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The Neuroethics of Pleasure and Addiction in Public Health Strategies Moving Beyond Harm Reduction: Funding the Creation of Non-Addictive Drugs and Taxonomies of Pleasure

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Abstract We are unlikely to stop seeking pleasure, as this would prejudice our health and well-being. Yet many psychoactive substances providing pleasure are outlawed as illicit recreational drugs, despite the fact that only some of them are addictive to some people. Efforts to redress their prohibition, or to reform legislation so that penalties are proportionate to harm have largely failed. Yet, if choices over seeking pleasure are ethical insofar as they avoid harm to oneself or others, public health strategies should foster ethical choice by moving beyond current risk management practices embodied in the harm reduction movement. The neuroscience of pleasure has much to offer neuroethics and public health strategies. Distinguishing between 'wanting' and 'liking' fosters new understandings of addiction. These hold promise for directing the search for pharmacotherapies which prevent addiction and relapse or disrupt associated neuromechanisms. They could inform new research into creating lawful psychoactive substances which give us pleasure without provoking addiction. As the health and well being of human and other animals rests upon the experience of pleasure, this would be an ethical objective within public health strategy. Were ethical and neurobiological obstacles to ending addiction to be overcome, problems associated with excessive consumption, the lure of unlawful psychoactive substances and the paucity of lawful means to achieve pleasurable altered states would remain. Non-addictive designer drugs, which reliably provided lawful access to pleasures and altered states, would ameliorate these public health concerns insofar as they fostered citizens' informed, ethical choices according to a neurobiological taxonomy of pleasures.

Keywords Addiction · Designer drugs · Harm reduction · Pleasure · Public health

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Introduction

The conflation of addiction with that designated in policy discourses as the abuse of unlawful psychoactive substances is profoundly unhelpful. Not all psychoactive substances are addictive, not all addictive psychoactive substances are unlawful and not all addictions are to exogenous psychoactive substances, while the correlation between legality, addictive potential and harm is imperfect [1–3]. Nor does excessive consumption necessarily constitute addiction (though habitual excess may harm health) [4, 5, 6]. Hence any consideration of the neuroethics of addiction must begin with delineating the boundaries of inquiry. Addressing social, political and economic factors such as deprivation fostering addiction or the merits of the harm reduction movement falls outside the scope of neuroscience, as do suggested remedies

such as raised taxes on alcohol, fostering social inclusion and redressing global poverty [7–9]. Rather, this article will focus on ethical issues provoked by the neuroscience of addiction with respect to differences between individuals, species and psychoactive substances in order to evaluate future options to minimise harmful outcomes of addiction. It will conclude with some wider policy implications for public health.

Any consideration of the neuroethics of addiction must begin by acknowledging that mammals became hardwired to seek pleasure in order to enhance learning, health and survival in situations where sources of pleasure such as food, alcohol and MDMA were scarce or nonexistent compared to their relative plenitude today. Yet while all of us may find some pleasure in various substances or activities like sugar or gambling, our susceptibility to becoming addicted to these varies markedly. Neuroscience, in combination with pharmacogenomics and epigenetics, holds the promise to provide us with a means of determining the addictive potential of a range of substances and activities for each individual. Research which constructed a taxonomy of pleasures which could be matched according to their addictive potential for each individual could enable us to make ethical choices between pleasures on this basis. Ethical choice in this context implies a concern to avoid harm to oneself or one's health as well as harm to others, whether this involves ill-health, the squandering of family resources in gambling or criminal activity to fund addictions. Moreover, ethical choice also implies the freedom to make informed choices about the pleasures we seek, including achieving altered states, or cognitive liberty [10].

Public health strategies directed towards addiction and psychoactive substances, both lawful and unlawful, tend to seek to persuade us to moderate or abstain from consuming them on the grounds that we may harm our own health, or the health of others through depleting healthcare resources. Ethics is framed as harm avoidance or reduction. The relationship between pleasure, cognitive liberty and addiction is not considered [10, 11]. Given the pleasure-seeking nature of humanity, the eradication of all potentially addictive substances seems unlikely. Yet public health policy-makers are not free simply to advise us to consume more of less harmful substances and less of the more harmful, as those which are more harmful and more addictive, eg tobacco and alcohol, are lawful, whereas those which are less harmful and less addictive, eg MDMA, are not. While public health authorities can promote regulations to reduce consumption of lawful addictive and harmful substances like raising prices and banning smoking in public places to reduce consumption of nicotine, they cannot support the less harmful and less addictive unlawful alternatives.

Many have called for public health policies and legal reform of substance misuse laws linked to evidence-based assessments of harms associated with psychoactive substances [2, 3]. Yet scientific evidence alone has so far proved insufficiently persuasive. The partnership between politicians' drugs policy and public health policy-makers is an uneasy one, often hampered by the incoherence of rhetorical terms like the 'drugs problem' [1] and the tendency of politicians to adduce evidence selectively rather than use it to guide and shape policy [12]. For instance, the chair of Britain's Advisory Council on the Misuse of Drugs, Professor David Nutt, was sacked recently after stating in a lecture that illicit drugs should classified according to harm and that alcohol and tobacco were more harmful than LSD, cannabis and ecstasy/MDMA [13].

Taxonomies of licit and illicit drugs classified according to harm potential (including but not limited to addiction) have been constructed [2]. Neuroscientists have proposed classifications of pleasures [14]. The starting point of this article is that these should be integrated as part of a taxonomy of pleasures. In addition, the taxonomy should be informed by evidence on neural mechanisms linking pleasure, addiction and psychoactive substance or activity, as well as from the phenomenological accounts of those who have sampled psychoactive substances and pleasurable activities, in order to construct an inclusive taxonomy of pleasures. Public health strategies seeking to minimise addiction are often informed by harm reduction taxonomies of drugs arranged according to harm potential. Yet without data on the corresponding potential to provide pleasure, citizens are unable to make fully informed, ethical choices between pleasures. Were this taxonomy to be supplemented by information on individual susceptibility to the addictive potential of each of the pleasures, it would be easier for us to make ethical choices embodying cognitive liberty while eschewing harm.

Given that many pleasurable psychoactive substances are currently illegal, despite campaigns to align illegality with harm, a logical way forward for public health authorities would appear to be funding research into not only constructing such a taxonomy but also into creating non-addictive designer drugs.

In a desirable possible future, neuroscience would assist citizens to make ethical, informed choices over consuming pleasures, including those promoting altered mental states, in order to avoid addiction, harm and unlawful acts. Pre-conditions for this might include an expanded range of non-addictive pleasures to foster our making such ethical and informed choices. Additional measures to minimise addiction could include providing citizens with the means to ascertain their individual vulnerability to become addicted to specific substances or activities, a taxonomy of pleasures from which to choose and pharmacotherapies eliminating addiction. This future represents the promise of neuroscience. Whether it can be delivered is a separate matter. In the context of public health policy vis a vis politicians outlined above, public health strategies drawing upon neurobiological research to address addiction could help bring this future into being. Policy makers would need to emphasise not only the importance of social and fiscal measures [8, 15, 16] but also to acknowledge the promise of neuroscience to provide accurate information on the pleasures afforded by psychoactive substances, the means to assess individual pharmacogenomic vulnerabilities and pharmacotherapies to treat addiction. This promise, however, raises specific neuroethical difficulties, which will be explored below.

