162,230,338]. A facilitation of mating behaviour could have been strongly selected for in evolutionary times.

Psychostimulant drugs are also used to improve chances for partner seeking and approach behaviour. However, they may later impair physical performance during sexual intercourse, particularly the erection in males [172,334]. One may speculate that the acute effects of psychostimulant drugs on DA activity in the mesolimbic system might particularly render an individual more responsive to sexual cues. A potential partner may appear more attractive [121,149]. However, psychostimulant consumption in this context may also enhance vulnerability to the later development of drug addiction, as shown in male rats [158].

4.3. Improved cognitive performance and counteracting fatigue

Sophisticated cognitive skills are required for many cultural behaviours in present-day human societies [210]. Cognitive monitoring

improves the outcome of complex goal-directed behaviours in animals and humans [11,126,127]. However, human cognitive capacity is not constant throughout the day. Even during the waking period, and depending on work load, cognitive capacity fluctuates and may decline towards the end of the period. Thus, pharmacological means of artificially prolonging periods of high cognitive capacity are beneficial for most other behaviours shown during this time.

Currently, there is little evidence for a significant increase in cognitive performance in a healthy individual with full mental capacity after any kind of psychoactive drug. However, many studies show now that mild impairments due to exhaustion, fatigue, or mood swings can sometimes be compensated for by psychoactive drugs [27,29,30,165,196,226,275,298]. A high pressure on the efficacy of cognitive activity and resulting behaviour is evident for many micro-environments, be it at the workplace or during spare-time activities. This is often perceived as stressful, and the relief from the stress after psychoactive drug use is a negative reinforcing effect. Psychoactive drugs are used as 'every day doping' for neuro-enhancement [264,347]. For many decades in the neuroenhancement debate, the active search, development, and authorized use of psychoactive substances has been advertised as instrumental drug use to explicitly enhance cognitive performance [277].

Caffeine, the psychoactive component of coffee, tea, chocolate, and soft drinks, is a legal psychoactive drug that is widely used to keep people awake [30]. It has even been shown to enhance long-term memory consolidation in humans when consumed post-trial [21]. The neuropharmacological action takes place in the adenosine system. Brain adenosine levels steadily increase during the waking period. After long time in this period, adenosine eventually triggers fatigue and sleep by its action at the adenosine A1- and A2A receptors [112,116,239]. Caffeine works as an A1- and A2A-receptor antagonist and blocks the action of the accumulated adenosine [43].

Nicotine is a major psychoactive compound in tobacco [163]. It is legal and also used for this instrumentalization goal. Comparative studies have shown that rats may learn to increase their nicotine intake before a cognitively demanding task [212]. This behaviour may be interpreted as an attempt to instrumentalize the cognitive-enhancing effects of nicotine for an anticipated high cognitive effort. Nicotine is an agonist of the nicotinic ACh- receptors [179]. Nicotinic ACh-receptor stimulation in the brain is a major mechanism to drive attention, which is also a prerequisite for learning and memory [274,316]. In animal studies, nicotine enhanced attention and the performance of cognitive tasks [59,96]. Similar effects have also been reported in non-smoking humans [250]. In human smokers, however, cognitive abilities usually decline after smoking cessation. This effect can be reversed by a new nicotine dose [175].

Once the nicotine has reached the brain, it increases both acetylcholinergic and noradrenergic activity [193,349]. Both transmitter systems work synergistically to maintain arousal and attention. Furthermore, as nicotinic ACh-receptors are localized at dopaminergic neurons, their stimulation may directly enhance mesolimbic DA activity, though to a lesser degree than other substances, such as psychostimulant drugs [179,183,238,350]. Through this effect, nicotine may enhance the rewarding properties of a non-drug reinforcer [100,141].

