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Evolutionary and dual inheritance models of initiation and use of psychoactive substances, including novel psychoactive substances

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Abstract

***Introduction*: Research into drug use has typically been restricted to studies of proximate models (i.e. biological mechanisms). However, an evolutionary/ultimate perspective may be uniquely relevant to understanding drug-seeking behaviours. In fact, a range of competing evolutionary models have emerged which explain why humans evolved through natural selection to use psychoactive substances.**
***Objectives*: We aimed here to critically review evolutionary, cultural and dual inheritance perspectives on drug initiation and use, including considerations on novel psychoactive substances (NPS).**
***Methods:* A literature search was conducted using key resources including PubMed with a focus on drug use and human population data. This was supplemented by personal archives.**
***Results:* A range of evolutionary models of why humans initiate and continue using psychotropic substances was identified. They include: a) Increasing reproductive fitness; b) Psychotropic self-medication (pharmacological manipulation of emotions); c) Pharmacophagy and infection control; d) Mismatch theory; e) Evolutionary Constraints; f) Trade-offs; g) Costly Signalling and Handicap theories; h) Placebo, ritual and healing effects; i) Drug use in spirituality or religion (e.g. the role of psychedelic drug use by "neo-shamans" and "psychonauts"). Some of these models are conceptually similar or overlapping. They are not mutually exclusive and may interact in unpredictable (i.e. non-linear) ways.**
***Conclusions/Importance:* Evolutionary, cultural and dual inheritance models of drug initiation and use reveal functional origins and adaptive advantages of psychotropic drug use. An evolutionary perspective is particularly helpful in understanding the specific dangers of the new phenomenon of NPS. Evolutionary perspectives suggest new directions for research and treatment.**

KEY WORDS: evolutionary models; psychiatry; drug addiction; drugs; novel psychoactive substances; NPS; emotions; psychonauts; shamanism; evolution.

Introduction

Research into drug use has hitherto largely been restricted to understanding the proximate/immediate mechanisms of how the body and drug interact. An evolutionary perspective is required to explain why natural selection has left the human brain vulnerable to these common problems. Evolutionary concepts advance consideration of the adaptive functions (either now or in historic environments) of drug use and how drug use may be a phenotypic characteristic that occurs as a by-product of the evolution of some other adaptive phenotypic characteristic (i.e. an exaptation or "spandrel" to use an architectural metaphor). The evolution recognises that bodies are not designed machines but products of millions of years of natural selection. Furthermore, natural selection maximizes reproduction, not health (1).

Many different classes of substances are available for abuse, including several hundred novel psychoactive substances (NPS) (2-4). Some of these drugs are entirely synthetic and others occur naturally in plants, or are chemically modified from plant compounds (2, 3). Many NPS are so new they cannot have been formally tested in animals yet, let users at risk (3, 4). However, without knowing a NPS's profile, or have safety/toxicity data, their street use is dangerously experimental, good effects are serendipitous and use is risky (4, 5).

People have used a range of natural substances to modify their minds, for recreational/psychedelic purposes, over millennia. Most commonly abused natural drugs and nowadays, NPS, cause changes in systems that alter consciousness or affect moods/emotions in some way (6).

The history of the coevolution of humans with some of these plant toxins is well documented (7). Animals evolved to exploit plants as sources of energy/materials, sometimes for some substances, but in response plants (co)-evolved. Plants with mutations that led to effective defences, such as toxins which disrupted predators' biological systems, had increased likelihoods of surviving grazing than their non-toxic conspecifics, i.e. toxin production was adaptive (8).

The biological value of consuming plants comprises the benefits of useable macronutrients (carbohydrates, fats, and proteins) plus micronutrients (as vitamins, minerals and other trace chemicals), minus the costs of toxin exposure (8). Plant toxins generally occur at highest concentrations in organs, like leaves/unripe fruit, which are critical for plant growth/survival/reproduction. Toxins occur in low concentration in other organs, like ripe fruits, which evolved to be consumed by herbivores to aid seed dispersal, which is beneficial for the plant (8). Plant toxins such as caffeine/nicotine /cannabis/cocaine were naturally selected for because they interfered with neuronal signalling in herbivores, including insects/worms/other parasites (9). These toxins disrupt biological mechanisms including: a) neurotransmitter synthesis/storage/release/binding/re-uptake; b) receptor activation/function; and, c) key enzymes involved in signalling (9). Herbivore enzyme and detoxification systems co-evolved and adapted to this changing environment to be able to metabolise such chemicals. Those organisms most able to utilise such plants and chemicals had a fitness advantage.

