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## The Addicted Self: A Neuroscientific Perspective

*One of the charms of drunkenness unquestionably lies in the deepening of the sense of reality and truth which is gained therein. In whatever light things may then appear to us, they seem more utterly what they are, more 'utterly utter' than when we are sober.*

William James  
Principles of Psychology, 1890

Intoxicants are remarkable; they arouse us and incite us to action. This emotional excitement gives us pleasure and a greater belief in the intoxicant and the reality of the pleasure it provides. This primary self-consciousness is provided for by the brainstem and the limbic, or hedonic, system that act in tandem to regulate bodily functions concerned with consummatory and defensive behaviours. It is a value system; a system whose extensive connections adjust the response of hormones and the autonomic nervous system to emotional demands. It responds slowly, in seconds to minutes. Unlike the cortex, which has discrete functional regions designed to deal with signals from the exterior, the limbic-brainstem loop system has evolved to match the body. Heart rate, sweating, appetite, digestion, sex and sleep are all regulated by this system; it deals solely with the interior and maintains our state of well-being. This is homeostasis, the mechanism that maintains stability within the physiological systems and holds all parameters of our internal milieu within limits that allow us to survive (Sterling and Eyer, 1981).

Intoxicants not only alter our primary self-consciousness; the emotional context of their use can unknowingly influence our judgements of their effects. For example, the whole history of witchcraft and early medicine involves human belief in intoxicants; any remedy is a relief once accompanied by emotional circumstance such as the laying on of physician's hands or the rhythmic chanting of the shaman (Vitebsky, 2001). It would seem that normal responses become separated from information based on our learning and memory of prior associations and inferences. The amygdala is a brain structure believed to be involved in such post-perceptual processing and is closely located to brain regions involved in information processing, such as the hippocampus. The amygdala also receives visual information stored in the cortex and uses this to influence perceptual processing in other brain areas. In this way, the social significance of stimuli being processed by the amygdala influences our memory, decision-making, and other more general cognitive functions (LeDoux, 1996; Damasio, 1994).

Sensory signals from exterior environments are delivered to our cortex by a second major system termed the thalamocortical system, a structure within the centre of the brain. The thalamus delivers signals, in milliseconds to seconds, to regions that are discretely mapped on the cortex and simultaneously deal with our sensory modalities such as sight, sound, touch and taste. In addition to controlling signals from the cortex to our voluntary muscles, the thalamus orchestrates the extensive connections of the cortex to all other brain regions, such as the striatum and amygdala and hippocampus, that primarily deal with timing of motion, emotion and memory. The thalamocortical system categorizes our environment and the limbic-brainstem system applies value adjustments to physiological needs. This is crucial to the learning and behaviour necessary to adapt to increasingly complex environments of our exterior (Edelman, 1992) (see accompanying figure).

Finally, it is important to note that the patterns of behaviour that we adapt to the signals emerging from these complex and ever-changing environments are specific to each individual. We are gregarious individuals who desire to please and attract. We pursue individual intellectual, moral, and spiritual ideals. We have, it seems, as many selves as there are individuals who recognise us and carry images of us in their minds. Such images are frail and can be altered by memory loss, false recollections and insane delusions. Indeed, sometimes, our moral and spiritual convictions are more profound on some occasions than others and we seem able to suspend our self-beliefs in the presence of a more emotionally exciting experience. Intoxicants can provide such exciting experiences and in extremes of intoxication, as William James puts it, *every man's soul will sweat with conviction, and be all the while unable to tell what he is convinced of at all.*

## Behavioural plasticity

Humans and other animals readily learn to take addictive drugs; this requires the specific recognition of drug-associated cues and the performance of specific, often complex, actions. This process of associative learning, by which the drug abuser connects specific cues, such as a particular place, with drug-induced states leads to the consideration of drug addiction being an aberrant form of learning, perhaps mediated by maladaptive recruitment of certain memory systems of the brain (Torregrossa et al., 2011). The notion that certain events promote change in behaviour cannot be considered a unitary process but one comprised of several independent functions, some or all of which can be active simultaneously. Therefore, understanding learning and memory processes is essential to the analysis of changes in behaviour produced by different addictive drugs.