Addiction, Excess, Pleasure and Health

The word 'addiction' has both clinical and colloquial uses. It is often used quite loosely as a rhetorical term in public health campaigns seeking to reduce excessive consumption, eg binge drinking, which is clinically distinct from addiction itself as defined below [10]. Policy-makers tend to frame addiction pejoratively in terms of excess, risk and harm reduction and to condemn it. Public health campaigns deploy rhetoric emphasising the virtues of health read as self-discipline, whereas criminology focuses upon associations between addicts committing crimes of property and their consumption of unlawful psychoactive substances, on the assumption that drugs cause crime rather than criminals take drugs [11]. This pathologisation or condemnation of common practices obscures the fact that most humans through time have sought pleasure, sometimes via ingesting psychoactive substances [1, 3, 17, 18] and engaging in potentially addictive behaviours like gambling or recreational sex. Policies based on moralising also fail to acknowledge the increasing evidence that pleasure is essential for mammalian health and wellbeing [11, 18–20]. This has prevented a focus on a central issue for the neuroethics of addiction: how research might provide us with the facility to make informed and ethical choices between ethical pleasures, including psychoactive substances, which do not promote addiction.

Within clinical and philosophical thought, addiction is defined in relation to motivation and reward. Schroeder combines neuroscience and philosophy to suggest that desire is a natural kind, or part of the natural order which can be investigated as a unified and meaningful scientific entity [21]. He sees it as having three faces, motivation, pleasure and reward. Much of cognitive and affective neuroscience concerns the inter-relationship between motivation, pleasure and reward and how this impacts on awareness. In essence, animals, including humans, depend upon basic biological processes such as eating, breathing and sleeping in order to survive. Many of these basic processes take place outside awareness. Our bodies perform them automatically via the autonomic nervous system. If they demanded awareness, we would become overwhelmed by information and unable to function [22, 23]. Some, such as the fight-or-flight response, may be neurologically hardwired, since in dangerous situations instinctive responses rather than thoughtful evaluations foster survival. Aside from autonomic or instinctive behaviour, living entities need to learn specific skills in order to survive in novel situations. Motivation to engage in this information processing occurs via neurological mechanisms known within cognitive and affective neuroscience as the reward system. Animals appear to gain pleasure from learning, presumably as a result of evolution, ie partly to enhance their chances of survival [24]. This is a specific example of a more general attribute, insofar as pleasure promotes wellbeing and reward motivates action, including learning [19].

This model of animals, including humans, as information processing entities who learn through a reward system's providing reward or punishment as feedback suggests how inter-relations between pleasure, reward and learning operate in addiction while also shedding light on the nature of consciousness. Distinctions between 'liking', or the experience of pleasure, and 'wanting', or a compulsive craving, help explain how addiction operates, insofar as addicts persist in destructive behaviours despite their conscious wishes and are prone to relapse after lengthy periods of abstinence [25]. Addicts are driven not simply by conscious choices to seek pleasure but by powerful compulsions embedded in pathological learning. For instance, both rats and humans will focus on acquiring and consuming psychostimulants like amphetamine and cocaine to the exclusion of other goals in a process conceptualised as a pathological usurpation of neurological processes that normally serve reward-related learning [26]. Yet this constitutes an experience of constant craving rather than pleasure [27]. Addicts may experience some addiction-seeking actions as beyond their control. This has ethical implications for prevention and treatment strategies.

Current neurobiological research focuses upon those whose disorders of desire include psychoactive substances, compulsive gambling, disordered eating, sex and other repetitive behavioural practices, where commonalities of neuromechanisms appear to prevail [28–30]. With the exception of work by Berridge, Robinson, Kringelbach and colleagues, explored below, in this sphere, clinical explanations have tended to explain addiction in a neutral terminology of reward, hedonics, or positive reinforcement, marginalising or ignoring the role of pleasure as a separate factor. For instance, an accepted clinical definition of drug addiction or substance dependence is as a chronically relapsing disorder characterised by firstly, a compulsion to find and take the substance, secondly, loss of control in limiting uptake and thirdly, the emergence of a negative emotional state such as dysphoria, anxiety and irritability reflecting a motivational withdrawal system when the drug is inaccessible [31]. Homeostatic neuromechanisms, governing motivation among other things, rely on feedback to return systems to pre-existing setpoints. Changes in addicts' motivation are often explained as disruptions of homeostatic brain reward/antireward and hormonal stress systems, meaning addicts experience fewer rewards and greater stress as setpoints alter, more or less permanently. setpoints are chronically disturbed, they may be replaced by allostatic neuromechanisms. These rely upon feed-forward rather than feedback to alter setpoints according to changes in needs and resources. In this model, addiction results in chronic alteration in reward setpoints, dysregulated reward circuits and recruitment of brain and hormonal stress responses [32]. Top-down inhibitory control becomes lost [30] as impulsive choices become less conscious while consumption is driven by habitual stimulus-response compulsions [33] which remain intact after withdrawal, fostering relapse despite conscious intent.

Classically, then, neither clinical nor drug policy discourses have foregrounded pleasure as a factor in addiction. Recently, however, research addressing the role of neuromechanisms associated with pleasure, happiness, liking, wanting, craving, motivation and learning in daily life as well as addiction [19, 20, 23, 25, 34–39] provides new evidence for what I would envisage as a neuroethics of addiction. This research offers a finely articulated vocabulary of pleasure, reward and motivation as anchored in neuromechanisms. It enables ethical analyses based upon evidence of why and how pleasure-seeking forms a basis of mammalian life, yet promotes vulnerability to addiction [10].

I draw upon this work to argue that without an accepted neurochemical and neuroethical literacy of pleasures, we do not know enough to choose how to experience a range of ethical happy experiences reliably. Social contact amongst friends and family, altruistic acts towards strangers and taking prozac all increase happiness through neuromechanisms. Eating chocolate, taking ecstasy and falling in love produce neurochemical bliss. Mind-altering psychoactive substances creating pleasure may be produced endogenously [internally] by bodily activities such as strenuous exercise, lovemaking and meditation or consumed exogenously [ingested] like chocolate, fat, sugar and cocaine. All may be seen loosely as addictive, but are not ethically equivalent. Hence policies on mind-altering psychoactive substance use which fail to focus on the fact that pleasure motivates many, if not most, human actions are flawed.

A neurochemically informed taxonomy of pleasures associated with endogenous and exogenous

psychoactive substances would foster non-addictive choices and strategies. Pleasures associated with recreational psychoactive substance use include boundary loss [MDMA], spiritual enlightenment [LSD, mescaline], dissociation [ketamine] and intense energy [amphetamine]. Interdisciplinary research into how the phenomenological experience of pleasures relates to daily life and psychoactive substances would help us to understand and address the neuroethics of addiction, to make informed and ethical choices of non-addictive pleasures and to achieve sound rationalisations of drug laws. The following section of this article seeks to demonstrate how evidence from cognitive and affective neuroscience could contribute to such a taxonomy of pleasures. As the neuroscience of pleasure involves reward, motivation and learning as well as addiction, informed ethical inquiry into interventions into addiction is essential since these mechanisms may be disrupted, with ethical consequences for decision making abilities. Evidence from cognitive and affective neuroscience should inform ethical analyses of addiction treatments blocking pleasurable effects of psychoactive substances, designer drugs enhancing capacities or experiences and the ways in which we make sense of addiction. It also has implications for our notions of the unified self and how this relates to individual responsibility and treatments. Moreover, this neuroethical framing has implications for public health, law and policy which will be explored further below.

Neuroscience of Pleasure: Reward, Motivation, Learning and Addiction

Paleontology, genetics and evolutionary biology tell us that,

> '[l]ooking back through billions of years of change, everything innovative or apparently unique in the history of life is really just old stuff that has been recycled, recombined, repurposed, or otherwise modified for new uses. … our bodies and minds have emerged from parts common to other living creatures' [105 at 201].