Plant toxins may actually be co-opted by herbivores for other functions such as to kill parasites/other microorganisms (8). Many psychotropic chemicals, widely distributed in plants, were probably discovered by ancient hunter-gatherers prior to the Neolithic agricultural revolution. Humans have learnt how to cultivate/modify/exploit these chemicals and pass on this cultural knowledge to others. This combination of biological adaptation and cultural learning is referred to as *Dual Inheritance Theory* (DIT). Culture itself is of course only possible with high levels of social communication/organisation, which in turn requires considerable brain evolution. In this sense, the capacity of a species to develop culture itself is a product of evolution (10). Moreover, ritualistic/spiritual use of psychoactive drugs has a long history among ancient tribes/shamanic communities (11, 12), suggesting some evolutionary benefits related to the historical spread of plant-derived compounds, mostly entheogens/hallucinogens. Nowadays, the current drug users (i.e. psychonauts) belong to a new sub-culture, which seems to resemble to shamanic communities.

Evolutionary concepts open new perspectives on why/how these natural plant substances were identified, (and later cultivated) and exploited by our ancestors, and how our ancestors evolved adaptations in response to plant toxins. Conversely, the short time-frame from NPS synthesis to exploitation means natural evolution of tolerance/resistance to them cannot possibly have taken place. In fact, NPS, even though act on the same evolutionarily-conserved biological systems (biomediators/neurotransmitters systems) which are found widely in many bacteria/plants/animals, being a novel aspect of the environment, need an adequate period of human evolutionary adaptation (13).

We aimed here to review evolutionary, cultural and dual inheritance perspectives on drug initiation/use, including considerations on NPSs. We will address: a) Why are drugs of misuse harmful? b) Why do people use mind-altering drugs even though they are harmful? c) What are the motivations underlying drug use? d) Why did natural psychoactive drugs that affect emotions evolve? e) Why do people initiate taking drugs? f) Why is drug use is so frequent among young people? g) Why is drug use so frequent among the socially disadvantaged? h) Why is psychedelic drug abuse related to spirituality? i) Has the human brain/body undergone evolutionary changes as a result of being habitually exposed in psychotropic drugs? l) Are there evolutionary advantages of shamanism, and is this relevant to an understanding of its relationship with mental illnesses like schizophrenia?

Methods/literature search strategy

A literature search on PubMed was conducted using the terms: *"Designer drugs"/"Novel Psychoactive Substances". "Evolution"/"Evolutionary psychiatry"/ "Darwinian psychiatry"/"Darwinian medicine"/"Evolutionary medicine"* were used combined with "*drug use*"/*"drug abuse"*. No filters were applied to limit the retrieval by study type, although there was a primary focus on human population data. The search was not restricted to English Language documents. Articles of relevance were used as sources of further articles via references.

Evolutionary and ethological perspectives on drug initiation and abuse

The ethologist Nico Tinbergen (14) suggested that four aspects of causation were required to adequately

explain a natural phenomenon: a) *proximate causation* (e.g. the immediate causal mechanism within/outside the individual, including immediate stimuli/meanings/learning/neuro-chemical substrates); b) *ontogeny* (e.g. the more distal causal influences in that individual's development from conception onwards); c) *ultimate mechanisms-functions* (e.g. the adaptive functions of that behaviour, understanding what it is good/bad for, and how does it aid survival/reproduction); d) *phylogeny* (e.g. the evolutionary history of that behaviour). Tinbergen, by introducing an evolutionary framework to causation, provided an overarching theoretical framework that permits the integration of different levels of explanation (14). No single aspect of causation has primacy, the different aspects are complementary and all are required to provide a full understanding. Thus, no single viewpoint can provide a complete understanding of substance misuse.

Nesse and Dawkins (1) proposed six categories of evolutionary explanations for vulnerability to disorders, including substance use disorders:

1. Mismatch theory is based on the idea that we possess traits (including behavioural patterns) that have been selected for/preserved by natural selection because of their adaptive function in a specific environment (the *Environment of Evolutionary Adaptation* or EEA), which for most of our evolutionary history was unlike current environments. Most human adaptations either emerged during the Pleistocene (2.6 million years ago to 12,000 years ago), or were maintained by stabilizing selection during the Pleistocene. Our "ancient" adaptive traits are thus frequently "mistuned" to the current environment. Many disorders are related to the excesses of current culture (i.e. over-availability of foods/chemicals that interfere with bodily processes and traits that evolved to be adaptive in a different time) (15). Because our social/physical environment is evolving at a rate faster than our ability to genetically adapt, we are increasingly "mismatched" to our environment. Similarly, the capacity of the human genome to evolve defences against plant/other toxins has been outstripped by the recent (10,000 years) pace of cultural change and technological development, such as the recent purification and chemical manipulation of plant alkaloids and the engineering of previously mostly unknown NPS.

