FREE CHOICE, MOTIVATION-DRIVE AND DOPAMINE: FROM SPONTANEOUS BEHAVIOUR AND LEARNING TO DRUG ADDICTION

Dragomir P Lubomirov

Keywords
learning, behaviour, addiction, dopamine (DA), VTA, striatum, amygdala, insula, PBN

The American Psychiatric Association (1994) describes addiction as a chronic relapsing disorder, which is characterised by three major elements: (1) compulsion to seek and take drugs; (2) loss of control in limiting drug intake; and (3) emergence of negative emotional state upon withdrawal from the drug (drug dependence) (Koob & La Moal, 1997). Drug addiction is a gradual process of transformation from impulsive to compulsive drug taking, which involves multiple repeating binge/intoxication, withdrawal/abstinence and craving/anticipation cycles (Koob & Volkov, 2010).

The midbrain dopamine (DA) system is extensively implicated, by both animal and human brain imaging studies, in all the stages of the addiction cycle (Volkov et al, 2004). The addiction process is closely linked to the interactions between the limbic and frontal cortical regions with the DA / striatal systems and the transformation from spontaneous behaviour, which is experienced as rewarding, through associative and instrumental learning, to habit formation (Everitt & Robbins, 2005, Ikemoto, 2007).

This addiction transformation process leads to neuro-adaptive and plastic changes within the DA system, striatum, limbic and cortical regions, which are expressed by altered salience of drug and natural reinforcing stimuli and corresponding changes in behavioural motivation-drive (Kalivas & Volkov, 2005). In other words, addiction is characterised as a dysfunctional goal-directed behaviour caused by faulty decision-making, based on short-term, rather than long-term outcomes (Vardejo-Garcia & Bechara, 2009).

The aim of the following sections is to examine in detail the complex relationship between, goal-directed behaviour, DA, learning and addiction from an evolutionary and system's level perspective, in the hope of bringing new understanding to this complex subject-area in light of recent discoveries.

Behaviour

From the moment of conception, the life of each and every organism on this planet is characterised by continuous strife to obtain life-sustaining substances from the environment. The need to fulfil these physiological demands, combined with the need to procreate (to sustain oneself after death) are the principle motivating and driving forces of living organisms' behaviour (the natural reinforcers of behaviour). On the other hand, organisms need to recognise useful from harmful and initiate appropriate approach or withdrawal behaviour (Lang et al, 1998). Thus, behaviour is a complex outward manifestation of a process of continuous and endless moment-by-moment choice-making and decision-taking.

As the information content of the external environment is endless and ever changing, it is only logical for living organisms to develop systems, whose function is to generate and maintain appropriate behaviour (Doya, 2008). These systems enable organisms to extract, discriminate, evaluate, associate and retain information in regards to the environment, as well as the interaction process itself – in other words learn. These systems also provide the necessary feedback and incentive by coupling 'good' choices with reward and 'bad' choices with reward withdrawal/punishment, and make life exciting, pleasurable and worth living. The capacity to learn allows organisms to adapt to their surroundings and optimises their behaviour in respect of fulfilling their physiological needs. This capacity to learn and optimise the utilisation of environmental resources is the driving force behind natural selection as well as evolution of the species – the spirit of life.

This inherent similarity of the variation-selection processes of evolution, behaviour and learning haven't escaped researchers' attention. Thorndike (1911) pointed that when an animal is challenged in a novel environment it acts in an impulsive trial-and-error manner and while some of the actions are diminished others are strengthened, leading to their recurrence. Decades later, Staddon and Simmelhag (1971) proposed that both evolution and learning can be viewed as the outcome of two independent processes: "a process of variation that generates either phenotypes, in the case of evolution, or behaviour, in the case of learning; and a process of selection that acts within the limits set by the first process" (p. 19). Ikemoto (2007) linked the function of the behaviour variation-selection processes to the function of the striatum as part of the cortical, limbic and arousal systems: meso-ventromedial striatal dopamine (DA) system participating in the variation process and spontaneous (unconditioned) responding; while meso-ventrolateral striatal in

combination with meso-dorsal striatal DA systems modulating associative learning, selecting behaviour pattern and generating automated behavioural response.