Kringelbach, Robinson, Berridge and colleagues have demonstrated how neuromechanisms of ancestral reward and motivation systems, evolved to foster learning and survival, underpin human conscious and unconscious experience of pleasure [14, 18–20, 23–25, 34–36, 38–40]. This necessarily affects how we think about the neuroethics of pleasure and addiction. From an evolutionary perspective, we mammals are forced to seek out food, bodily safety, sex and social contact if we are to survive and flourish, and to learn optimum strategies to do so. Under conditions of uncertainty, emotions code risky choices [41]. Experiencing pleasure from natural rewards such as food and sex motivates us to continue this iterative learning [24, 42], without experiencing the disorders of desire associated with addiction which would prejudice survival. We may 'like' food or sex as they provide us with pleasure but are unlikely to 'want' or crave them in the same way as some of us 'want' or crave addictive substances or activities. This means that it is difficult to become addicted in living situations which preceded technology.

This is because natural rewards and addictive psychoactive substances differ insofar as neurobiological processing of the former, but not the latter, is embedded in homeostatic mechanisms with setpoints maintained by satiety, or the feeling of having had enough [18, 43]. Genetic inheritance and environmental circumstances may alter natural rewards' setpoints. Take food. Where repeated consumption of only one type of food results in feelings of satiety, this may have evolutionary advantages insofar as it promotes a varied diet enhancing health [18]. Hedonic hunger, or eating for pleasure [44] may fulfil similar functions. These mechanisms, which have evolved in previous times, may become problematic when the context changes. For instance, limited calorific intake in conjunction with high fat/high sugar diets may alter metabolic rate setpoints or instantiate compulsive 'wanting' through pathologised incentive salience mechanisms. This evolutionary strategy may once have enhanced mammalian survival in hard times, but which given today's access to a plenitude of high fat/high sugar foods, it now promotes obesity and disturbed eating. Bingeing on sugar, a processed natural substance, is associated with addictive-type behaviours and neuromechanisms [45]. Applying this model to psychoactive substance use, many of these in their unprocessed form are akin to natural rewards in that they may provide non-addictive temporary surcease from the rigours of life without adverse effects or addiction [46]. Chewing coca leaves assuages hunger and the limited oxygen supply

characterising high altitudes [7], whereas, processed into crack cocaine, their intense stimulation provokes compulsion and addiction.

Why all this matters is that given that the neurobiology of pleasure is embedded in mechanisms which have evolved to enhance survival, ethical issues arise over how far addiction should be condemned as morally blameworthy, labelled as an illness or treated to reduce pleasure. If pleasure is central to health and well being, we should be encouraged to experience it and laws and policies should acknowledge its worth. In order to preserve health and cognitive liberty, access to various pleasures should be limited only on grounds of harm. Informed choice between pleasures should be fostered by the construction of taxonomies of pleasure. Citizens should be provided with the means to ascertain their individual vulnerability to becoming addicted to specific activities and substances which are sources of pleasure in order that they can make informed and ethical choices. Currently, not enough is known to construct such a taxonomy of pleasures in order to foster ethical choices, according to individual susceptibilities to addiction. Nor is it inevitable that the mismatch between the legality and potential to cause harm of psychoactive substances will be rectified anytime soon. Consequently, I argue that public health strategies seeking to minimise addiction and maximise health should promote research into non-addictive designer drugs.

A promising starting point appears to be the cognitive and affective neuroscience of pleasure, since this establishes a fine tuned vocabulary and a model of the neuromechanisms underlying pleasure and addiction. Kringelbach, Robinson, Berridge and colleagues have individually and together published a body of work establishing pleasure as necessary for health and central to mammalian life [14, 18–20, 23–25, 34–36, 38–40]. Kringelbach defines pleasure and pain as positive and negative or unpleasant dimensions within the more general category of hedonic processing [38]. More colloquially, Frijda defines pleasure as feeling good [14]. In this model, sensory information is processed in terms of pleasure and displeasure in order to guide choices and learning. Emotions, or the subjective experience of the affective component of hedonic processing, may be seen as arising from the sensed experience of internal states, or interoception [47–51]. Not all emotional states will reach awareness and thus be available for conscious decision-making. This impacts upon the differentiation between the experience of pleasure as 'liking' and the experience of 'wanting', or compulsion, which does not involve pleasure, as mediated principally by the opioid and dopamine neurotransmitter systems respectively. When we like something and we get it we experience pleasure. When we are addicted to it, so that we want it or compulsively crave it, getting it does not bring us pleasure, merely a temporary relief from compulsion.

Robinson and Berridge suggest that addiction results from incentive salience, where brain mesocorticolimbic systems are rendered hypersensitive by drugs, leading to pathological compulsive wanting, or attentional processing biased towards drug-associated stimuli and impaired executive control over decision-making [40]. This means that it becomes very difficult to think about anything other than that we crave, which changes how we control our decisions and actions. Excessive consumption of stimulants, opioids and alcohol is associated with reduced frontal lobe metabolism in humans, leading to compromised self-control and decision-making capacity [52]. The initial pleasure associated with taking drugs declines as only the neural systems mediating 'wanting', the motivational process of incentive salience, become sensitised with repeated drug use. Thus, pleasure or 'liking' previously associated with the drug disappears, while drug-seeking behaviour becomes compulsive even after withdrawal and despite conscious intentions. Cognitive decision-making abilities decline while impulsivity rises as inhibitory neuromechanisms become dysfunctional [53]. Natural rewards such as food, sex, and social interaction become less appealing [54].

The ethical and policy implications of the fact that only some individuals are susceptible to becoming addicted in this fashion are crucial. Genetic inheritance renders some more prone to addiction to specific substances, and others less so. Certain genetic formations, for instance, compromise the ability of some to metabolise alcohol, rendering its consumption less pleasurable and hence addiction unlikely, while others inherit a predilection for alcoholism [55]. Interactions between genetic inheritance and environment also affect neuromechanisms and hence vulnerability to addiction, as in the postulated link between low status, stress, social

neglect and low dopamine receptor binding in non-human primates [56].

Thus, although many may try out various psychoactive substances, only a few are likely to become addicted to them, or to other pleasures like high fat/high sugar food or risk associated activities such as gambling or extreme sports [57]. Consequently public health policies seeking to reduce addiction should distinguish between the costs of excessive but non-addictive consumption and addiction in terms of assessing social and health-related harms. Public health funded research should aim to ascertain factors associated with vulnerability to addiction, to provide evidence-based treatments for addiction and to investigate and evaluate alternative sources of pleasure, such as designing, ascertaining and promoting psychoactive substances or activities which could promote 'liking' without provoking 'wanting'. Pleasure should be normatively and culturally reframed from its traditional pigeonholing as a questionable urge to be contained via inculcating the virtues of moderation, self-control and delayed gratification [18]. The present flawed system of psychoactive substance regulation is underpinned by this moralising approach to pleasure, with self-evidently problematic consequences. The rest of this article will focus on the ethics of treatments of vulnerability to addiction and the challenge of anti-addictive policies promoting 'liking' over 'wanting'.