Psychostimulant drugs are well known to increase cognitive performance for many hours [11,57,90,165,185,248,310,314,339]. This effect can be observed in a dose range that does not induce major euphoria effects. Psychostimulants have been shown to increase arousal and attention in humans for long periods of time and are used to enhance cognitive and behavioural performance [108,264,306]. They may also attenuate cognitive deficits caused by sleep deprivation [76]. It is assumed that the acute effects on noradrenergic activity in particular mediate this action [89,129,291,324]. Altogether, several lines of evidence support the view that various groups of psychoactive drugs can be instrumentalized to enhance cognitive performance. However, the long-term regular use of these drugs may induce tolerance for the cognitive improvement effects and even lead to cognitive deficits [104,207,330,348].

4.4. Facilitated recovery and coping with psychological stress

In present-day societies, humans are required to perform complex behaviours or cognitive activities for long periods of time [10], which takes up their performance resources. During the waking period, people have little time to efficiently recover and cope with psychological stress caused by these activities. In interview studies, people report several psychoactive drugs that can improve recovery and enhance stress coping [8,15,196,231,290]. The drugs used for the instrumentalization goal of 'facilitated recovery and coping with psychological stress' are alcohol [49,50,159], cannabis [19,360], cocaine [166,334], methamphetamine [165], barbiturates, benzodiazepines, and other sedative anxiolytic drugs [24,299].

Reward devaluation and the extinction of previously rewarded behaviour may induce stress and mild depression [117,118]. This also enhances the preference for alcohol and benzodiazepines in a self-medication paradigm in rats [176,177]. Alcohol can attenuate stress levels by inhibiting excitatory glutamatergic transmission and enhancing inhibitory GABAergic activity in the brain [303]. Furthermore, barbiturates and benzodiazepines most likely exert their stress-reducing effects by the modulation of $GABA_A$ receptors [119], although at different binding sites from alcohol. They also allosterically increase the responses to GABA [5]. Enhanced $GABA_A$-receptor signalling is known to attenuate anxiety. Furthermore, sedative drugs like alcohol may attenuate the memory of aversive events through their interaction with neocortical $GABA_A$-receptors [56].

The self-administration of psychoactive drugs with the effect of improving stress coping has been observed in various animal models. Heroin is self-administered intravenously by rats. This self-administration increases when rats are exposed to an unavoidable food shock stress [292]. However, whether biological stress markers are attenuated and stress-related behaviour is reduced was not investigated. In another study on mice, it was shown that social defeat stress can increase morphine consumption. In mesocorticolimbic brain areas, stress induces an increase in ΔFosB immunoreactivity [52,219]. This effect has also been observed during the establishment of drug addiction [233]. Nevertheless, the extent to which morphine reduces stress-related behaviour or re-establishes homeostasis in the brain remains to be investigated.

A widely used psychoactive drug for the instrumentalization goal of stress coping is cannabis [25,26], which contains Δ9-tetrahydrocannabinol (THC) as its main psychoactive compound [120]. THC binds to the cannabinoid (CB) receptors [188]. In particular, THC activity at the CB1 receptor can enhance the extinction of aversive memories [180].

Social stress can also lead to an increase in the self-administration of non-sedating drugs with a stimulant profile of action, such as cocaine. It has been suggested that this might support an active coping strategy by enhancing a 'flight or fight' response [201]. Stress alters the function of the mesolimbic DA system [156,191], as well as its excitatory [80] and inhibitory inputs [187,237]. It may cross-sensitize this system for the behavioural effects of psychostimulants and enhance drug self-administration behaviour [55,191]. It has been shown that just a single social defeat stress episode can increase mesocorticolimbic expression of the immediate early gene cFos as an indicator of neuronal activation [52,191].

Psychostimulant drugs increase cFos expression [191,279]. However, cocaine may counteract the c-fos activation effects of social defeat stress in distinct brain regions [191,219]. This exemplifies how cocaine induces a seemingly paradoxical effect that may work towards the re-establishment of homeostasis in a stressed animal. However, several days after the initial stress coping, an augmented effect has been

observed. This may suggest that an acute instrumentalization effect of the drug may revert after repeated drug consumption and render a sensitized state in an organism that may facilitate the development of addiction [191]. In the brain, μ- and κ-opioid receptor signalling and their activation by the endogenous neurotransmitters, encephalin and dynorphin, are enhanced after stress [187,219,237]. This effect might directly mediate stress-induced immobility and analgesia. It may also enhance sensitivity for cocaine reward and the reinstatement of drug self-administration when emerging in the VTA-NAc mesolimbic projection [187,191,237].