The remarkable array of repertoires of behaviour in each individual suggests that they are subject to the laws of genetic variation and natural selection, a process by which genes and traits propagate or are lost by differential mortality and reproductive success. In truth, however, genes do not alter behaviour, they act in complex ways to alter the physical nature of brain and body which, in turn, alters behaviour. Song birds, for example, have an innate vocalization pattern yet they require to hear the song of con-specifics before they acquire the mature song necessary for successful mating (Nottebohm and Liu, 2010). This requires structural change to occur in the song-generating motoneurons and this leads to extraordinary behavioural consequences. This is an example of epigenetics, the word being derived from the Greek *epi* meaning “upon” and genetics.

The idea that complex behaviours are formed from both genetic and epigenetic components was originally proposed by Conrad Waddington (1957) and later expanded to include the phenomenon of plasticity by Mary Jane West-Eberhard (2003). Epigenetics, West-Eberhard argues, gives rise to alternative phenotypes which are the observable features and behaviours of an organism. She further suggests alternative phenotypes to be important as they can give rise to traits that are novel and that these traits might lead to genetic divergence and so give rise to speciation. As in the example given for songbirds above, the environment can induce alternative phenotypes and thereby take a lead in genetic evolution. This is a facet of Darwinian evolution that remains to be more fully explored.

The phenomenon of plasticity implies that experience impacts on the neuronal network in a manner that modifies the efficacy of information transfer beyond that which is innate. It also implies that the synapse, the connection among neurons and ultimate element of the neural system, can be modified by experience and result in changes that are both structural and behavioural. The brain, therefore, may be considered to be a highly dynamic organ in permanent relation with the environment as well as the individual and their acts.

Such neural representations of the environment have been described in the work of O’Keefe and Nadel (1978). They have identified ‘place cells’, neurons that exhibit greater activity whenever an animal is in a specific location in a given environment. Moreover, they have demonstrated that the firing patterns and locations of these neurons change when the animal is placed in a different environment. Similarly, Wolf Singer (1993) has used brain imaging techniques to demonstrate that visual perception is mediated by neurons within different neuronal assemblies that fire in synchrony to unite different features of neuronal representations. These features can include shape, motion, color, depth, and other aspects of perception. The synchronous activation of these neuronal assemblies for a few milliseconds binds aspects of external reality into a single neural representation or perception.

Neuronal assemblies are formed during early development through directed migrations of newborn cells to their eventual position in the cortex by the dynamic regulation of cell and substrate adhesion molecules, cell process extension and activity-dependent matching of connections. This idea has been elegantly encapsulated by Gerald Edelman in his Theory of Neuronal Group Selection (Edelman, 1987). In the first tenet of his theory, Edelman argues the formation of neuronal cell assemblies involves selection of specific neurons from populations engaged in topological or spatial competition, that the genetic code does not provide a specific wiring pattern but a set of constraints that regulate the epigenetic selection

of the primary repertoire of neurons. The second tenet assumes that, during behaviour, synaptic connections in the assembly are selectively strengthened or weakened by specific biochemical processes, a mechanism that underlies memory, to form a variety of functioning circuits by selection, the so-called secondary repertoire. The third tenet requires that the primary and secondary repertoires to form maps, functionally segregated (e.g., for colour and movement in the case of the visual system) but with reciprocal connections that allow interaction by a process called re-entry whereby widely distributed groups of neurons achieve integration through synchronized firing. This underlies how brain areas coordinate with each other to yield new functions and, importantly, link psychology to physiology. The unit of selection is not the individual nerve cell, but is a rather closely connected collection of cells called a neuronal group.

These cortical maps are dynamic, not static. The acquisition or learning of new behaviours, for example, produces structural and functional changes in the neurons of these maps that lead to alterations in their pattern of interconnections between the various systems associated with the learning of a task. Thus maps in the adult cortex can continually change in response to increased activity arising from change in the extent of their use. Given that we are all reared in different environments and, later, acquire our perceptual and motor skills through exposure to unique combinations of environmental stimuli, our brain architecture will be modified in unique ways. This diversity sets the biological basis for our individuality.