The variation-selection theory of behaviour and learning emphasises the specific neural substrates and mechanisms, underlying these processes, leaving aside the motivational states driving these processes. Radically different approach was taken by Damasio (1994) in his somatic marker theory (SMT). SMT model places neural substrates, which regulate homeostasis, emotion and feeling in the core of the decision-making process – a systems-level neuro-anatomical and cognitive framework, which guides behavioural choices according to long-term outcomes, rather than short-term ones. Somatic markers are a selection of body- and brain-related responses, which have been linked by associative learning to anticipated future outcomes – negative somatic markers act as 'alarm bells', while positive somatic markers act as 'beacons of incentive' (Damasio, 1994). In this context goal-directed behaviour is the expression of the interaction of two principle systems – 'reflective/projective' (frontal cortical) and 'impulsive' (limbic). The result of this interaction modulates effector neural structures (Hypothalamus, midbrain and brain stem nuclei), which in turn alter internal body milieu and visceral, as well as central nervous systems (CNS) functions.

In this context, addiction can be seen as a specific, dysfunctional, maladaptive goal-directed behaviour caused by impaired, disadvantageous decision-taking, in which the midbrain DA system plays a major instrumental role (Bechara & Damasio, 2002; Vardejo-Garcia & Bechara, 2009).

Dopamine, Basal Ganglia, striatum and learning

The striatum comprises forebrain neural structures, which include the basal ganglia - Caudate, Putamen and Pallidial complex, also known as neo-striatum or dorsal striatum, and nucleus Accumbens (NAc), olfactory tubercle and the ventral part of the Pallidium (vPall) - the ventral striatum. The striatum takes part in cortico- striatal-thalamic-cortical circuits, which are anatomically and functionally inseparable from the midbrain DA system – the ventral tegmental area (VTA) and substancia nigra pars compacta (SNc). The striatum is involved in regulation and expression of goal-directed behaviour, which includes integration of emotional and motivational drive, cognition that plans strategies and chooses appropriate motor patterns and finally, execution of the behavioural plan through action

(Haber, 2003). The key to understanding the functioning of the striatum in behaviour and learning lies in the intimate organisation of its circuitry.