2. Constraints. The speed of adaptation to new circumstances in a population depends on the random production and dissemination of adaptive genetic mutations or changes in frequency of existing alleles. This may take many millennia. There are therefore constraints on how fast, for example, liver detoxification mechanisms can evolve or existing mechanisms adapt compared to the speed of production of NPS by chemists. The relative time frames differ by many orders of magnitude. Only evolved detoxification mechanisms are available to detoxify/metabolise drugs. Flexible as these enzyme systems may be, they have not evolved to deal with entirely unfamiliar NPS.

3. Trade-offs between different functions that keep any trait from being truly perfect. Natural/sexual selection has resulted in many suboptimal 'systems'. Evolution cannot predict the future so cannot make any trait perfect for all circumstances. Selected traits often involve trade-offs. For example, humans become exhausted when running away. The psychological identification of fatigue presumably serves some function itself (possibly to limit further effort in order to prevent injury/collapse) but may also put one at risk from a determined predator. Overriding such fatigue by use of a painkiller/stimulant that blocks fatigue may allow the individual to continue exercising and incur the damage that fatigue evolved to protect against. If the alternative to over-riding a defence is possible death, risking the trade-off may be a worthwhile gamble.

4. Traits that increase reproduction at the expense of health. A trait that significantly increases reproduction will tend to spread, even if it harms health. Investments in competitive ability are seen to produce greater reproductive pay-offs for males than for females. Consequently, men have been shaped (by selection) to take more risks and to invest less in bodily repair. This concept will be adequately explained in the specific section.

5. Defences. Anxiety is an adaptation that is useful in certain situations for survival (i.e. by warning about a threat). Anxiety is over-expressed in ways that Nesse (16) calls '*false alarms*' when there is no real threat. However, selection has not 'made a mistake' in its over-representation with false positives, because the costs of not expressing such responses when needed may be so huge relative to the costs of false alarms that the optimal threshold allows for many false alarms. So, it is better to be anxious when walking through a strange environment if that heightened perception of threat allows a predator to be evaded, even if a predator attack is unlikely, than to be calm and risk being eaten ('*Smoke detector principle*') (16).

6. Pathogens. Toxic substances that protect plants frequently affect the functioning of many organisms. Plant toxins not only interfere with parasites, insects, worms and bacteria (bactericidal/antiparasitic function) but also mammals such as humans (by acting on neurotransmitters/biomediators) (7, 13). Amongst humans, this antiparasitic effect may have originally been an unintentional by-product of the diet or substance use and selection for a taste for such substances and adaptation (17-19), as supported by findings of self-medication behaviours in many non-humans species (8). In fact, animal defences against pathogens include not only immune system responses, but also behavioural responses (*behavioural immunity* or *non-immunological defence*), including self-medication (10, 19-21).

Evolutionary basis of human emotions

Since drugs are used to modify moods, evolutionary basis of these processes was here provided. Produc-

tion of emotion/affect is attributed mainly to the limbic system and the monoamine systems (22-25). Emotions/affects give organisms a selective advantage by adjusting physiological/mental processes to deal with situations that have repeatedly influenced fitness over the course of evolution (26).

Single-celled organisms have evolved two basic behaviours: move towards resources (BAS or behavioural activation) or away from danger (BIS or behavioural inhibition). These systems have evolved because they increase fitness in situations characterized by opportunity/gain or threat/loss (27-30).

The emotional systems of the brain have an evolutionary history. A major development occurred between *Amniota* (vertebrates including reptiles, birds and mammals) and older phyla (primitive vertebrates including amphibians, fish and invertebrates) regarding monoamines, particularly dopamine production. The behaviour of pre-Amniotes appears limited to reflex behaviour and learnt stimulus response behaviour. The capacity to acquire taste aversion/sensory pleasure in decision-making and expression of emotional tachycardia appeared first in *Amniota*. This suggests the emergence of a common hedonic mental pathway that uses pleasure/displeasure, as means to regulate behaviour (31), underpinned by substantial changes in dopamine production (32, 33).

The stimulus for the evolution of a hedonic system may have been the increasing complexity of life in terrestrial environments, where existence/survival/reproduction required ever more complex stimulus-response pathways for the creature to compete/survive/reproduce (34). This has been termed the *Red Queen hypothesis* (35), which proposes that organisms must constantly adapt/evolve/proliferate not merely to gain reproductive advantage, but also simply to survive while pitted against ever-evolving opposing organisms in an ever-changing environment. Eventually, a point was reached where stimulus-response behaviours became inefficient due to increasing numbers of stimuli requiring attention, and conflict between different stimulus-response systems. The emergence of a hedonic system allowed for weighting different stimuli and potentially conflicting responses (i.e. simultaneous urges to eat/mate/fight/flee). Different possible responses for a given set of circumstances were thus compared/judged according to the degree of pleasure/pain they evoked, in order to maximize pleasure/minimize displeasure. The existence of a hedonic system necessarily implies the existence of a rudimentary form of awareness, because pleasure/pain/reward/suffering must be experienced in order to have effect. Emotions are almost all positive or negative because neutral situations do not influence fitness. Natural selection has differentiated generic positive/negative states into more specialized emotions that are helpful (on average) in the specific situations that a species has encountered (16).