There are interindividual differences between organisms that render them vulnerable to stress and its behavioural effects [134]. Coping with social stress by enhanced cocaine self-administration has been predominantly observed in animals with low spontaneous activity [131]. This may suggest a dependency of drug instrumentalization efficacy on personality traits. Altogether, several classes of psychoactive drugs are currently used to facilitate recovery and coping with stress in non-addicted drug users. However, the chronic and escalating use of psychoactive drugs for this instrumentalization goal may eventually result in restlessness and a hyper-anxious state during withdrawal, as well as compulsive drug use [207].

4.5. Self-medication for psychiatric disorders and mental problems

Mental disorders are characterized by a persistent mental state that is perceived as aversive or causes significant problems. A mental disorder causes suffering for the affected individual and compromises well-being and the interaction with others. The neurobiological underpinnings of a permanently altered mental state can be a temporary, recurrent, or continuous dysfunction in the homeostasis of one or more modulatory transmitter systems of the brain [137,144,157,246,278]. Specific psychiatric disorders are associated with an enhanced consumption of particular types of drugs and an enhanced risk for developing drug addiction [254]. Drug action in such individuals is often different from individuals without co-morbid psychiatric disorders. In such patients, a psychoactive drug may provide at least a temporary relief from suffering from the disorder, as well as enhance 'functioning' in everyday life to a certain extent [165,226]. This may also apply for mental states that give rise to psychological problems, such as being in a depressed mood, but not fulfilling the diagnostic criteria of a psychiatric disorder [23,26,27,196].

In Western societies, a legal drug that is frequently used for this instrumentalization goal is alcohol. Moderate consumption of alcohol has been associated with better health, more close friendships, and more family support than total abstinence [195,201,231,259,301,313,318]. It has also been linked to lower rates of stress-induced depression [318], and it appears to reduce the risk of somatic disorders, anxiety disorders, and depression when compared to people who completely abstain from alcohol [231,301]. Therefore, it has been suggested that alcohol may provide relief from negative affect in non-addicted consumers [231]. In clinical samples, however, a high co-morbidity appears between diagnoses of 'major depression' and 'alcohol addiction' [37,242]. Nevertheless, this may subsume different populations with possibly distinct pathogenic pathways. Major depression disorder may give rise to alcohol abuse behaviour and frequently to alcohol addiction. In the majority of co-morbid cases, it appears that an established alcohol addiction may induce major depression [262,280–283].

Neurobiological mechanisms of how a psychiatric disorder may shape alcohol use behaviours have recently been characterized. Mammalian cell membranes predominantly consist of sphingolipids, cholesterol, and (glycero)-phospholipids. Sphingolipids are composed of a hydrophilic head group and a ceramide molecule. Ceramide consists of D-erythro-sphingosine and a fatty acid of variable length with 2–36 carbon atoms in the acyl chain [271]. The molecular interactions of sphingolipids are mediated by membrane cholesterol in cell membranes, among others [34,170,189]. Cholesterol interactions of sphingolipids result in an ordered membrane structure with stable membrane domains [34,98,170,189,295]. These membrane domains are segregated though adjacent to other glycerophospholipids in the membrane. Due to their membrane floating properties, these domains have been named lipid rafts [68,295].

The most abundant sphingolipid in the brain is sphingomyelin [118,208]. It can be hydrolyzed into ceramide, which has a tendency to spontaneously self-associate resulting in the formation of ceramide-enriched membrane microdomains. These microdomains may even fuse into larger ceramide-enriched macrodomains [75,87,88,327]. Receptor proteins within small plasma membrane domains are a major prerequisite for neurotransmitter-induced transmembrane signalling [91]. After learning or stress, cholesterol or sphingomyelin temporarily decreases in a brain-area selective way in animal studies [118,223]. This changes the composition of lipid rafts, which can directly affect receptor functions [74,220,247].