Neuroethics of Addiction Research and Treatment

Both designing drugs which would provide us with the pleasures of liking without the compulsive cravings of wanting and addiction and research on addiction using human subjects provoke questions of causation and research ethics. It is difficult to distinguish between coding, correlation and causation of neuromechanisms using neuroimaging techniques [44, 58]. Neurobiological research into addiction also raises specific ethical issues. Much evidence on addiction relies upon animal models of self-stimulation, addictive behaviour and procedures which do not necessarily mimic human behaviour and may be regarded as ethically inappropriate for human subjects [40]. Translatability issues arise insofar as animal models may provide evidence only about mechanisms shared amongst species. Research involving drosophila or fruit flies and cocaine-induced behavioural plasticity has revealed various signalling pathways and biological processes which also appear in mammals, apparently through evolutionary conservation [59]. Yet addiction-driven disruptions of higher cognitive and affective functions restricted to higher mammals like the workings of spindle cells or Von Economo neurons cannot be ascertained from the rodent models which form the basis of much addiction research. Nor can the impact of pharmacotherapies with potential side effects associated with the symptoms of psychiatric disorders be fully evaluated without long term studies involving human research subjects.

Moreover, human subjects who are addicted constitute ethically problematic research subjects insofar as questions of their capacity to provide informed consent arise. As detailed above, compromised cognitive and affective neuromechanisms associated with decision-making characterise pathological learning and impulsivity associated with addiction. Yet clinical research involving addicts has undoubted potential for directly benefitting them [8]. Hence careful assessments of decisional competence must precede enrolment as research subjects. For instance, substance use affects neuromaturation in adolescents [22, 60]. Nicotine appears to act as a gateway drug in adolescence, sensitising reward pathways to the addictive effects of other psychostimulants [61]. Given evidence suggesting that children's neurobehaviour disinhibition and early tobacco use are associated with significant substance abuse, compromised neuromaturation and health problems in later life, research on this vulnerable population could prove beneficial, yet issues of consent, stigma, confidentiality and exploitation arise [62, 63]. Researchers must also design trials which take into account the fact that addicts often suffer from co-morbidities and mental disturbances with confounding factors arising from multiple drug use [8, 10]. This implies that pharmacotherapies for addictive substances which are commonly co-abused, like nicotine and ethanol must be evaluated in concert as well as separately [64]. In addition, research into the inter-relationship between genetics, environment and addictive substance or behaviour is crucial if successful pharmacotherapies are to be developed [55, 65].

The search for non-addictive substitutes for addictive substances has an unhappy history in that

supposedly non-addictive substances may turn out to be the reverse: heroin was synthesised chemically and commercially marketed in the late 1800s as a non-addictive opiate treatment for cough and asthma [66]. Nonetheless, pharmacotherapies created to disrupt or prevent the addictive process are a flourishing field. Combining neurobiology with pharmacogenomics in this context [67] promises the ability to diagnose individual vulnerabilities to specific psychoactive substances, enabling choices which would avoid addiction without precluding pleasure. One challenge is the translation of preclinical research into pharmacotherapy [68]. More germane to the arguments of this article are the ensuing ethical difficulties. Biomarkers identified in children and adults potentially predisposing them to addictions to specific substances would assist informed, ethical choices between pleasures. Those with specific genetic formations associated with alcoholism [55], might be well advised to eschew alcohol in favour of an alternative social lubricant. Yet how far obtaining such information might be seen as value-neutral is problematic. Public health research and resources would undoubtedly benefit from accumulating population wide databases of genetic information, correlated with ongoing medical records and lifestyle practices. Yet issues of privacy, consent, third party access to information, ineffectual anonymisation, stigma, human rights and civil liberties arise [8, 10, 69]. Similar concerns are associated with over-the-counter sales of genetic tests which could provide individuals with information over their vulnerability to specific modalities of addiction, along with issues to do with the over-interpretation or misinterpretation of the results. Reductionist and misleading interpretations of vulnerability to addiction attributed solely to genetic variations without acknowledging social factors like poverty and deprivation would marginalise important risk factors, hampering treatment [8, 16, 70].

More specifically neurobiological ethical concerns arise in that pharmacotherapies tend to target neuromechanisms associated with specific potentially addictive substances or activities [71]. Current multiple brain substrates targeted include dopamine transporters, dopamine D3 receptors, neuronal nicotine receptors, opioid receptors, serotonergic (5-HT3) receptors, cannabinoid receptors and the glutamate receptor system [68]. These may be cross-matched in investigations with various stages in the addictive process, as in contrasting the operation of natural reward reinforcers such as food with addictive substances like cocaine in providing or circumventing feedback promoting hypothalamic control over reinforcement circuit development [54]. Pharmacotherapies which attempt to reverse neuroadaptations [72, 73] and system dysregulations caused by pathological learning in addiction [74] or to restore pre-addiction homeostatic functions are logical ways forward. Neurobiological evidence that suggests that emotionally significance enhances memory and learning may also prove helpful [75, 76].

Yet side effects are problematic. Addiction to psychoactive substances or behaviour patterns shares commonalities with psychiatric disturbances [77]. Indeed, compulsive gambling has been categorised as an obsessive compulsive spectrum disorder as well as an addiction [29, 77]. This means that some psychiatric medications may be used to treat addiction [78] and that some psychoactive substances used recreationally, like ketamine, may have anti-addictive properties [79], but also that the side effects of pharmacotherapies for addiction may foster psychiatric symptoms or cognitive decline [78]. Moreover, the reward system and the emotions are closely connected [80]. Given the centrality of pleasure to mammalian life, it is predictable that pharmacotherapies attempting to modify the reward system risk promoting anhedonia, or loss of pleasure, together with accompanying symptoms of psychiatric disturbance like anxiety and depression. For instance, pleasure in natural rewards such as food is reduced by pharmacotherapies manipulating the endocannibinoid system to block the reward system to reduce the rewarding effects of opioid, ethanol, nicotine and stimulants [81]. Psychiatric conditions may also ensue from pharmacotherapies blocking the reward system. Licences were withdrawn or denied for rimonabant, a medication targeting the endocannibinoid system to combat over-eating, when it was found that taking it was associated with anxiety and obsessive compulsive disorder in some human subjects [82]. Thus reversibility and precise targeting of anti-addiction pharmacotherapies manipulating the reward system is ethically crucial.

This is so as well in relation to activities crucial to daily life besides pleasure which may be vulnerable to such interventions. For instance, pharmacotherapies targeting nicotine addiction through manipulating the

hypocretin/orexin system may adversely affect sleep and its disorders including narcolepsy, arousal and attention mechanisms [83]. Targets may also be misguided—interventions intended to eliminate impulsivity in adolescents may disrupt valuable iterative learning processes [84]. Disrupting one aspect of addiction, such as preventing the insular cortex from sensing bodily needs through interoception, may create aversion [85] but may also impact upon subjective experience and mood [86] as modulated by the associated neuromechanisms. Those designed to reverse pathological learning may affect memory and identity. Both memory and learning functions are compromised by addiction [87] and poor memory scores are associated with greater cocaine use after inpatient treatment [74]. Indeed, neurobiological therapies associated with memory manipulation are also ethically problematic insofar as they impact on patients' sense of identity and self, eg the therapeutic implantation of false memories or the extinction of traumatic memories [88].

A central ethical issue is what the aim of pharmacotherapies should be. Some aim at guaranteeing total abstinence from an addictive substance by ensuring that its consumption is accompanied by unpleasant experiences, while others reduce risk of relapse, often without interrupting consumption or affecting reinforcing properties [89]. These difficulties overlap with those addressed above in relation to how public health strategies might find a balance between providing information, urging moderation and preventing harms associated with excessive consumption and addiction.