MacLean (36-39) described the evolution of a hierarchically organised triune brain. Schematically this comprises: a) a phylogenetically ancient basal ganglia, midbrain and brainstem, corresponding to the peak of reptilian brain evolution, functioning with innate behavioural knowledge/instincts/habits concerned with primitive survival, b) a less ancient paleomammalian limbic system, using affective knowledge and c) a more recent neo-mammalian neocortex that uses declarative knowledge.

Panksepp (40) has elaborated the phylogenesis of distinct primary emotional systems. He identifies a fundamental appetitive motivational system, which he names SEEKING which is required for exploration/feeding. Phylogenetically subsequent primary motivational systems are LUST, RAGE and FEAR, so called *reptilian* emotions geared towards dominance/sexuality. Most recently evolved are CARE, PANIC and PLAY which motivate *mammalian* attachment, parenting and social relationships. Panksepp describes the anatomical locations and specific neurotransmitters mediating these six primary emotional systems (40).

These primary emotional systems conferred sufficient reproductive benefits to have been selected for within the *EEA* (41, 42). They regulate behaviour in response to appraisals of environmental opportunities/threats, and act via hedonic means, inducing feelings of pleasure/pain to the extent that this promotes survival and Darwinian fitness.

Different neurotransmitters have more/less specific effects on emotional systems. Panksepp (40) classifies neurotransmitters in four groups: a) *aminoacid transmitters* (e.g. glutamine); b) *biogenic amines* (e.g. noradrenaline/dopamine/serotonin); c) *peptide neurotransmitters* (i.e. endogenous opioids/pituitary peptide hormones/hypothalamic releasing hormones, etc.); d) *other miscellaneous neurotransmitters* (i.e. acetylcholine/adenosine).

Recreational drugs activate specific primary emotional systems. Dopaminergic drugs (stimulants/hallucinogens) activate SEEKING and CARE. Opiates activate SEEKING and PLAY and reduce PANIC. Cannabinoids activate PLAY. Cholinergic drugs activate PLAY and RAGE (40).

The use of recreational drugs permits decoupling of emotional responses from the environment. Emotional rewards are obtained independent of any corresponding change/success in the environment. Thus, cocaine can make one can feel “amorous and excited”, whilst opiates can take away painful feeling of loneliness, even when one remains isolated and indeed whilst making one more isolated. Thus, these drugs provide a shortcut to the emotional rewards (or reduced punishments) that give the feeling of success, while there is no success. By obtaining the rewards without any need for achieving success, real success may become less likely. In this way, the manipulation of these emotional systems leads to impaired reproductive fitness (10).

Therefore, emotional responses modify our behaviour. The stimuli for responses are our perceptions of the internal/external, material/psychosocial environments, now or in the near future, particularly the state of our social interactions, which lead us to

an affective/cognitive appraisal of the situation. Recreational drugs affect these motivational systems and in doing so undermine their adaptive functions. The emotional rewards of drug use are reinforcing and lead to further use. By undermining the normal function of the emotional systems, the drug-using individual disrupts feedback from their emotional systems, thus impairing their ability to pursue biological goal. When free from drugs, and able to attend once again to neglected biological goals, the increased negative affective feedback causes greater dysphoria and may increase the likelihood of further drug use, in an attempt to reduce the dysphoria (40).

Thus, treatment of drug use based simply on abstinence will expose the individual to the dysphoria they were trying to block out with the drugs, and consequently lead to non-compliance (30). Consequently, we hypothesise that for treatment to be effective an individual formulation is required that identifies the environmental factor(s) leading to the dysphoria that the drug use is attempting to compensate for, and that treatment must be directed towards ameliorating the environmental cause of the unhappiness (40).

Reproduction at the expense of health

Although counterintuitive, a trait that increases reproduction may spread, even if it harms the health. Reproduction at the expense of health may explain cultural phenomena such as some aspects of substance use, which whilst manifestly harmful to the individual, may lead to increased sexual activity and numbers of sexual partners. Such a behavioural trait, particularly acting in an environment without contraception, would be strongly selected for.