Ceramide generation in the plasma membrane can be mediated by the enzyme acid sphingomyelinase (ASM) [107]. Several neutral and alkaline sphingomyelinases have been identified according to their optimal pH for enzyme activity [107,153]. It has been reported that the disruption of the sphingolipid rheostat in the brain may induce major depression and anxiety disorder [92–94,152,205,359]. Mice over-expressing ASM (tgASM) display higher ASM activity and ceramide production in the hippocampus [92]. An increase in hippocampal ceramide may directly attenuate local neurogenesis, neuronal maturation, and neuronal survival [92,93]. This effect is a neurobiological marker associated with a depression-like phenotype [272].

tgASM mice display a depression/anxiety-like phenotype in behavioural tests [92,152,208]. Many antidepressant drugs work as functional inhibitors of ASM [3,150,151], and they can attenuate the depressogenic effects of chronic unpredictable stress on behaviour in wild-type (WT) and tgASM mice. However, they have no effect on mice lacking ASM (ASM knockout). These findings suggest a new pathway of sphingolipid-mediated depression that can be triggered by either a genetic mutation or by stress [88,92,94,152,208].

In a sub-population of alcohol addiction/major depression co-morbid patients, depression manifests first. Thereafter, enhanced alcohol consumption is observed and may finally lead to addiction [262,280–283]. It has been suggested that in such patients, alcohol is used and instrumentalized to attenuate the suffering from depression or anxiety [201,204]. Animal models have shown that voluntary alcohol self-administration may reduce depressive symptoms, and this effect may sustain high consumption rates [46,318].

A mechanism for the paradoxical therapeutic effects of alcohol has been suggested. Mice with an ASM hyperfunction are not only depressed, but also drink significantly more alcohol in a free-choice paradigm. Furthermore, they escalate consumption after withdrawal [208]. Free-choice alcohol consumption partly reversed the ASM hyperactivity in tgASM mice, but forced injections of equivalent amounts of alcohol did not. The alcohol self-titration normalized the depressive behavioural symptoms in these animals. ASM hyperactivity reduced the levels of the most abundant sphingomyelin species in the NAc and dorsal hippocampus (DH). Alcohol drinking in WT mice had a similar effect on the sphingolipid rheostat. In tgASM mice, however, alcohol drinking had a paradoxical effect: it reversed the genetically induced sphingolipid deficit in the NAc, but not in the DH.

Depressive tgASM mice also showed a gross attenuation of DA and 5-HT tissue levels in the brain [208], but DA responsiveness to an acute alcohol challenge was enhanced [133,134]. Alcohol drinking almost completely reversed the monoamine tissue deficit in tgASM mice but had an opposite effect in WT mice [208]. These studies showed how a psychoactive drug may lead to a paradoxical reversal of psychiatric disease symptoms by having a different action in an affected brain in comparison to a healthy one. This may also suggest that psychoactive drugs may have different effects depending on the mental state of an

organism [206].

Enhanced consumption of psychoactive drugs and addiction diagnoses have also been associated with post-traumatic stress disorder (PTSD) [255,305]. Severe stress may cause an enhanced responsiveness to mild stressors at endocrine and behavioural level. Stress also enhances the reinforcing effects of psychostimulant drugs, such as alcohol and opiates. It increases self-administration and the resistance to extinction acutely and for a long time after the stress has ended [169,235,236].

After PTSD emerges, it may trigger the development of drug abuse and addiction. However, drug abuse may also enhance vulnerability to stressful events that cause PTSD. The self-medication hypothesis suggests that patients consume psychoactive drugs to better control their PTSD symptoms [143,144]. Alcohol is frequently reported to dampen arousal and reduce physiological reactivity to stressors [293,303]. The subsequent reduction of tension has been considered to act as a negative reinforcer, which further drives the alcohol consumption [48]. Furthermore, alcohol can reduce fear and avoidance behaviour and intrusive cognitive symptoms in humans, such as distressing recollections of the aversive event [304]. In animal models, the increase in alcohol consumption does not occur immediately, but with some time delay. This also depends on the type of stress used to model PTSD symptoms [325,326]. Acute severe stress sensitizes the reward system for psychoactive drug effects and thus make one more vulnerable to addiction development [174,354].