Public Health Strategies: Liking, Wanting, Pleasure and Addiction

I have argued above that public health policies should support research into creating psychoactive substances which allow us to experience the pleasure of 'liking' without the addictive compulsions of 'wanting' The flipside of this is that pharmacotherapeutic research should aim to produce treatments which promote pleasure while eliminating compulsive craving or eradicating addictive wanting. This is a complex task, in that treatments which reduce 'liking' alone may not reduce consumption or diversion [90], while patient compliance is reduced by unpleasant side effects [91]. Ethical considerations demand finely tuned risk/benefit analyses based upon detailed knowledge of the neuromechanisms involved. The need for this is highlighted by the case of ibogaine, the primary alkaloid of the iboga plant from central Africa, used by healers in Gabon to create a near-death experience in initiation ceremonies. This has proven efficacious in eliminating addicts' desire to take any drugs, but is nonetheless prohibited as an illegal drug in most western countries as at least eight people have died after taking it. Maas and Strubelt hypothesize that these deaths occurred as a result of cardiac arrhythmias caused by dysregulated autonomic systems, which are often associated with sudden and unexplained death syndrome, vagal dominance where the vagus nerves slow the heart rate, and 'feigned death' as a mammalian survival strategy. Gabonian healers avoid such outcomes by isolating initiates from normal life for some days after initiation [92].

The example of ibogaine has several ethical implications for the neuroethics of addiction. Firstly, it provides some evidence that a single procedure can eliminate addictive cravings without lasting side-effects like lack of the ability to experience pleasure or psychiatric disturbance. Moreover, it indicates the need for addiction neurobiology researchers to recognise the local knowledge and subjective experiences of those involved in psychoactive substance use. Had those treating addicts ascertained the practices of the Gabonian healers and taken appropriate precautions, adverse consequences could have been avoided. While ibogaine is now being used to treat acute opioid withdrawal, its exact anti-addictive neuromechanisms remain speculative [93].

The story of ibogaine demonstrates the value of those researching addiction accepting the local knowledge and subjective experiences of participants. This is an ethical issue over the power relations of knowledge, as the experiences of those perceived as lowly may be under-valued. Research into addiction and other medical conditions has been hindered as the stigma associated with recreational experimentation with drugs has prevented research into promising clinical applications of unlawful psychoactive substances until relatively recently [94]. Given that many of those who use unlawful psychoactive substances do so in order to self-medicate [95], their experiences could suggest fruitful ways forward, like the use of

oxytocin to address co-morbidities such social and psychological difficulties [96]. Insofar as addictive psychoactive substances have positive effects, the subjective experiences of addicts could be used to map pleasurable effects which could then act as a basis for creating taxonomies of pleasure as well as non-addictive equivalents. They could also suggest new strategies for medications: cocaine may not only improve performance in certain tasks but also normalises activity in the lateral and medial regions of the prefrontal cortex [95]. Given pharmacotherapies' problems with compliance, medications which provided some of the positive effects of the addictive substance could improve this [83]. Guidelines for research into therapeutic benefits of some unlawful psychoactive substances which are also recreational drugs have been produced (55) [97], assisting investigation of applications such as ecstasy or MDMA for post traumatic stress disorder, psilocybin at end-of-life [94] and ayahuasca for panic and hopelessness [98], while the benefits of medical marijuana are increasingly apparent [17, 99].

An allied issue is the degree to which addicts may be seen as competent or legally responsible. Neurobiological evidence can go some way to establishing how far addiction compromises autonomy and free will or represents a disorder of the will [100, 101]. Cognitive and affective dysfunction as a result of addiction is common [5, 65, 102]. Loss of cognitive control in the form of impulsivity is a risk factor for relapse [33]. Neurocognitive dysfunction may reflect chronic dysregulation of decision-making faculties [95]. Addiction-related damage to distributed neural networks responsible for emotional processing may compromise emotionality and decision-making in ways similar to the dementias or ventromedial prefrontal cortex lesions [103–107]. This empirical evidence has policy implications [108]. In the same way that much of bodily processing is accomplished by automatic or non-conscious processes [22], addicts are likely to experience some aspects of addiction-fostering decisions like drug-seeking as being outside their conscious control.

This is distinct from the experience of operating on automatic pilot. As we learn specific skills which are performed often, these may become delegated via heuristic repetitions. For instance, many humans have driven to work, done housework and so forth in a distracted state, or on automatic pilot, while thinking about something quite different. Rather than assuming that we have one self who breathes or drives to work and another who thinks and feels, legal and ethical theories of responsibility assume a unitary self. If we kill a pedestrian while driving on automatic pilot, we are liable under the criminal law. Suggestions by Craig and others that the insular cortex modulates addiction [48–51, 109, 110], with consequent impairments in insight [111], correspond with the phenomenology of addiction, which reveals a profound disruption of the sense of self. The subjective experience of being a unified self who reflects, chooses and acts is challenged by the neuroscience of addiction [109, 112, 113]. Addicts may desire to eschew that to which they are addicted, yet be unable to resist the urge to consume it, while experiencing that urge as foreign to the self with which they identify [22, 114]. Their craving may have the force of an irresistible automatic process like breathing. This has ethical implications for the law's assessment of capacity or competence which have yet to be fully explored, particularly with respect to related forms of dysfunctional decision-making neuromechanisms associated with the dementias and traumatic brain injury [94].

Conclusion

I have argued that the neuroethics of addiction should be placed within the context of the neurochemistry of pleasure as motivating how we act in daily life as well as how we use drugs and other substances or experiences to make us feel good. Addiction scholarship focused on psychoactive substances' harm to health or crimogenic potential sidelines the crucial role of pleasure. Insofar as drug policies based on containing or eradicating addiction fail to acknowledge the centrality of pleasure in motivating mammalian behaviour, public health and criminal justice systems' functioning is compromised. Irrational substance abuse legislation based upon contingent sociohistoric factors, rather than categorising psychoactive substance use according to harm potential, clogs criminal justice systems, enriches narco-economies and diverts funding from innovative, translatable research which could address psychoactive substance use and addiction in a broader context.

We are unlikely to stop seeking pleasure, as this would prejudice our health and well being. Yet many

of the psychoactive substances providing pleasure are currently outlawed as illicit recreational drugs, despite the fact that only some of them are addictive to some people. Efforts to redress the prohibition of psychoactive substances, or to reform legislation so that penalties are in proportion to harms have proven largely unsuccessful so far. Yet if choices over seeking pleasure are ethical insofar as they avoid harm to oneself or others, public health harm reduction strategies should foster ethical choice by moving beyond current risk management practices. I suggest public health authorities should fund neuroethically informed research into the creation of non-addictive psychoactive substances which would provide individual citizens with a variety of lawful pleasures. This would enable us to exercise cognitive liberty and to experience a range of pleasures without risking addiction or breaking the law. Moreover, I suggest that research leading to the construction of a taxonomy of pleasures, linked to means of ascertaining individual susceptibility to become addicted to specific substances and activities, would allow us to make ethical informed choices to avoid harms associated with addiction.

The neuroscience of addiction could seed this research, through affording evidence for the construction of a taxonomy of pleasures to foster ethical choices eschewing addiction. Anti-addiction public health strategies should support creating and promoting designer drugs which provide pleasure without addictive cravings. Increasing the range of non-addictive pleasures, including means of attaining altered states, would assist citizens to make ethical choices between pleasures. Public health strategies should ensure that these choices are informed as well as ethical by supporting initiatives to provide citizens with comprehensive neurologically based understandings of their individual vulnerabilities to addiction to specific psychoactive substances or behaviours. Interventions would need to take place outside contexts of coercion, stigmatisation and invasion of privacy [8, 10, 11]. Finally, public health policy should promote rationalised drug use regulatory structures which conserve public health and criminal justice system resources while promoting cognitive liberty [10] in order to minimise social harms and maximise informed choice.