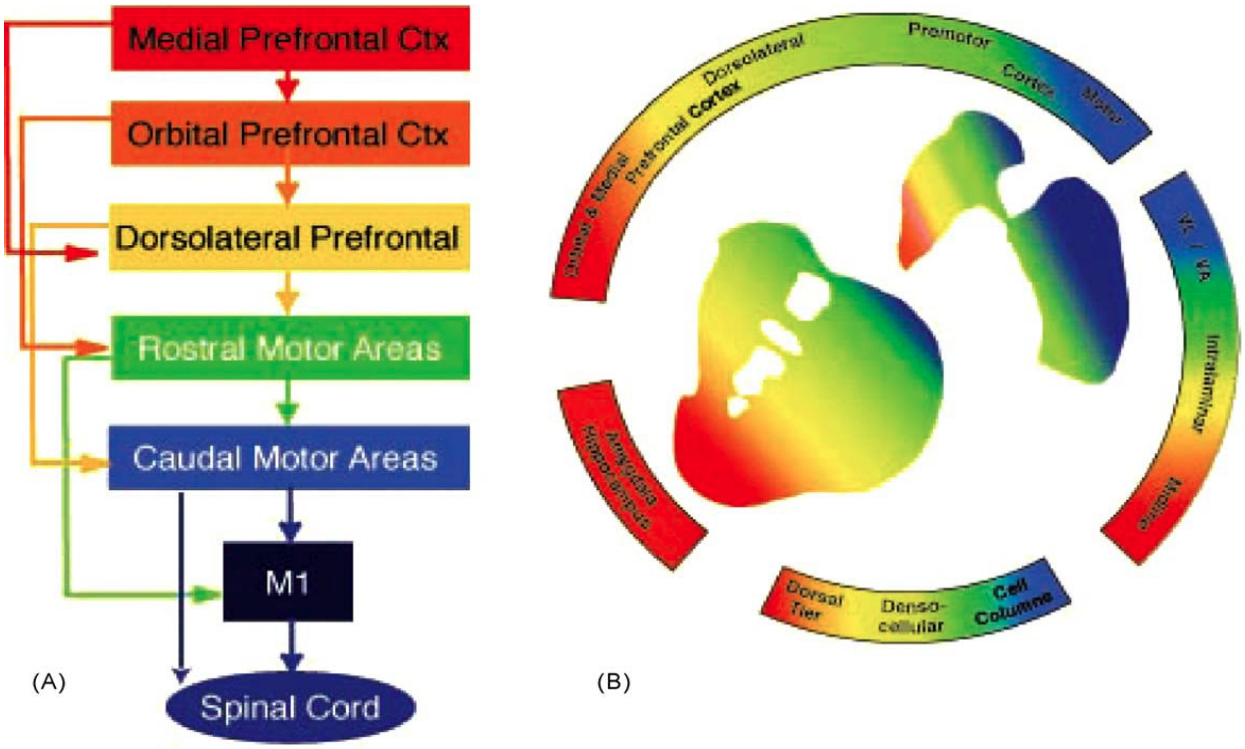

Figure 1. Parallel striatal circuits (Haber, 2003)

There are two types of striatal circuits - parallel and integrative circuits. The parallel circuits (Figure 1 above) are formed by topographically arranged descending connections from prefrontal cortex (PFC) regions, which through straito-pallidal, as well as subthalamic nucleus (STN) loops connect topographically to specific thalamic nuclei, which in turn complete the circuit by projecting topographically back to the cortex (Siegel & Sapru, 2006). The PFC connections run on a ventral to caudal seamless gradient, which is mirrored in the striatum – medial ventral prefrontal cortex (VMPFC) projecting to the most ventral and medial part of the NAc – the shell (shNAc), the orbitofrontal cortex (OBFC) projecting to the NAc core, the dorsolateral prefrontal cortex (DLPFC) projecting to the medial dorsal striatum, and the pre-motor and motor cortices projecting to the lateral dorsal striatum (Haber, 2003). As different PFC areas are associated with different functions – VMPFC, which includes the anterior cingular cortex (ACC), is involved in emotion regulation, OBFC – goal setting, DLPFC – working memory and executive control, and premotor and motor cortices - pattern generation and execution of voluntary movements, the reciprocal striatal areas are associated with the same functions as their cortical connections (Haber et al, 2000; Haber, 2003).