Another major psychiatric disorder is schizophrenia. Patients often show enhanced use of nicotine and cannabis [115,194]. However, these drugs may exacerbate the positive symptoms of the disorder, such as hallucinations [234]. In contrast, nicotine might improve the negative symptoms, such as the flattening of affect and cognitive impairments might [241,250]. Reports from patients and experimental investigations suggest that some psychoactive drugs may attenuate the negative symptoms in particular, as well as improve cognitive impairments to a certain degree [65,216].

Improved cognitive deficits have been demonstrated in a rat model of schizophrenia. Maternal immune activation (MIA) with lipopolysaccharide (LPS) during gestation can induce schizophrenia-like cognitive deficits, as measured in the paradigms of latent inhibition and delayed non-matching to sample test. In the offspring, MIA did not enhance nicotine self-administration. In the MIA group, nicotine self-administration was able to ameliorate the cognitive deficits, but not in the saline control group [335].

Nicotine also improved the cognitive deficits in a mouse model of schizophrenia that resembles a specific human genotype. A human genome-wide association study on schizophrenia patients identified the single nucleotide polymorphism (SNP) rs16969968 in the CHRNA5 gene to be significantly associated with the disease condition. The CHRNA5 gene codes for the nicotinergic ACh receptor (nAChR) α5 subunit [276]. This SNP polymorphism leads to a substitution of aspartic acid by asparagine at the 398 locus of the human nAChR α5 subunit. A mouse model was used to investigate the functional implications of this SNP.

Transgenic mice expressing the human α5 SNP displayed impaired social behaviour and disrupted sensorimotor gating, which both model typical symptoms of schizophrenia. Impaired function of the nAChR α5 subunit led to a decrease in prefrontal cortex layer II/III microcircuit activity, which was dependent on GABAergic interneurons. This effect mimics frontal brain hypoactivity as it is observed in patients with schizophrenia. In α5-deficient mice, continuous nicotine administration normalized the firing of neurons, but not in normal mice [154]. These findings suggest that nicotine self-administration is particularly effective in ameliorating cortical dysfunction in a subpopulation of schizophrenics: those with a polymorphism of the α5 nAChR [154,206].

Altogether, several psychoactive drugs can be identified that are used by individuals suffering from psychiatric disorders to ameliorate at least some disease symptoms or subjective suffering for at least some time. Continuous and escalating use of psychoactive drugs for this goal, however, may eventually potentiate disease symptoms and result in a co-morbid addiction disorder [207,254]. The use of psychoactive substances for self-medication may also enhance the risk of missing more effective, evidence-based clinical pharmacotherapies for the respective disorders.

4.6. Sensory curiosity – expanded perception horizon

In the absence of novel sensory inputs, humans perceive boredom as a mildly aversive mental state. The search for novel information and new environments is a driving force to expose an individual to new stimuli and environments. In those environments, new stimulus–reward contingencies may exist and be learned, which later provide a direct advantage to the individual [138,201,315]. Novelty and new sensations can work as a primary reinforcer [336,361]. In humans, novelty seeking has been shown to be a risk phenotype for drug abuse with a shared genetic base [192,361]. When a psychoactive drug is consumed for the first time or in a new environment, the drug-induced mental state may serve as a novelty. Up to a certain time, this novelty effect may drive repeated drug consumption. After repeated exposure, the drug effects on mental state are no longer novel, and other than the rewarding, novelty effects are required to maintain drug seeking and consumption. If no other instrumentalization goals are established for a particular psychoactive drug, its consumption may eventually be ceased [218].