In the EEA males and females have different investments in offspring due to the energy/time investment in gestation/breastfeeding. Access to sexual partners therefore appears to constrain male reproductive success more than female reproductive success, which is constrained more by the availability of resources. Therefore, investments in competitive ability give greater reproductive rewards for males than for females. In mammalian species males are sexually selected to engage in risky behaviour (i.e. dangerous driving/sports, drug use, etc.) to display their genetic quality (43-46). Due to differential parental investment in offspring, human males can statistically achieve greater reproductive success from pursuing short-term goals (i.e. a larger number of short-term relationships), impulsivity and sexual opportunistic behaviours (47).

Social demographic studies of drug abuse demonstrate that mortality rates for men at the age of sexual maturity are about three times higher than that for women (48). This may provide an explanation as to why young males smoke/use drugs/alcohol "to show off", to impress potential sexual partners. Once such "display" behaviour becomes established as a successful mating strategy it becomes subject to powerful selection pressure and it may also be imitated through learning, i.e. via culture.

"*Signalling theory*" explains the evolutionary value of apparently wasteful behaviour, such as altruism (49). High quality signallers are more successful in acquiring mates/allies. To be successful, the signals must incur more benefit than cost. Signals can be directed at anyone who stands to benefit from information the signaller is sending, such as potential sexual partners/allies/competitors. Signals can be honest, indicating superior biological value, or false (cheating), where they mislead about biological value. Some signals incur high biological cost; these signals cannot be faked, a weak/slow male would not be able to bear the survival cost of their extravagant display, thus *costly* signals guarantee the high value of the signaller (i.e. honesty). Some displays are independent of biological value and do not incur costs to the signaller (dishonest signals). Widespread adoption of dishonest signalling would be damaging to the population, therefore there is evolutionary pressure to evolve mechanisms to detect false signalling. Nonethe-less low levels of dishonest signalling evolve in stable populations. The "*Handicap principle*" (50) is an evolutionary mechanism to reduce dishonest signalling. The handicap principle can be applied to drug taking. This suggests that males attempt to impress potential mates by demonstrating their capacity to withstand the physiological/behavioural disadvantages of drug consumption to demonstrate their strength/fitness qualities. Males take substances that place them at a disadvantage relative to their rivals (i.e. binge drinking) and if they can still demonstrate superiority, such as winning a fight, this demonstrates their strength/fitness/bravery to potential mates. From this perspective drinking vast quantities of alcohol and then fighting while drunk "proves" what a big man you are. This "hard drinking" then may become culturally advantageous for some. A similar possibility (51) is that the early use of psychoactive substances is a high-risk strategy that signals bravery and thereby increases the chance of reproduction. This would explain why it is young males who are drawn to risky behaviour and psychoactive drugs as one instance of risky behaviour. There is good evidence that early drug taking does indeed lead to precocious sexual activity and teenage pregnancy (52).

Research on neurodevelopmental processes may also help us to understand why adolescents/youngsters are at increased risk for substance use (5, 53, 54). Often, young people have a sense that death or other severe consequences of drug use will not affect them personally. Although adolescents may accurately assess the risks of certain behaviours, they place greater value on the benefits/rewards rather than the risks of the behaviour and hence seek out stimulating experiences (30). This tendency to display risky behaviours is influenced by the individual's age/gender/socio-sexual status (55). Young/post-pubescent/unmarried males are the most likely to engage in risky drinking and drug use (51), with those who view

Table 2. Scores Million T0→T1 total sample.

themselves as having little likelihood of surviving/thriving as adults, i.e. who feel that they have little to lose, being at greatest risk (56-58).

Why would disadvantaged young people take more risks than those with better life prospects? Life history theory takes as its starting point that events in a person's lifetime are shaped by natural selection to produce the largest possible number of surviving offspring. It focuses on childhood development/age of sexual maturation/first reproduction, number of offspring and level of parental investment (59). Two principle strategies are described: an R (*rate*) strategy which focuses on producing the maximum number of offspring, by having large families early on and minimising parental investment, hence, as to maximise the opportunities to have more children; and a K (*Kapazität/Konstante*: Capacity/Constant) strategy which emphasises maximising the survival chances of offspring. It is achieved by careful mate selection, monogamous relationships, higher levels of maternal/paternal investment, and smaller numbers of offspring (60, 61). Modelling indicates that when life opportunities are good, a K strategy is superior, but when life opportunities are poor, then a R strategy is superior. Within certain biological constraints it appears that some organisms are able to shift their reproduction strategy towards r or K according to the evaluation of environmental opportunity. Therefore, precocious sexual behaviour among the disadvantaged is an example of a behavioural adaption; for those who have little to lose it increases their chance of reproductive success.