This notion has been elegantly supported by Michael Merzenich and colleagues (1983) who have demonstrated neuronal groups to undergo competition for interaction with neighbouring neurons by strengthening their synaptic connections in map boundaries of cortical regions that control the sensation of touch. Merzenich encouraged monkeys to use their middle three fingers at the expense of other fingers to rotate a disk for the purpose of obtaining a food reward. This resulted in the area of the cortex devoted to the middle finger becoming greatly expanded. Practice, or continual exposure to the task/stimulus therefore, may act on preexisting patterns of connections and strengthen their effectiveness. The mechanisms involved in the creation and interlinking of these neuronal groups can re-occur at certain times and places by changing synaptic strengths and, even in a developed brain, sprouting can occur in which new neural processes form additional synapses.

Thus, in summary, there are two components, parallel but different: a genetic component and an environmental or behavioural component, which are linked in a special way in the phenomenon of plasticity. The internal environment of the body also influences plasticity. The tendency towards stability in the body is called homeostasis and this is controlled by the brainstem-limbic system which also regulates emotional behaviour. Emotions reach consciousness and thought and conversely, higher cognitive functions affect emotions. Not surprisingly, therefore, the brainstem-limbic system has reciprocal connections with the cortex. The hippocampus and amygdala are also involved through reciprocal connections between the cortex and brainstem-limbic systems as these regions are necessary to process information acquired during learning, particularly for behavioural responses that require coordination of information from different sensory modalities or, in the case of the amygdala, the association of a stimulus and an emotional response. The interplay between the neural activity of the brainstem-limbic system and the activity of higher cortical centres results in emotional experiences that we describe as fear, anger, pleasure and contentment. There is not only recall of our perceptual representations, emotional awareness also accompanies perception. These are the feelings saved up along with their perceptual representations. Antonio Damasio (2000) terms these feelings as being somatic markers, a body memory of some sort. Further, we are not always aware of the somatic states that may accompany the evocation of a perceptual representation.

The activation of this limbic-brainstem system by the sensory cues in our environment provides us with a survival mechanism that allows us to learn to discriminate between dangerous and harmful stimuli and those which provide us with pleasurable and strengthening behaviours associated with natural reinforcers such as food, water, and sexual contact. The crucial point is that addictive drugs activate this neuronal circuitry by chemical means, so bypassing the need for evolutionarily useful behaviours.

## **Addiction and the dysregulation of bodily homeostasis**

Many now accept that addiction arises from a progressive malfunctioning of the brain reward system that ultimately leads compulsive drug use and loss of control over drug intake, an eventual state that renders the individual vulnerable to relapse long after drug-taking has ceased (Koob and LeMoal, 2001, 2006; Everitt and Robbins, 2005). This is based on the idea that the constancy of the internal environment of the body is the result of a system of control mechanisms that limit the variability of body states. As was mentioned above, this tendency toward stability in the body is called homeostasis. The key neuronal mechanisms relating to maintaining homeostasis are located in the brainstem-limbic system that receives information directly from the internal environment. This control system regulates all variables within a certain range, a desired value or set point.

In addiction there is a spiraling dysregulation of the brain reward system in which many, if not all, physiological functions become increasingly activated, or suppressed, as the initial hedonic effects of the intoxicant become masked overtime. As the individual becomes increasingly addicted, motivation and drive for drug taking behaviour changes from one of positive reinforcement arising from the euphoric effects of the intoxicant to the negative reinforcement of the withdrawal state. This leads to further drug-seeking and drug-taking behaviours and these ultimately lead to craving and relapse. The latter is further exacerbated by the individual becoming sensitized to the effects of the drug whereby the increased effects of the drug add to its motivational value, lead to compulsive wanting of the drug, and increased salience of the drug and/or drug-associated stimuli. Koob and LeMoal (2001) describe this as an allostatic state in which normal body and brain physiological functions no longer operate around the set point critical for survival. The reward set point has been increased to a point in which the addicted individual is in a state manifested by compulsive drug-taking and loss of control over drug-taking. The addict seems to be enveloped by an unusual emotional state in which their compulsion to imbibe a drug is remarkably unencumbered by the negative withdrawal consequences of drug-taking. Thus, it would appear that many brain and hormonal systems combine to produce the dynamic adaptation, or allostatic state, that underlies the pathology of addiction.