Hallucinogenic drugs used by humans include natural compounds, like mescaline and psilocybin, as well as semi-synthetic drugs, like lysergic acid diethylamide (LSD). These drugs are used to change the sensation and perception of the external world and to increase self-understanding and self-discovery [25–27,42,196,218,320,321]. The enactogenic drug MDMA exerts hallucinogenic effects but also induces a unique feeling of 'divine oneness' with the world [97] and is used for this instrumentalization goal [25,26]. Other drugs include phencyclidine, ketamine, and γ-hydroxybutyrate (GHB), which are used in the club and rave scene. At high doses, these drugs can have profound hallucinogenic effects [32,102,103,337,346]. There are also reports that suggest the use of cannabis to expand environmental and self-perception [19,360]. Chronic and escalating drug use for this instrumentalization goal may result in dangerous behaviours and aversive perceptions, including schizophrenia-like psychoses [207].

4.7. Euphoria, hedonia, and high

Human beings show a strong motivation to pursue euphoria and happiness throughout their lifetimes [178,312]. Humans are the only known species that can report about the subjective state of happiness. From such reports, it is known that this subjective feeling may occur during or after the receipt of a primary or secondary reward or with an unexpected change in reward contingencies. This occurs when a formerly meaningless stimulus now predicts reward availability. The biological function of the subjective perception of euphoria is far from clear as it does not directly control behavioural adaptations [4]. Nevertheless, the amount of happiness that is subjectively perceived by an individual shapes individual well-being [132]. Well-being may serve as the subjective perception of an endogenous adaptation signal, which informs the central nervous system about the general status of the organism and of the functionality of established behaviours [210].

It has been argued that mood enhancement and euphoria may facilitate virtually all kinds of previously established goal-directed behaviours [164,201,231]. Numerous psychoactive drugs can induce a profound but temporary feeling of euphoria and well-being at middle to high doses, like heroin, morphine, cocaine, amphetamine, methamphetamine, methylphenidate, and MDMA [123,249]. Furthermore, non-addicts may use these drugs for this goal [23,186,314,357]. A less intense euphoria can also be induced by other drugs of abuse, such as alcohol, cannabis, LSD, benzodiazepines, and nicotine [25–27,294].

Since euphoria levels are not very strong, these drugs are not primarily consumed for this goal alone.

Psychoactive drugs have been assumed to produce euphoria-inducing effects by a massive increase of extracellular DA activity in the NAc [61,63]. The NAc is a key structure of the mesolimbic DA system that is crucial for reinforcement learning in the brain [64,267,343,344]. Detailed descriptions have been provided for how different classes of psychoactive addictive drugs converge on the mesolimbic DA signal [9,62,147,183,329]. Drug-induced euphoria is usually more intense than naturally occurring euphoria, which is paralleled by greatly enhanced increase in DA in the NAc after most drugs compared to natural stimuli [6,198,199,269].

However, the major role of DA in drug-induced euphoria and learning has been questioned [268], and this view has been further elaborated by a psychological differentiation between stimulus-induced 'wanting' and 'liking' [16,256]. Accordingly, DA may not be a signal of euphoria, but rather code for stimulus 'wanting' and inform about the reward-prediction error in the evaluation of behavioural outcome [111,284]. This has been shown for pleasant appetitive stimuli as well as aversive stimuli [31,181,356]. In contrast, euphoria and the 'liking' of a stimulus may be mediated by endogenous opioid and GABAergic signals [16,17]. Current views also recognize important roles of other neurotransmitter systems in the subjective euphoria-inducing and behaviour-reinforcing effects of psychoactive drugs [72,106,135,148,204,209,215,342]. The over-instrumentalization of a psychoactive drug for this goal most likely results in the development of tolerance for the euphoria effects and an escalation of drug intake. Acute withdrawal effects are characterized by dysphoria and a depression-like mental state, which may develop into a drug addiction [106,201,207].

4.8. Improved physical appearance and attractiveness

In modern societies, idealized cognitive concepts of males and females have emerged and are maintained as a developmental guide. They include expectations for sex-specific non-genetically inherited behavioromes [210] and 'ideal' norms for physical appearance. Given the natural genetically/epigenetically and environmentally caused variation among human physical phenotypes, people feel pressure to perform behaviours that also adapt their physical appearance to these norms [210]. There are distinct effects of psychoactive drugs that are used to serve the instrumentalization goal of 'improving physical appearance and attractiveness'.