The neuroscience of pleasure has much to offer neuroethics and public health strategies. As an analytic tool, the distinction between 'wanting' and 'liking' fosters new understandings of addiction. It holds promise for directing the search for pharmacotherapies which prevent addiction and relapse or disrupt associated neuromechanisms. Moreover, it may form the basis for new research into creating lawful psychoactive substances which give us pleasure without provoking addiction. I have argued that as the health and well being of human and other animals rests upon the experience of pleasure, this would be an ethical objective within public health strategy. This is distinct from the debate over the ethics of neuroenhancement, which has focused upon increasing capabilities such as memory, intelligence and athleticism, prescription drug diversion and concerns over social justice and neuroenhancement related diseases [115–119]. Were the ethical and neurobiological obstacles to ending addiction to be overcome, problems associated with excessive consumption, the lure of unlawful psychoactive substances and the paucity of lawful means to achieve pleasurable altered states would remain. Drugs designed to be without addictive potential, which reliably provided lawful access to pleasures and altered states, would ameliorate these public health concerns insofar as they fostered citizens' informed, ethical choices according to a neurobiological taxonomy of pleasures.

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References

1. Boland, P. 2008. British drugs policy: problematising the distinction between legal and illegal drugs and the definition of the 'drugs problem'. *Probation Journal* 55: 171–187.
2. Nutt, D. 2009. *Estimating drug harms: a risky business? Briefing 10, October 2009. Centre for Crime and Justice Studies.* London: Centre for Crime and Justice Studies. http://www.crimeandjustice.org.uk/estimatingdrugharmspr.html . Accessed 3 November 2009.
3. RSA Commission. 2007. *Drugs—facing facts: the report of the RSA Commission on illegal drugs, communities and public policy.* London: Royal Society for the Encouragement of the Arts, Manufacture and Commerce (RSA).
4. Hall, W., and T.F. Babor. 2000. Editorial: cannabis use and public health: assessing the burden. *Addiction* 95: 485–490.
5. Stephens, D.N., and T. Duka. 2008. Cognitive and emotional consequences of binge drinking: role of

amygdala and prefrontal cortex. *Philosophical Transactions of the Royal Society. Series B* 363: 3169–3179.
6. Hall, W. 2009. The adverse health effects of cannabis use: what are they, and what are the implications for policy? *International Journal of Drug Policy* 20: 458–465.
7. Edwards, G. 2004. *Matters of substance: drugs—and why everyone's a user*. London: Allen Lane.
8. Hall, W., L. Carter, and K.I. Morley. 2004. Neuroscience research on the addictions: a prospectus for future ethical and policy analysis. *Addictive Behaviors* 29: 1481–1495.
9. Lankenau, S., et al. 2008. Towards an explanation of subjective ketamine experiences of young injection drug users. *Addiction Research & Theory* 16: 273–287.
10. Mackenzie, R. 2006. Addiction in public health and criminal justice system governance: neuroscience, enhancement and happiness research. *Genomics, Society and Policy* 2: 92–109.
11. Mackenzie, R. 2008. Feeling good: the ethopolitics of pleasure, psychoactive substance use and public health and criminal justice system governance: therapeutic jurisprudence and the drug courts in the United States of America. *Social & Legal Studies* 17: 513–533.
12. Monaghan, M. 2008. Appreciating cannabis: the paradox of evidence in evidence-based policy making. *Evidence and Policy* 4: 209–231.
13. Travis, A., and D. Summers. 2009. Alan Johnson orders snap review of drugs advice body. *Guardian*. http://www.guardian.co.uk/politics/2009/nov/02/drugspolicy-drugs/print . Accessed 2 November 2009.
14. Frijda, N.H. 2010. On the nature and function of pleasure. In *Pleasures of the brain*, ed. M.L. Kringelbach and K.C. Berridge, 99–112. New York: Oxford University Press.
15. Degenhardt, L., W. Hall, and M. Lynskey. 2003. Exploring the association between cannabis use and depression. *Addiction* 98: 1493–1504.
16. Stenbacka, M., and Leifman Anders. 2001. Can individual competence factors prevent adult substance and alcohol abuse in low and high income areas? *Alcohol* 25: 107–114.
17. Iverson, L. 2007. *Science and medical use of marijuana*. Oxford: Oxford University Press.
18. Leknes, S., and I. Tracey. 2010. Pain and pleasure: masters of mankind. In *Pleasures of the brain*, ed. M.L. Kringelbach and K.C. Berridge, 320–336. New York: Oxford University Press.
19. Berridge, K.C., and M.L. Kringelbach. 2008. Affective neuroscience of pleasure: reward in humans and animals. *Psychopharmacology* 199: 457–480.
20. Kringelbach, M.L., and K.C. Berridge. 2009. Towards a functional neuroanatomy of pleasure and happiness. *Trends in Cognitive Science* 13: 479–487.
21. Schroeder, T. 2004. *Three faces of desire*. New York: Oxford University Press.
22. Clark, R.E. 2009. Resistance to change: unconscious knowledge and the challenge of unlearning. In *Changing institutions, environments and people*, ed. D.C. Berliner and H. Kupwermintz, 75–94. New York: Routledge.
23. Kringelbach, M.L., and K.C. Berridge. 2010. Fundamental pleasure questions. In *Pleasures of the brain*, ed. M.L. Kringelbach and K.C. Berridge, 7–26. New York: Oxford University Press.
24. Cabanac, M. 2010. The dialectics of pleasure. In *Pleasures of the brain*, ed. M.L. Kringelbach and K.C. Berridge, 113–124. New York: Oxford University Press.
25. Berridge, K.C., T.E. Robinson, and J. Wayne Aldridge. 2009. Dissecting components of reward: 'liking', 'wanting' and learning. *Current Opinion in Pharmacology* 9: 65–73.
26. Hyman, S.E., R.C. Malenka, and E.J. Nestler. 2006. Neural mechanisms of addiction: the role of reward-related learning and memory. *Annual Review of Neuroscience* 29: 565–598.
27. Leyton, M. 2010. The neurobiology of desire: dopamine and the regulation of mood and motivational states in humans. In *Pleasures of the brain*, ed. M.L. Kringelbach and K.C. Berridge, 222–243. New York: Oxford University Press.
28. Figlewicz, D.P., and S.C. Benoit. 2009. Insulin, leptin and food reward: update 2008. *American Journal of Physiological Regulation Integrating Comparative Physiology* 296: R9–R19.
29. Potenza, M.C. 2008. The neurobiology of pathological gambling and drug addiction: an overview and new findings. *Philosophical Transactions of the Royal Society. Series B* 363: 3181–3189.
30. Volkow, N.D., et al. 2008. Overlapping neuronal circuits in addiction and obesity: evidence of systems pathology. *Philosophical Transactions of the Royal Society. Series B* 363: 3191–3200.
31. Koob George, F., and N.D. Volkow. 2009. Neurocircuitry of addiction. *Neuropharmacology Reviews*. doi:np/npp.2009.110.
32. Koob, G.F., and M. Le Moal. 2008. Addiction and the brain anti-reward system. *Annual Review of Psychology* 59: 29–53.
33. Everitt, B.J., et al. 2008. Neural mechanisms underlying the vulnerability to develop compulsive drug-seeking habits and addiction. *Philosophical Transactions of the Royal Society. Series B* 363: 3125–3135.
34. Berridge, K.C. 2009. 'Liking' and 'wanting' food rewards: brain substrates and roles in eating disorders. *Physiology & Behavior* 97: 537–550.
35. Berridge, K.C. 2007. The debate over dopamine's role in reward: the case for incentive salience. *Psychopharacology* 191: 391–431.
36. Berridge, K.C., and T.E. Robinson. 2003. Parsing reward. *Trends in Neurosciences* 26: 507–513.
37. Kowe, M.R., and M.L. Butryn. 2007. Hedonic humger: a new dimension of appetite? *Physiology & Behavior* 91: 432–439.
38. Kringelbach, M.L. 2010. The hedonic brain: a functional neuroanatomy of human pleasure. In *Pleasures of the brain*, ed. M.L. Kringelbach and K.C. Berridge, 202–221. New York: Oxford University Press.
39. Kringelbach, M.L. 2005. The orbitofrontal cortex: linking reward to hedonic experience. *Nature Reviews Neuroscience* 6: 691–702.
40. Robinson, T.E., and K.C. Berridge. 2008. The incentive sensitisation theory of addiction: some current issues. *Philosophical Transactions of the Royal Society. Series B* 363: 3137–3146.