It is also worth noting that addiction is not a unitary process. Different drugs produce different patterns of addiction, individual differences in the stages of addiction, and different types of drug users (Regan, 2000). There are three major components in the addiction cycle – intoxication and bingeing, the negative effects of withdrawal, and preoccupation and anticipation of these actions and effects. Nicotine, for example, is not associated with intoxication but characterized by an intake pattern that is so compulsive that daily activities become constrained. Yet individuals exist who smoke regularly but do not escalate their intake – non-dependent ‘chippers’ in the American lexicon of Koob and colleagues (George and Koob, 2010). Opioids and alcohol, on the other hand, produce the most intense negative withdrawal effects that lead to compulsive drug-seeking and drug-taking. Marijuana addiction shares aspects of both nicotine and opioid addiction. Initially there is intense bingeing and intoxication but this is then followed by a more titrated use of the drug. In all cases, use of these intoxicants can be associated with an intense dysphoria, anxiety, and the loss of motivation for naturally rewarding stimuli (anhedonia). As such, these cognitive and affective representations, the essential qualities that constitute our uniqueness or self, become altered by the constant use of addictive substances.

## **Reward pathways**

While the full diversity of drug effects is mediated by multiple neurotransmitters acting in different brain regions, most addictive drugs share the common property of increasing release of the dopamine neurotransmitter in the striatum from neurons emanating from the ventral tegmental area (VTA; see Figure). The ventral striatum includes the nucleus accumbens which mediates the most rewarding effects of addictive drugs. Dopamine is not only important in mediating the instant pleasurable effects of addictive drugs, but also in the arousing effects that are predictive of the impending reward.

While the dopamine-containing neurons that emanate from the VTA may be centrally involved in early acute exposure to all classes of intoxicants, the later plasticity changes that underpin the addicted state engage many other discrete brain regions. Striatal dopamine levels set thresholds for action, they modulate behavioural reactivity. Loss of the dopamine input to striatum, for example, results in Parkinson's disease, a condition characterised by slowness in initiating actions. The striatum also exhibits a functional topography. The cortex projects mainly to more dorsal parts of the striatum, while other regions such as the hippocampus and amygdala project mainly to the ventral part of the striatum. As a consequence, the impact of intoxicants on this system not only has rewarding actions but can influence higher-order functions including cognition and memory. For example, the VTA can critically assess reward value and, through its connections with the hippocampus, control the entry of this information into long-term memory, perhaps by attaching the motivational connotation of the intoxicant experience. Moreover, human brain imaging studies have shown the same neural circuits respond similarly to drug administration, or drug-related stimuli in abstinent abusers, suggesting these pathways are also key elements in drug craving and relapse.

Neurons from the VTA also project onto the cortex, especially the prefrontal cortex, which in turn sends projections to most cortical and subcortical structures. The prefrontal cortex plays a key role in decision-making and, based on its relation to processes of attention, working memory, long-term memory formation, and emotionality, may reasonably be expected to be involved in the development of drug-taking behaviours. Individuals with strong neural activity in discrete regions of prefrontal cortex (dorsomedial area), for example, are risk-averse whereas those with strong activity in the ventromedial area are more likely to make risky decisions (Bechara, 2005). This defines individuals that may be vulnerable to the initiation and maintenance of drug self-administration. Thus, addiction has been argued to be a failure in self-regulation and that this relates to deficits in brain structures which regulate information-processing, attention, planning, reasoning, self-monitoring, or inhibition of a specific brain function or behaviour.

Loss of control in addiction is often ultimately attributed to impaired regulation in the different cognitive systems that are under the control of the prefrontal cortex. An important role of the prefrontal cortex is the mobilization and integration over time of simpler units of behavior into more complex ones. This integration develops a hierarchical structure for behavior that leads to the pursuit and attainment of a goal. This single-minded drive towards a target can persist over long, discontinuous stretches of time and requires the suppression of numerous behaviours and the urge to respond to competing internal and external stimuli.

### **Susceptibility of individuals to drug addiction**

The different neurobiological systems within this multi-system framework of discrete brain regions described above may equally contribute to inter-individual differences in susceptibility to addiction. Based loosely on the ideas of Jerry Fodor (1983), that significant parts of the mind, such as perceptual processes, are structured in terms of modules, Koob and colleagues have used this concept of modularity of mind to help understand the neural basis for individual differences in vulnerability to drug addiction (George and Koob, 2010).