In Western societies, there is a pressure towards a lean appearance among females and towards a muscular appearance among males. A frequently reported motive for tobacco smoking is the reduction of body weight. Epidemiological data suggest that smokers weigh less than non-smokers on average, even though smokers do not eat less or consume fewer calories than non-smokers. It has been suggested that nicotine may cause less efficient storage of calories through its action in the gut, [331]. Nicotine also reduces weight gain following the cessation of smoking [232]. It has been suggested that the action of nicotine with ACh-receptors in the lateral hypothalamus is the predominant neuropharmacological mechanism of how nicotine may control hunger and feeding behaviour [125].

The use of psychostimulant drugs has also been reported for their anorectic action (i.e. hunger and eating-suppression effects), including cocaine, amphetamine, and its derivatives [25–27,79]. These anorectic effects are most likely mediated by the noradrenergic effects rather than by the serotonergic or dopaminergic effects of psychostimulant drugs. In particular, hypothalamic α1 receptor stimulation has been considered to be crucial for the drug-induced reduction of food intake [22,270].

A muscular appearance is considered an ideal in males. While there are natural means achieving this goal, such as physical exercise or body building, psychoactive drugs may support it as well. Androgenic-anabolic steroids, such as testosterone or nandrolone, are used with the goal of achieving a more muscular appearance [86]. Anabolic-androgenic steroids increase muscle growth, most likely by a peripheral mechanism [146]. Nevertheless, they also have direct psychoactive effects, such as an increase in self-esteem [351,352]. Improved physical appearance is self-perceived and may give rise to psychological feedback. This can increase self-confidence and thus affect other behaviours, such as social interaction or mating behaviours [351]. These effects are slow acting and may require the endogenous opiate systems. In animal studies, chronic treatment with androgenic-anabolic steroids increased levels of the endogenous opioid β-endorphin in the limbic system and changed opiate receptor densities. Androgenic-anabolic steroids also have modulatory effects in the 5-HT system, which may account for the effects on aggression levels [136,245].

Altogether, several psychoactive drugs are used to facilitate or inhibit behaviour directed towards a modification of physical appearance. Weight reduction appears to be one supported goal among females, while a muscular appearance is a predominant goal among males. There is a sex-specific drug choice for this instrumentalization goal, as weight reduction can be achieved by nicotinic receptor stimulation or NA activation. The facilitation of muscle growth requires stimulation of a peripheral mechanism involving androgen receptors.

4.9. Facilitation of spiritual and religious activities'

Religion appears to be a unique human phenomenon. It provides a metaphysical base and cognitive set of beliefs that can explain the world and the self in it. From a biological point of view, religions may effectively 'synchronize' cognitive sets and behaviour of social groups. They may foster altruism within the group and enhance resistance against threat from outside. Thus, religions may provide health and well-being benefits as a potential adaptive advantage [14].

In mono- and polytheistic religions, there are gods with a higher understanding of the world and a superhuman power to influence the environment or the fate of humans. All religions commonly feature restricted exchange with the supreme deity. Under normal circumstances and in a normal mental state, ordinary believers may not have access to the 'divine' and may not understand its actions or direct it in any way. While both would be highly desired by the believers, some religions have established a mediating mechanism. This may allow some of the believers a contact of a believed to be causally acting nature. This special exchange is felt to allow enhanced insight into the divine intentions and plans or a perceived way to influence their action and solve problems of the individual or the group.

Moro and Noreika [197] suggested that in a defined context, the purpose of hallucinatory drugs may be to increase self-understanding and self-discovery and to address ultimate questions that shape or shake the fundamental world view. Changing one's mental state for better communication with the divine entity can be achieved by natural means, such as meditation and particular thinking patterns, but a more powerful way is using psychoactive drugs [201,202]. This behaviour has been widely abandoned with the arrival of monotheistic religions, such as Judaism, Christianity, and Islam, and has exchanged for meditation and prayer. However, it is still in place in some natural religions, like those in the Amazonian basin [124] or American Indian religions [243].