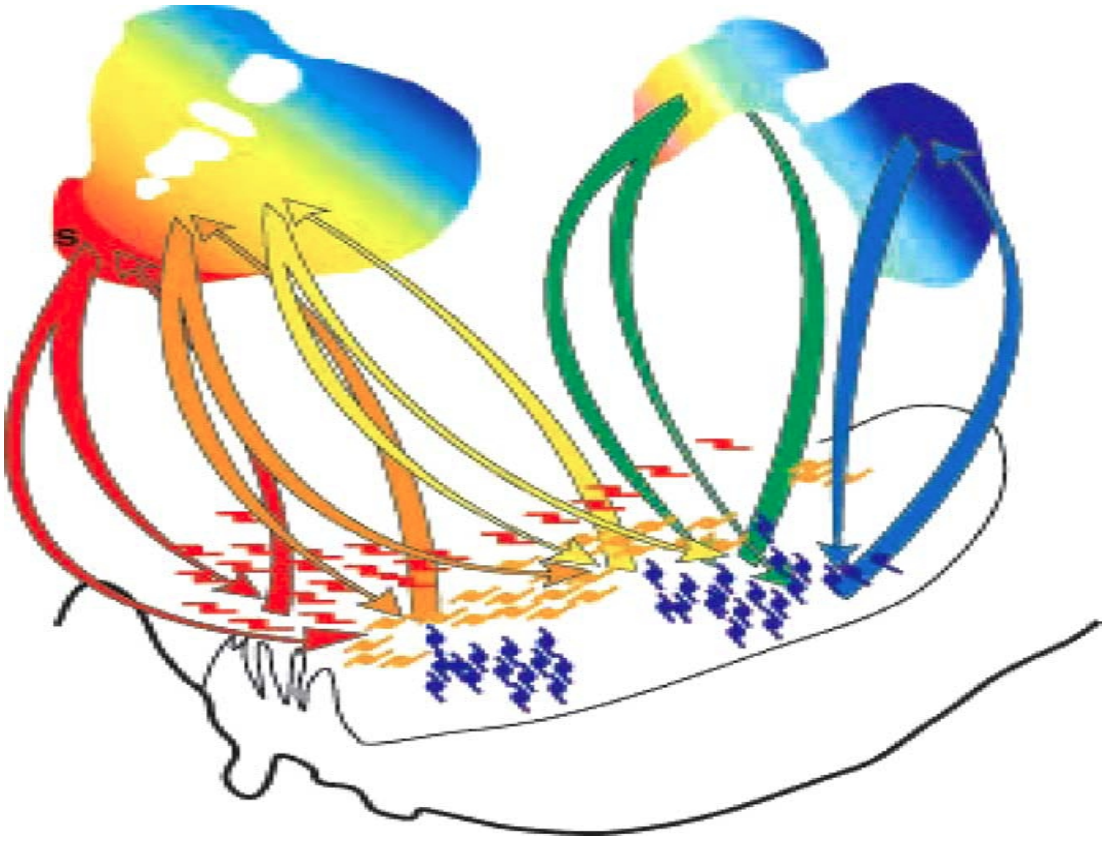

Figure 2. Integrative striatal circuits (Haber, 2003)

The integrative striatal circuits (Figure 2 above), on the other hand, are formed by both reciprocal and non-reciprocal connections between the striatum and the midbrain DA system – VTA and SNc. The connections between the striatum and the DA system run at ~45° mediodorsal to ventrolateral gradient – the mediodorsal VTA projects to shNAc, the lateral VTA – to NAc core, medial and central SNc – to dorsomedial striatum, and ventral SNc – to dorsolateral striatum (Haber 2003; Ikemoto, 2007). The non-reciprocal arms are formed by striatal connections, which project more laterally into the DA system. A simplified example is the shNAc projections – one reciprocal to the mediodorsal VTA and one non-reciprocal to the more lateral VTA. This striatal organisation has few important functional implications. It allows a lateral flow of information through the striatum, from limbic through associative to motor parallel loops. In other words striatal-DA interactions allow limbic input to create associations with outcomes, alter patterns and modulate motor output (Haber, 2003, Ikemoto, 2007). These are all hallmarks of learning and behavoiur – from incentive approach, to forming conditioned associations, to instrumental learning and habit formation (for in-depth review see Ikemoto, 2007), which are only possible when there is normal DA system function.

Another important aspect of DA system is illustrated well by debilitating clinical conditions like Parkinson's disease, as well as attention/motivation deficits and psychiatric conditions - DA is fundamental for the normal functioning of not just the striatum, but also the limbic and cortical brain structures. DA neurons of the most medial and dorsal VTA give rise to the meso-limbic and meso-cortical projections, which are unique in respect to their phenotype and electrophysiological properties – lack of D_2 auto-receptors, increased tyrosine hydroxylase (TH), decreased Dopamine transporter (DAT) and higher (20-30Hz) burst activity patterns (Lammel et al, 2008). These distinct properties of the meso-cortical and limbic VTA projections reflect the specifics of their function – to be able to maintain high DA levels in structures, crucial for the execution of behaviour in response to biologically salient environmental events (Lewis & O'Donnell, 2000). So the midbrain DA system modulates not just the specific parallel and integrative striatal circuits, but also the cortical regions, which initiate these circuits.

The importance of these issues becomes apparent in light of the complexities of midbrain DA system regulation and especially the meso-cortical and limbic VTA projections. Beside the reciprocally connected strital (NAc shell and core) structures, VTA receives topographical input from vPall, subthalamic nucleus (STN) and substancia nigra pars reticulata (SNr), which are part of the striato-pallidal-SNr-thalamic connections (Haber, 2003). The anatomical position of the VTA in the midbrain tegmentum places it in close proximity of the mesencephalic and pontine Reticular Formation (RF) arousal system. It is no surprise that VTA receives substantial noradrenergic (NA), cholinergic (Ach), and serotonergic (5-HT) excitatory enervation from adjacent locus coeruleus (LC), pendunculo-pontine (PPN) and latero-dorsal tegmental nuclei (LDT), as well as median and dorsal raphe nuclei (Simon et al, 1979; Devoto et al, 2005; Mena-Segovia et al, 2008; Winn, 2006; Ikemoto et al, 2000; Zachary et al, 2005). These enervations are also topographically distributed (Mena-Segovia et al, 2008), pointing to highly specific and complex regulation of VTA. VTA receives Glutamergic (Glu) excitatory inputs in much greater extent from sub-cortical regions, compared to ones descending from the cortex (Geisler & Zham, 2005; Geisler et al, 2007). GABAergic inhibitory input, beside the striatal one (Groenewegen et al,1993), arises from lateral Habenula (Matsumoto & Hikosaka, 2007), PAG, as part of the central Amg motor output (Omelchenko & Sesack, 2009), and especially the recently discovered Rostromedial tegmental nucleus (RMTg), which Jhou and colleagues (2009) proposed to be the neural substrate for aversive, punishment signalling to the VTA.