41. Quartz, S.R. 2009. Reason, emotion and decision-making: risk and reward computation with feeling. *Trends in Cognitive Science* 13: 209–216.
42. Shubin, N. 2008. *Your inner fish: a journey into the 3.5-billion-year history of the human body*. London: Allen Lane.
43. Chiara, G.C., and V. Bassareo. 2006. Reward system and addiction: what dopamine does and doesn't do. *Current Opinion in Pharmacology* 7: 69–75.
44. Lowe, M.R., and M.L. Butryn. 2007. Hedonic hunger: a new dimension of appetite. *Physiology & Behavior* 91: 432–439.
45. Avena, N.M., P. Rada, and B.C. Hoebel. 2009. Sugar and fat bingeing have notable differences in addictive-like behaviour. *Journal of Nutrition* 139: 623–628.
46. Halpern, J.H., et al. 2005. Psychological and cognitive effects of long term peyote use among Native Americans. *Biological Psychiatry* 58: 624–631.
47. Singer, T., H.D. Critchley, and K. Preuschoff. 2009. A common role for the insula in feelings, empathy and uncertainty. *Trends in Cognitive Sciences* 13: 334–340.
48. Craig, A.D. 2009. How do you feel—now? The anterior insula and human consciousness. *Nature Reviews Neuroscience* 10: 59–70.
49. Craig, A.D. 2004. Human feelings: why are some more aware than others? *Trends in Cognitive Sciences* 8: 239–241.
50. Craig, A.D. 2003. Interoception: the sense of the physiological condition of the body. *Current Opinion in Neurobiology* 13: 500–505.
51. Craig, A.D. 2002. How do you feel? Interoception: the sense of the physiological condition of the body. *Nature Reviews Neuroscience* 3: 655–666.
52. Franklin, T., et al. 2002. Decreased grey matter concentration in the insular, orbitofrontal, cingulated and temporal cortices of cocaine patients. *Biological Psychiatry* 51: 134–142.
53. Lubman, D.L., M. Yucel, and C. Pantelis. 2004. Addiction, a condition of compulsive behaviour? Neuroimaging and neuropsychological evidence of inhibitory dysregulation. *Addiction* 99: 1491–1502.
54. Zombeck, J.A., et al. 2008. Neuroanatomical specificity of conditioned responses to cocaine versus food in mice. *Physiology & Behavior* 93: 637–650.
55. Mayfield, R.D., R.A. Harris, and M.A. Schuckit. 2008. Genetic factors influencing alcohol dependence. *British Journal of Pharmacology* 154: 275–287.
56. Nader, M.A., et al. 2008. Positron emission tomography imaging studies of dopamine receptors in primate models of addiction. *Philosophical Transactions of the Royal Society. Series B* 363: 3223–3232.
57. O'Brien, C.P. 2008. Evidence-based treatments of addiction. *Philosophical Transactions of the Royal Society. Series B* 363: 3277–3286.
58. Beveridge, T.J.R., et al. 2008. Parallel studies of cocaine-related neural and cognitive impairment in humans and monkeys. *Philosphical Transactions of the Royal Society. Series B* 363: 3257–3266.
59. Heberlein, U., et al. 2008. Drosophila, a genetic model system to study cocaine-related behaviours: a review with focus on LIM-only proteins. *Neuropharmacology*. doi:10.1016/jneuropharm.2009.07.023.
60. Squeglia, L.M., J. Jacobus, and S.F. Tapert. 2009. The influence of substance use on adolescent brain development. *Clinical EEG & Neuroscience* 40: 31–38.
61. McQuown, S.C., et al. 2009. Age-dependent effects of low-dose nicotine treatment on cocaine-induced behavioural plasticity in rats. *Psychopharmacology* 207: 143–152.
62. Kirisci, L., et al. 2006. Individual differences in childhood neurobehaviour disinhibition predict decision to desist substance use during adolescence and substance use disorder in young adulthood: a prospective study. *Addictive Behaviors* 31: 686–695.
63. Moolchan, E.T., and R. Mermelstein. 2002. Research on tobacco use among teenagers: ethical challenges. *Journal of Adolescent Health* 30: 409–417.
64. Gulick, D., and T.J. Gould. 2008. Interactive effects of ethanol and nicotine on learning in C57BL/6 J mice depend on both dose and duration of treatment. *Psychopharmacology* 196: 483–495.
65. Crabbe, J.C. 2008. Neurogenetic studies of alcohol addiction. *Philosophical Transactions of the Royal Society. Series B* 363: 3201–3211.
66. Le Merrer, J., et al. 2009. Reward processing by the opioid system in the brain. *Physiological Review* 89: 1379–1412.
67. Montoya, I.D., and F. Vocci. 2008. Novel medications to treat addictive disorders. *Current Psychiatry Reports* 10: 392–398.
68. Rahman, S. 2008. Editorial: hot topic, drug addiction and brain targets, from preclinical research to pharmacotherapy. *CNS & Neurological Disorders—Drug Targets* 7: 391–392.
69. Hall, W. 2005. Will nicotine genetics and a nicotine vaccine prevent cigarette smoking and smoking-related diseases? *PLoS Medicine* 2: 860–863.
70. Wong, C.C.Y., and G. Schumann. 2008. Genetics of addictions: strategies for addressing heterogeneity and polygenicity of substance use disorders. *Philosophical transactions of the Royal Society. Series B* 363: 3213–3222.
71. Lawrence, A.J., P.M. Beart, and P.W. Kalivas. 2008. Neuropharmacology of addiction: setting the scene. *British Journal of Pharmacology* 154: 259–260.
72. Kalivas, P.W. 2007. Neurobiology of cocaine addiction: implications for new pharmacotherapy. *American Journal of Addiction* 16: 71–78.
73. Kalivas, P.W. 2009. Glutamate transmission in addiction. *Neuropharmacology* 56: 169–173.
74. Fox, H.C., E.D. Jackson, and R. Sinha. 2009. Elevated cortisol and learning and memory deficits in cocaine dependent individuals: relationship to relapse outcomes. *Psychoneuroendocrininology* 34: 1198–1207.
75. Imordino-Yang, M.H., and A. Damasio. 2007. We feel, therefore we learn: the relevance of affective and social neuroscience to education. *Journal of Compilation* 1: 3–10.
76. Wittmann, B.C., et al. 2008. Mesolimbic interaction of emotional valence and reward improves memory formation. *Neuropsychologia* 46: 1000–1008.
77. Grant, J.E., and S.W. Kim. 2006. Medication management of pathological gambling. *Minnesota Medicine* http://www.