Optimal Foraging Theory

Poverty/parental alcohol/drug abuse/lack of stable attachment figures, and other adverse environmental conditions are important predisposing/risk factors for alcohol/drug abuse. Early use of alcohol/drugs in adolescence increases the risk for later development of tolerance/dependence (47). The concept of assortative mating describes the predisposition to select partners of similar disposition and may be used to explain why individuals exposed in childhood to alcoholic displays from parents choose partners who demonstrate similar behaviours (62). Clinical experience shows that many people begin to use drugs because they want pleasurable changes in moods (63). Some adolescents seem to want to escape reality, possibly because their reality feels too painful and the future too bleak (64).

Optimal Foraging Theory analyses the decisions that organisms make to maximise their food intake under specific EEA (65-67). It demonstrates that under conditions of scarcity (i.e. low prospect of future success) a strategy of caution will lead to death, but a high-risk strategy may lead to survival. Conversely under conditions of abundance (i.e. high prospect of future success) a strategy of caution/low-risk is superior to a high-risk strategy. From this perspective, people who feel, rightly or wrongly, that they have little to lose and "everything to gain", it is an adaptive strategy to engage in greater risk taking. However, these behavioural mechanisms evolved in the EEA. While risk taking, promiscuity, and precocious sexual activity, may have been adaptive in the EEA and therefore subjected to evolutionary selection, in the contemporary environment they may be maladaptive and contribute to ill health, failure in life and lowered reproductive success (47). As adolescence is the start of fertility and the period of maximal sexual fertility, it should be expected that behavioural mechanisms associated with reproduction will be at their strongest during this period. As substances misuse is so strongly linked to sexual signalling, it follows that adolescence is a period of heightened vulnerability for the development of substance use problems (68, 69).

Cultural, ritualistic and spiritual use of psychoactive drugs

DIT, also known as gene-culture coevolution or bio-cultural evolution (70) explains how human behaviour is a product of two different/interacting evolutionary processes: genetic (Darwinian) and cultural (*Memic* or *Dawkinsonian*) evolution (71).

Different drugs come with a "*cultural reputation*" for giving pleasure/relief of physical/emotional pain (15). Naming/branding/packaging are some of the ways in which the meaning of different drugs is manipulated to influence consumers (72). Some attraction to drug use may stem from the meaning/rituals of taking drugs within a culture as opposed to the intrinsic chemical property of the drug. Therefore, both neuropharmacology and meaning may influence drug use (5, 54). The "reputation" of recreational drugs is amplified by the virtual dissemination through the internet/social networks (5, 54, 73-75). Moreover, the cultural use of psychoactive drugs may be associated with some evolutionary benefits and even fitness enhancement (76). Culture here may stipulate/limit dosages/frequency of consumption, such that harms are limited/outweighed by benefits (64). Many of the harms currently associated with plant toxins used as recreational drugs are linked to technological/cultural changes resulting in huge increases in availability. This arises from cultivation/storage and increased concentration, achieved by selective breeding/purification/concentration and chemical processing e.g. industrial scale fermentation/distillation/purification/hydroxylation of opium/cocaine/etc.

The genome has evolved far more slowly than human culture (and technology) and lags behind contemporary patterns of drug use (64). This is especially true for NPSs, with numbers of molecules increasing on a daily/weekly basis (2-4). In fact, the use/sales of

NPSs for psychotropic purposes depends on cultural factors such as fashion/attractive naming/labelling/the internet and 'word of mouth' knowledge. Convenient labelling of NPS maintains that they are "*not for human consumption*", this loophole allowing them to be distributed cheaply, remain legal and easy to obtain. This strategy represents circumvention of legislation that forbids drugs that are "substantially similar" to already classified drugs from being sold for human use (54, 76). The efficacy/quality/safety profile of NPSs is unclear, but their supposed properties are rapidly disseminated through social networks/internet (54, 75). These means of distribution bypass the traditional cultural/medical/scientific routes but also outstrip the much slower evolutionary safety mechanisms such as adaptation of liver/other detoxification systems. Consequently, dangerous preparations may be widely distributed/used before they can be identified/studied/regulated and before human bodies and culture can adapt to the chemicals' presence (76).

Similarly, drugs used for ritualistic/religious purposes are clearly central to some cultural processes. In fact, religion/spirituality appear to have co-evolved with a larger hominid brain capable of consciousness and a sense of agency (77). Natural selection is the primary causal process that explains the evolution of such complex behaviours. Some adaptations arise from co-opting of existing biological traits that evolved for different purposes but which are put to new purposes, these are known as "*exaptations"* (78, 79). Gould (80) suggests that phenomena such as religion/language/commerce/art/warfare, although primarily evolutionary in origin, are incidental '*spandrels*' of the large human brain.