Modules are groups of neurons that have separate classes of input and information processing and in principle cannot be influenced by activity arising in another module. Numerous studies have established modularity of cognition with classic examples being the high specificity of activation of cortical areas during the presentation of words, colours, faces, or places, as described previously. It is now generally accepted that sensation, perception, motor action, and even different types of memories, are represented by different cognitive modules with dedicated neural systems that are more or less independent in their functioning. Organizing, selecting, and consolidating information that derives from different modules into a coherent and unified experience requires an adapted cognitive control system, such as that provided by the modules of the prefrontal cortex (Everitt and Robbins, 2005), to ensure flexible, goal-directed behaviours. Meshing the idea of self-regulation with the concept of cognitive function being organized in a modular manner has the potential to provide a neural

basis for understanding how individual differences exist in terms of plasticity and vulnerability to drug addiction. Modularity of brain structure can, for example, explain the role of stress in the development of the addicted state.

Stress is associated with the activations of the hypothalamus-pituitary-adrenal (HPA) axis, a brainstem-limbic modular structure, and individual differences in the extent of HPA axis activation increases sensation- and novelty-seeking and the propensity for drug self-administration (Piazza and LeMoal, 1998). Increased activity in the HPA axis also drives the mesolimbic dopamine system arising from the VTA and this augments the positive reinforcing effects of drugs, increases their incentive salience, and leads to more profound drug-seeking behaviours. Further, the HPA axis can activate the amygdala which reinforces the emotional stimuli associated with gaining the drug reward, a drive that can ultimately lead to drug dependence. Importantly, these activations of the amygdala correlate with decreased activity in a discrete area of the prefrontal cortex, the ventromedial aspect. In some cocaine addicts, the structures of the fibre tracts between the cortex and the amygdala have been found to be abnormal (Lim et al., 2002). These fibre tract anomalies may be drug-induced or arise, for unknown reasons, in certain individuals during development. Such anomalies would explain how a specific dysfunction of the prefrontal cortex may lead to loss of control over a specific neurobiological response, such as activation of the amygdala during craving in one individual or to hyper-reactivity of the stress system in another. Brain region-specific mechanisms, therefore, can explain differences in vulnerability to drug addiction.

### **Cellular and molecular mechanisms of drug addiction**

At a more basic level, brain modules can be viewed as networks of neurons connected to each other by specialized structures known as synapses and it has long been assumed that structural and functional changes in this complex circuitry provide the basis for the acquisition and long-term storage of sensory information. Numerous studies have provided evidence for the involvement of many neurotransmitter systems in addiction, however, the current best hypothesis for a common final pathway to drug dependence involves changes in synaptic strength between neurons within the modules that form the basic functional structure of the addicted brain. This change in synaptic strength is a phenomenon commonly referred to as synaptic plasticity.

The two best studied forms of synaptic plasticity are long-term potentiation (strengthening of synapses, LTP) and long-term depression (weakening of synapses, LTD). These two processes have long been proposed to be cellular models of memory, respective mechanisms for learning and forgetting (Bliss and Collingridge, 1993). It also seems that these molecular mechanisms of synaptic plasticity may be engaged in behaviours involved in the pursuit of rewards, such as those provided by drugs. As a consequence, these cellular mechanisms may operate in areas of the brain essential for processing of rewards and so be involved in generating the addicted state. Studies in animals have confirmed that exposure to drugs of abuse, such as cocaine, causes the neurons of the VTA to become potentiated. Moreover, the concomitant release of dopamine, which occurs in the VTA as part of the drug action, and is associated with its reward response, can further activate the neurotransmitter receptors involved in this form of synaptic plasticity. This results in a form of LTP that persists for months (Dacher and Nugent, 2011). Synaptic plasticity, therefore, could serve as an ideal substrate for reward-based learning and motivated behaviours and that the aversive and addictive properties of drugs of abuse might arise through their interaction with learning mechanisms, suggesting that drug-associated memories are critical parts of the addiction process. It is not unreasonable to suggest, therefore, that the brain 'learns' to crave drugs.