minnesoatamedicine.com/PastIssues/September2006/ClinicalGrantSeptember Accessed 3 November 2009.
78. Berkus, E. 2007. The link between psychotic disorders and substance use. *Psychiatric Times* 24 http://www.psychiatrictimes.com/print/article/10168/46501?printable=true. Accessed 3 November 2009.
79. Ross, S., and E. Peselow. 2009. The neurobiology of addictive disorders. *Clinical Neuropharmacology* 32: 269–276.
80. O'Connor, M.-F., et al. 2008. Craving love? Enduring grief activates brain's reward center. *Neuroimage* 42: 969–972.
81. Solinas, M., S.K. Goldberg, and D. Piomelli. 2008. The endocannibinoid system in brain reward processes. *British Journal of Pharmacology* 154: 369–383.
82. Le Foll, B., D.A. Gorelick, and S.R. Goldberg. 2009. The future of endocannabinoid oriented clinical research after CB1 antagonists. *Psychopharmacology* 205: 1506–1507.
83. Corrigall, W.A. 2009. Hypocretin mechanisms in nicotine addiction: evidence and speculation. *Psychopharmacology* 206: 23–37.
84. Gullo, M.J., and S. Dawe. 2008. Impulsivity and adolescent substance use: rashly dismissed as all bad? *Neuroscience and Biobehavioral Reviews* 32: 1507–1518.
85. Naqvi, N.H., and A. Bechara. 2008. The hidden island of addiction: the insula. *Trends in Neuroscience* 32: 56–67.
86. Domschke, K., et al. 2009. Interioceptive sensitivity to anxiety and anxiety disorders: an overview and integration of neurobiological findings. *Clinical Psychology Review*. doi:10.1016/.cpr.2009.08.008.
87. Koob, G.F. 2009. Dynamics of neuronal circuits in addiction: reward, anti-reward and emotional memory. *Pharmacopsychiatry* 42: 532–541.
88. Evers, K. 2007. Perspectives on memory manipulation: using beta-blockers to cure post-traumatic stress disorder. *Cambridge Quarterly of Healthcare Ethics* 16: 138–146.
89. Boutrel, B. 2008. A neuropeptide-centric view of psychostimulant addiction. *British Journal of Pharmacology* 154: 343–357.
90. Fudala, P.J., and R.E. Johnson. 2006. Development of opioid formulations with limited diversion and abuse potential. *Drug and Alcohol Dependence* 83: S40–S47.
91. Mitchell, J.M., et al. 2009. Natrexone aversion and treatment efficacy are greatest in humans and rats that actively consume high levels of alcohol. *Neurobiology of Disease* 33: 72–80.
92. Maas, U., and S. Strubelt. 2006. Fatalities after taking ibogaine in addiction treatment could be related to sudden cardiac death caused by autonomic dysfunction. *Medical Hypotheses* 67: 960–964.
93. Alper, K., and H. Lotsof. 1999. Treatment of acute opiod withdrawal with ibogaine. *American Journal of Addiction* 8: 234–242.
94. Mackenzie, R. 2009. Reframing the good death: enhancing choice in dying, neuroscience, end of life research and the potential of psychedelics in palliative care. In *Law, Mind and Brain*, ed. M. Freeman and O. Goodenough, 239–263. London: Ashgate.
95. Garavan, H., J.N. Kaufman, and R. Hester. 2008. Acute effects of cocaine on the neurobiology of cognitive control. *Philosophical Transactions of the Royal Society. Series B* 363: 3267–3276.
96. McGregor, I.S., P.D. Callaghan, and G.E. Hunt. 2008. From ultrasocial to antisocial: a role for oxytocin in the acute reinforcing effects and long term adverse consequences of drug use? *British Journal of Pharmacology* 154: 358–368.
97. Johnson, M.W., W.A. Richards, and R.R. Griffiths. 2008. Human hallucinogen research: guidelines for safety. *Journal of Psychopharmacology* 22: 603–620.
98. Santos, R.G., et al. 2007. Effects of ayahuasca on psychometric measures of anxiety, panic-like and hopelessness in Santo Daime members. *Journal of Ethnopharmacology* 112: 507–513.
99. Hall, W., MacDonald Christie, and D. Currow. 2005. Cannabinoids and cancer: causation, remediation and palliation. *Lancet Oncology* 6: 35–42.
100. Burns, K., and A. Bechara. 2007. Decision making and free will: a neuroscience perspective. *Behavioral Sciences and the Law* 25: 263–280.
101. Northoff, G. 2006. Neuroscience of decision making and informed consent: an investigation in neuroethics. *Journal of Medical Ethics* 32: 70–73.
102. Vengeliene, V., et al. 2008. Neuropharmacology of alcohol addiction. *British Journal of Pharmacology* 154: 299–315.
103. Bechara, A., and H. Damasio. 2002. Decision-making and addiction (part I): impaired activation of somatic states in substance dependent individuals when pondering decisions with negative future consequences. *Neuropsychologia* 40: 1675–1689.
104. Bechara, A., S. Dolan, and A. Hines. 2002. Decision-making and addiction (part II): myopia for the future or hypersensitivity to reward? *Neuropsychologia* 40: 1696–1705.
105. Mackenzie, R., and M. Sakel. 2010. The neuroscience of cruelty as brain damage: legal framings of capacity and ethical issues in the neurorehabilitation of motor neurone disease and behavioural variant fronto-temporal dementia patients. In *Law and neuroscience: current legal issues*, ed. M. Freeman. Oxford: Oxford University Press.
106. Mackenzie, R., and J. Watts. 2009. Callous/unemotional conduct disorder as a learning disability. *Tizard Learning Disability Review* 14: 38–44.
107. Verdejo-Garcia, A., and A. Bechara. 2008. A somatic marker theory of addiction. *Neuropharmacology* 56: 48–62.
108. Jeste, D.V., and E. Saks. 2006. Decisional capacity in mental illness and substance use disorders: empirical database and policy implications. *Behavioral Sciences and the Law* 24: 607–628.
109. Gray, M.A., and H.D. Critchley. 2007. Interoceptive basis to craving. *Neuron* 54: 183–186.
110. Paulus, M.P., S.F. Tapert, and G. Schulteis. 2009. The role of interoception and alliesthesia in addiction. *Pharmacology, Biochemistry and Behavior* 94: 1–7.
111. Goldstein, R., et al. 2009. The neurocircuitry of impaired insight in drug addiction. *Trends in Cognitive Science* 13: 372–380.
112. Gray, M.T. 2005. The shifting sands of self: a framework for the experience of self in addiction. *Nursing Philosophy* 6: 119–130.
113. Shinebourne, P., and J.A. Smith. 2009. Alcohol and the self: an interpretative phenomenological analysis of the

experience of addiction and its impact on the sense of self and society. *Addiction Research & Theory* 17: 152–167.
114. Baler, R.D., and N.D. Volkow. 2006. Drug addiction: the neurobiology of disrupted self-control. *Trends in Molecular Medicine* 12: 559–566.
115. Folini, C., and E. Racine. 2009. Disagreements with implications: diverging discourses on the ethics of non-medical use of methylphenidate for performance enhancement. *BMC Medical Ethics* 10: 9–19.
116. Forstl, H. 2009. Neuro-enhancement: brain doping. *Nervenarzt* 7: 840–846.
117. Lenzken, L.C., et al. 2008. Cognition enhancers: between treating the body and doping the mind. *Pharmacological Research* 57: 196–213.
118. Soyka, M. 2009. Neuro-enhancement from an addiction specialist's viewpoint. *Nervenarzt* 80: 837–839.
119. Wolpe, P.R. 2002. Treatment, enhancement and the ethics of neurotherapeutics. *Brain & Cognition* 50: 387–395.