Religions involve rituals/signalling with costly and elaborate ceremonies/customs. These are typically carried out in public in order to demonstrate loyalty/allegiance to the group. "*Costly signalling theory*" hypothesises that these religious rituals should be costly enough to deter those not committed (81, 82). These rituals additionally have large placebo effects that may also confer advantage (83, 84). Extreme variants of religious beliefs may be maladaptive but still increase/maintain intra-group cooperation and reciprocal/altruistic behaviour (85, 86). The effects of religion on group survival, including healing effects, honest costly signalling (87) and the general health value (88) of religions have been recently demonstrated (89).

Substances influencing mood and thinking processes have been known to humanity at least from early Neolithic times in all known cultures (12). An interesting question is whether all this chemical indulgence throughout the millennia influenced brain evolution (90, 91). Many psychoactive substances fulfilled roles in religious ceremonies (11, 92). Social rituals such as becoming intoxicated/sharing spiritual experiences, may have conferred advantages by increasing group cohesion (93). They may also have had an important role in survival of a tribe by decreasing parasitic loads.

Among these substances, a particular interest regards entheogens (that literally means "*that which causes God to be within an individual*"), i.e. psychedelics/hallucinogens typically used in religious/spiritual/shamanic practices (94, 95). Shamans throughout the world incorporate entheogens in their arsenal of techniques to connect with the spirit world due to their capability to generate transcendental feelings/hallucinatory experiences (96-98). Móró et al. (99) suggested that the subject's attitude to take entheogens depends on the presence of pre-existing spiritual/religious beliefs/values, by underlining that indeed there is a relationship between spirituality/entheogens/mystical experiences reported by entheogens' users.

Shamanism originally refers to spiritual practitioners from Siberian nomadic cultures. Shamans and other magico-religious practitioners are traditionally believed to possess spiritual powers involving communication with a world beyond the observable realm (100). Shamans are often selected for having had visions/signs from gods and having gone through induced trance states through a variety of procedures, including consumption of hallucinogens/fasting/water or sleep deprivation/exposure to temperature extremes/extensive exercise/auditory stimuli (e.g. incantations/drumming/chanting)/social or sensory deprivation. Shamans are religious leaders in their communities with roles including healing the sick/presiding over "*rites of passage*" (e.g. birth/marriage/death) (101). The importance of shamans across cultures highlights how psychotic-like experiences have been valued in diverse cultures (102, 103). Polimeni and Reiss (104) have suggested that mild forms of schizophrenia and schizotypy could have enhanced a shaman's ability to conduct religious based rituals (105, 106). Schizotypy by increasing lateral thinking and novel approaches to problems might have been advantageous to shamans spearheading religious rituals and making decisions for the community (107). However, it is unclear if the plant-derived psychoactives have evolutionarily contributed to the appearance of shamanic practices or though shamanic phenotype has evolved to require psychoactive drugs (101).

Current drug use trends: evolutionary considerations on the psychonauts' phenomenon

Nowadays, the current phenomenon of NPSs and the information age have contributed to the spread of a new type of drug user, also called 'psychonaut'. These drug users intentionally take drugs, particularly NPSs and entheogen/hallucinogens, in order to induce altered states of consciousness in an attempt to investigate own mind, and possibly address spiritual questions (108, 109). Some consider psychonauts to be the new shamans (110, 111). Hallucinatory states, drug-induced or otherwise, are seen as revelatory

states of mind/different realities. The term "e-Psychonaut" is used in online pro-drug fora by individuals to identify themselves as psychonauts living in the information age (5). Typically, they are knowledgeable about pharmaceutical/chemical properties of drugs, experimenting on themselves with NPS in order to have new experiences and report their experiences to other "psychonauts".

Many e-psychonauts appear to regard their use of psychedelic drugs as a "prosocial" activity, not only "*taking psychedelics to get high*" but also to understand/familiarise themselves with the psychedelic landscape and share these experiences with others (5). The sharing of these experiences becomes the *trait d"union* of the e-psychonauts" community (5, 76). The sharing of psychedelic information becomes a ritual form of bonding, and discovery whilst facilitating the psychedelic information flow (112). There is some evidence that psychedelic drug users report greater concern for others compared to users of other drugs and non-drug users (113). In fact, cooperation/sharing/coordinating action with others have evolutionary benefits (114). Evolved social emotions in humans are experienced as a desire to become a member of a group with a sense of belonging and connectedness (115, 116), and a shift from "me-ness" to "we-ness" (117).

However, whether e-psychonauts" online preoccupation with mystical experience and belonging affects relationships and groups off line is unclear. The extent to which psychonaut communities exist other than as virtual communities is an empirical question that is currently unanswered.

Discussion

This evolutionary perspective sheds new light on some of the underlying mechanisms of drug initiation. The observation that psychotropic drugs act on evolutionarily conserved motivational systems is supported by the fact that other mammals demonstrate compulsive self-administration of the same drugs as humans do (118). The motivational systems that psychoactive drugs act on are anatomically/chemically/behaviourally conserved across mammalian species (119).