This longer lasting form of LTP is associated with the synthesis of new proteins that are required for the structural and functional changes that occur at the synapse in this form of plasticity. These structural changes have given rise to the 'synapse tagging and capture' hypothesis which, among others, has been promoted by Richard Morris and colleagues (Redondo and Morris, 2011). This idea suggests that LTP identifies, or 'tags,' synapses in a manner that allows directed delivery of plasticity-related proteins. In this manner, the synapses are strengthened, or 'captured,' and incorporated into the newly activated neural

network. Protein synthesis gives rise to increased size and shape of the synapses and even the growth of new synapses. In contrast, the induction of LTD prevents delivery of plasticity-related proteins and is associated with shrinkage of synapses and their possible retraction from the neural circuit.

In terms of neural modules, therefore, two types of synapse manipulation can be discerned. A form of plasticity in which the strength of existing cell synapses is retuned. This gives rise to the cell assembly hypothesis in which networks are distinguished by the composition of the cells that are co-activated. In the second discernment, the synapse assembly hypothesis suggests that new synapses are created by experience, incorporated into the network, and the redundant supernumerary synapses eliminated by a pruning mechanism. This allows the elaboration of a network of specific groups of novel synapses with a connectivity scheme that has been optimized for each experience.

Experimental studies in rodents have provided reasonable certainty that continued exposure to addictive drugs results in persisting structural change in the neuronal cells of brain regions associated with addiction and that these changes may be correlated to behavioural phenotypes associated with a drug-dependent state (Russo et al., 2010). One of the major types of structural plasticity observed in neurons is change in the extent of their branching, the dendritic arbor, and in the number and shape of synapses on these branches, the spine frequency. Morphine, for example, decreases the density of dendritic spines on neurons in the nucleus accumbens, a key brain reward region which is located in the striatum and receives input from the dopaminergic terminals arising in the VTA. This observation is consistent with a novel synapse assembly optimizing the functional response of the neural network to the presence of a drug. Moreover, the extent of this spine remodeling is much greater in animals which self-administer the drug, as compared to those who have the drug administered by the investigator, which suggests that intentional use of the drug is important in this form of plasticity and that the remodeling is likely influenced by other brain regions involved in aspects of volition. Consistent with this suggestion, opiates have also been found to decrease spine density on neurons of the medial prefrontal cortex and hippocampus, brain regions intimately involved in cognitive functions. Surprisingly, and in contrast to opiates, stimulants such as cocaine, amphetamines, and methylphenidate, consistently increase dendritic complexity and spine density of neurons in the nucleus accumbens, VTA, hippocampus, and medial prefrontal cortex.

The observation that stimulants and opiates induce opposite effects on the spine density in several brain regions is a conundrum, as both drug classes produce similar states of addiction. The same behavioural phenotypes associated with drug sensitization are observed with both drug classes and the same negative emotional states occur during their withdrawal. However, the devil may be in the detail. For example, several subtle differences in behavioural response exist in both laboratory animals and humans (Badiani et al., 2011). Rats, for example, when given unlimited access to stimulants develop an uncontrolled bingeing behaviour that is not seen when they are provided with an unlimited access to opiates. Human addiction to stimulants is associated with greater impulsivity as compared to that observed in those addicted to opiates and, further, imaging studies in humans indicate relapse to opiates and cocaine is controlled by different sub-regions of the prefrontal cortex. At the molecular level, we know that drugs of abuse exert their effects at different receptors. As a consequence, they activate separate signalling pathways that can lead to the regulation of different gene expression programs. This, in turn, has the potential to deliver plasticity-related proteins associated either with the elaboration of synapse structure or the retraction of synapses from the neural circuit. This idea is consistent with the separate and distinctive profiles of gene expression observed in nucleus accumbens post-mortem tissue of both cocaine and heroin abusers (Albertson et al., 2006). Indeed, in these studies, only a tiny fraction of gene transcript change ( $<0.05\%$ ) was common to both drug-dependent populations. The ability of opiates and stimulants to modulate spine and synapse structural plasticity also means they have the capacity to expand or compress networks in the immediate or more distant brain modules that they influence. In this manner they can strengthen or weaken connections with other brain areas and thereby drive distinct aspects of addictive behaviours that are controlled by these modules.