Drugs that are used for this instrumentalization goal include THC [1], cocaine [307], and nicotine [124]. Hallucinogenic drugs that are used include psilocybin, as well as mescaline, which can be found in the peyote cactus in south and middle Americas. In South America, dimethyltryptamine (DMT) is used as a powerful hallucinogen [83,124,218]. Drugs have even been labelled as 'entheogens' (from ancient Greek, "creating the divine within"), specifically indicating their use for religious instrumentalization [266]. The instrumentalization to facilitate spiritual and religious practice may actually have been among the first documented examples of drug instrumentalization in

humans [1,105,332].

5. From drug instrumentalization to over-instrumentalization and addiction

The vast majority of psychoactive drug-consuming humans control their consumption rather well with dose adjustments and abstinence periods based on the perception of negative drug effects [334]. However, a small percentage of people make the transition from controlled drug use and instrumentalization to addiction. A crucial factor in this process is potentially an attempted over-instrumentalization with escalating use of the drug [145]. With increasing drug exposition, numerous changes in brain function occur and induce behavioural inflexibility and compulsive drug use [71,204]. In this stage, the toxic and harmful effects of the drugs predominate over the potential instrumentalization benefits and outweigh them [2,201,207].

The brain mechanisms for the establishment of drug seeking and controlled use are increasingly understood [135,183,204], along with personality factors that facilitate them emerging at neurobiological level [302]. Nevertheless, little is known about the causal mechanism for the transition from controlled to compulsive drug use. We propose a psychological mechanism that arises from controlled drug-instrumentalization. The over-instrumentalization of a psychoactive drug describes the attempt of a person to enhance previously established drug instrumentalization to a level where it no longer provides a net benefit.

Personal development in humans changes developmental goals in an age-dependent manner. This yields distinct motives for a person's behaviorome [210]. For example, at the age of 18, socializing, the search for a partner, and professional education may be predominant behavioural motives and drug instrumentalization goals. Once the mating period has been successfully passed, a family is founded, and children need to be raised. In parallel, the professional career is established and may come along with increasing responsibilities and work stress. This requires new behaviours and yields other drug instrumentalization goals. As such, there are *quantitative* changes in instrumentalization goals. Thus, a given goal is pursued more intensely, which may yield a *higher frequency* of consumption episodes, an increase in drug dose, and in total drug intake. In parallel, there may be *qualitative* changes when the number of instrumentalization goals increases, and drug consumption is expanded to other drugs.

Although drug instrumentalization is a dynamic process with respect to changing goals and drugs used for it, there is only a small dose window for the optimal mental state for each drug that serves a particular instrumentalization goal. If this dose window is left by increasing the dose of the drug or frequency of use, drug instrumentalization may no longer be possible. For example, regular but well-controlled alcohol consumption is established and maintained with the goal of facilitating stress coping after working hours. If the work load is increased, such as by a promotion or more responsibilities, the well-established coping tool may be quantitatively expanded in its use—for example, by enhancing the number of drinks at each occasion.

Alternatively, it may see a qualitative expansion, such as by adding episodes of marihuana consumption. This consumption may then leave the dose/frequency range in which instrumentalization is possible. Toxic and organ-damaging effects of the drug emerge and become the predominant effects. A major adverse effect is the increased risk of losing control over drug consumption beyond any utility for instrumentalization and developing drug addiction. It may be concluded that drug instrumentalization requires a fine-tuned learning process in order to become established. It is subjected to developmental change and can be maintained only with a permanent self-titration by its net benefits and potential adverse effects [201,207].

6. Summary

Psychoactive drugs with addiction potential are widely used by people of virtually all cultures in a non-addictive way. To understand this behaviour, its population penetrance, and its persistence, drug instrumentalization has been suggested as a driving force for this consumption. A small percentage of people who regularly instrumentalize psychoactive drugs make a transition to addiction, which often starts with qualitative and quantitative changes in the instrumentalization goals. As such, addiction is proposed to develop from previously established long-term drug instrumentalization. Thus, preventing and treating drug addiction with an individualized medicine approach may essentially require understanding and non-pharmacological support of personal instrumentalization goals.

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