These motivational systems have been maintained over time by natural selection because they confer survival/reproductive advantages. Phylogenetic perspectives on the functions of emotions dispel the notion that adverse emotions are illnesses (90). Dysphoric emotions have evolved to motivate us to avoid situations where our Darwinian fitness is compromised. Appraisals of our environment that indicate that our chances of survival/reproductive success are low or falling will be aversive. In social animals, loss of status/strategic allegiances will indicate reductions in Darwinian fitness and result in dysphoria.

Analyses of humans' ancestral diets reveal wide use of psychoactive plant chemicals by early hominids. These chemicals conferred a number of advantages in small doses. They could reduce the effects of stress; provide physical benefits such as conferring alertness/overcoming exhaustion/increasing endurance/appetite suppression/bactericidal and antiparasitic properties; perform as substitute neurotransmitters during periods of deprivation (10).

Nowadays substance misuse is associated with a wide range of social disadvantages. Disadvantage/falling status negatively affects Darwinian fitness. If one is poor/oppressed/weak, without protectors, isolated/ill/abused or experiencing loss of status, one is less likely to be able to attract a high quality mate and experience reproductive success. Consequently disadvantage is a dysphoric state.

The association of substance misuse with disadvantage suggests that substance misuse is often an attempt to self-medicate/escape from dysphoric affect. Drugs may be used to inhibit grief, inflate self-esteem, create feelings of love/attachment security/sexual desirability, reduce fear/anxiety/panic, or produce a feeling in people that their lives are meaningful. It is clear that these feelings are not based on accurate assessments of loss/danger/attachment/emotional security/sexual desirability or how much meaning there is in one's life. Rather the drugs are commandeering the neural pathways that attach emotional valency to these perceptions. Therefore, paradoxically substance misuse may lead the individual further away from the goals that their pharmacologically stimulated brains deceive them into feeling that they are achieving.

Naturally occurring psychoactive substances are ancient and humans have had a long period of coevolution to develop the means to mitigate some toxic effects and sometimes to take advantage of effects. Rapid cultural/technological change has allowed intensive cultivation/concentration/storage/chemical manipulation and availability of psychoactive substances. There is a mismatch between the availability and strength of psychoactive substances and the mechanisms that humans have developed to cope with them. This leads to harmful substance misuse on a large scale. NPS are recent arrivals consequently there has been no period of coevolution and we are biologically unprepared for them. With increasing social complexity, psychedelic drugs may have conferred social benefits to social groups. Some individuals with an increased capacity for intuitive thought may have been able to use psychotropic drugs to gain influence/status as Shaman, and thereby increase their Darwinian fitness. The selection of this Shaman phenotype may explain the evolutionary selection of genes for schizotypy.

Despite the manifest harms of some substance misuse, evolved mechanisms may still confer benefits under some circumstances to harmful drug use: risk taking may signify value to potential mates, indicating bravery/vigour. Due to differential investment in pregnancy/breastfeeding, males have to compete more for females and intrinsically need to demonstrate these qualities to a greater extent than females. When the

prospects of success are very low, high-risk strategies confer at least the possibility of success, and are (at least in the EEA) adaptive. Those who perceive little likelihood of thriving or even surviving as adults may present with the highest risk levels (120).

By taking an evolutionary perspective we have been able to consider the function of behaviour in relation to reproductive advantage. We have demonstrated how ostensibly damaging behaviours may have had adaptive functions in the EEA, or indeed confer hidden benefits in the current environment via mechanisms such as reproduction at the expense of health/costly signalling/optimal foraging and life history r/K strategies. These concepts illustrate the need to investigate both conscious and unconscious motivations in drug initiation.

The ancient use of hallucinogens by shamans, commonplace in traditional societies, and a range of related cultural phenomena such as hallucinogenic states and intentionally-induced altered states of consciousness described by the new drug users, called psychonauts, may suggest a comeback to the shamanistic use of entheogens.

Conclusions

The standard model of substance misuse is restricted to understanding the mechanism of drug actions, the consequences of use, and listing correlations with risk for use/dependency. The evolutionary perspective elaborated here identifies the functions of the evolved behavioural traits/brain systems that motivate individuals to take drugs. This suggests interventions aimed at addressing the environmental triggers for substance misuse: the causes of dysphoria, the pressures to demonstrate mate value, and possibly the need for spirituality in individual/community life. Evolutionary models may suggest interventions directed at the underlying causes, rather than simply the manifestations of consequences of the behaviour. An appreciation of environment mismatch would suggest that the most dangerous drugs are those that are either highly modified or that we have not co-evolved with, i.e. NPSs and highly concentrated/chemically augmented drugs.

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Conflicts of Interest Statement

The Authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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