Finally, it is important to note that the majority of animal studies describing the effects of opiates and stimulants on synapse remodelling have been performed in juvenile rodents. In such animals, and in humans, the pruning of the excess synapses produced in early development continues into adolescence (Huttenlocher, 2002). It is, therefore, unlikely this process would have been complete in the animals used in these studies. This raises the question as to whether modulation of spine and synapse structural plasticity relates to impaired or excessive pruning of synapses during adolescence. This question requires being resolved. Adolescence is a period of increased vulnerability. It is a time when regions of the prefrontal cortex strengthen their connectivity with areas of the limbic system, regions that respond to risk and reward. This is a period governed by the affective systems of the brain and these are operating largely outside conscious awareness: 'gut feelings' of high emotional content (Steinberg, 2005).

### **Epigenesis and the mechanisms of addiction**

Addiction is not an automatic outcome of drug use and only a small subset of individuals (about 20%) experience the switch from controlled to compulsive drug use that defines the addicted state. The mechanisms that are responsible for the transition from initial drug use to chronic drug use and then to compulsive, relapsing drug abuse are significantly influenced by both the genetic constitution of the individual and the psychological and social context in which drug exposure occurs.

The genetic risk contribution for addiction is roughly 50% and, as yet, the nature of the genes involved is almost completely unknown. For example, monozygotic, or single egg, twins share a common genotype yet most twin pairs are not identical and exhibit differences in their individual susceptibilities to disease, a wide range of other anthropomorphic features, and drug addiction (Fraga et al., 2005). In addition, many individuals at risk of developing compulsive drug use often have distinct personality or psychiatric traits that are not only genetic but significantly influenced by environmental factors that include adverse life experiences, stress, and the psychological and social context in which drug exposure occurs (Kendler et al., 2007). There are several possible explanations for these observations but one is the existence of epigenetic differences.

Although the cells of an individual contain essentially the same genetic complement they can differentiate during development to form distinct tissues and organs. This involves environmental cues and cell-to-cell signals that invoke change in the transcriptional activity of each gene. The transcription of the genome is highly regulated and involves the unfolding of specific chromatin proteins to reveal the DNA structure to be transcribed. This also involves the activation or repression of the controlling transcription factors, proteins that bind to regulatory elements of the gene and control its expression. This physical control of the genome relies on cellular signals that are dynamically regulated by the behavioural and subjective stimuli provided by environmental context. There is now evidence to indicate that the processes involved in early development continue to regulate cellular adaptation to environmental signals in the adult, such as those involved in social interaction, and that many of the regulatory events concern genes involved in synaptic plasticity (Zhang and Meaney, 2010).

Evidence from laboratory animal studies supports the idea that epigenetic mechanisms are directly engaged by drugs of abuse. Many view these dynamic adaptations to be the allostatic mechanisms by which drugs induce highly stable changes in the brain and form the addicted phenotype. Long-lasting expression of  $\Delta$ FOSB, for example, a protein which forms a complex with other proteins to regulate gene transcription, is induced by chronic administration of virtually any drug of abuse. This drug-induced expression of  $\Delta$ FOSB has been shown to be all that is necessary to account for the increases in dendritic spines in the nucleus accumbens that accompany chronic cocaine administration. Further, animals genetically programmed to overexpress  $\Delta$ FOSB, specifically in the nucleus accumbens, exhibit behaviours that increase their vulnerability to drug addiction. Exposure of these animals to cocaine results in increased behavioural activation, such as increased locomotion, and a greater propensity for cocaine self-administration (Robison and Nestler, 2011). The mechanism of  $\Delta$ FOSB remains

to be established but is believed to alter the interactions of the chromatin proteins with DNA and, in the presence of cocaine, allow the expression of genes not otherwise transcribed.

Another form of epigenetic regulation involves the direct chemical modification of DNA through the addition of methyl groups onto cytosine bases in DNA. This modification has greatest impact when it occurs near gene transcription start sites as this effectively blocks gene expression. DNA methylation is a crucial event as it provides a more stable, if not permanent, state of gene expression (Zhang and Meaney, 2010). There are, however, few mechanistic insights into the processes that dictate where in the genome methylation is likely to be established and maintained and how this might contribute to states of addiction.

These epigenetic markings of DNA have been referred to as 'memorized states of gene expression' (Borelli et al., 2008) to describe how neural networks might collectively control the cognitive function and behavioural responses of each individual in a manner that endures for life.

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## Brain regions involved in addiction to drugs of abuse