VTA (especially the meso-cortical and limbic part) reciprocal connections with the lateral Hypothalamus (laHyp) are functionally important in the generation and expression of states of arousal. VTA DA neurons are potently excited by laHyp orexins (Siegel, 2004; Harris & Aston-Jones, 2006; Harris et al, 2005), CRF (Izzo et al, 2005) as well as the downstream effects of orexin/CRF activated HPA axis – glucocorticoids augment the DA effects in the VTA meso-limbic and meso-cortical target areas (Marinelli & Piazza, 2002; Barrot et al, 2001; Barrot et al, 2000). VTA DA activity is also differentially modulated by endogenous opioids (Zangen et al, 2002; Margolis et al, 2005; Ford et al, 2006; Murphy et al, 2004). The close functional relationship between the mesial VTA and laHyp is one possible explanation of the rewarding effects of intra-cranial electrical stimulation (IES) (Ikemoto, 2007) – beside reward (self-stimulation) IES produces elevation of DA in the NAc (Fiorino et al, 1993) and physiological alterations similar to the activation of HPA axis (Burgess et al, 1993). Interestingly, the rewarding effects of IES can be abolished by lesions of the pontine RF (Ikemoto & Panksepp, 1994).

In conclusion, the midbrain DA system is structurally and functionally organised in very target-specific and circuit-specific manner. The VTA meso-cortical and meso-limbic projections are in central position to participate and influence arousal and goal-directed behaviour, as well as initiate associative learning. The most surprising feature of the VTA is its almost exclusive regulation by sub-cortical brain structures, closely connected to the function of the un-differentiated Reticular Formation. This raises the fascinating possibility, that behavioural motivation-drive is controlled by ‘bottom’ CNS structures, rather than higher cortical regions.

Addiction

Evidence from extensive research in the area of addiction over the past few decades points overwhelmingly towards the central role the meso-limbic DA system plays in the mechanisms of addiction via activation of neural networks associated with mediation of reward from natural reinforcers (like food, water and sex) (Ikemoto & Wise, 2004; Koob et al, 1998; Volkov et al, 2004). The rewarding effects of drugs of abuse are well illustrated by animal studies.

Animal studies employ two main experimental paradigms – substance self-administration and associative conditioning of place preference (CPP), where administration of drugs of

abuse produces heightened locomotor activity and other stereotyped behaviours. Animals readily learn to self-administer psychostimulants like cocaine and amphetamines (Ikemoto, 2007; Zachary et al, 2005) cannabinoids (Zangen et al, 2006) and develop CPP to opiates (Fenu et al, 2006). The most effective areas for drugs self-administration are the midbrain ventral tegmental area (VTA) and the nucleus Accumbens (NAc), especially the medio-dorsal part of VTA and the shell region of NAc (shNAc) (Ikemoto, 2007; Ikemoto & Wise, 2004; Anderson et al, 2006). Furthermore, inter-cranial self-administration combined with pharmacological manipulations (co-administration of DA receptor-specific agonist and antagonists) has highlighted that the rewarding action of drugs of abuse are mediated only by joint activation of D_1 and D_2 receptors in the shNAc (Ikemoto et al, 1997; Anderson et al, 2006; Bari & Pierce, 2005).

The fact that drugs of abuse exert their rewarding effect, similar to intercranial electrical stimulation, almost exclusively via dorso-medial VTA and shNAc and not NAc core or the rest of the striatum (Ikemoto, 2007; Di Chiara, 2002; Di Chiara & Bassareo, 2007; Ito et al, 2004) is a confirmation of the functional heterogeneity of the midbrain DA system (Haber, 2003; Haber et al, 2000; Lammel et al, 2008). Unawareness or overlooking this fundamental characteristic of the midbrain DA system is one of the reasons for the abundance of theories ascribing various (reward and pleasure mediating; motivational “wanting” vs. consummator “liking’’; reward prediction error; salience-arousal; general energising), usually complementary but sometimes conflicting central nervous system (CNS) functions for DA (for critical review see Ikemoto, 2007). Animal cytotoxic lesions of VTA DA system impair both acquisition and performance of appetitive Pavlovian approach behaviour (Parkinson et al, 200; Parkinson et al, 2002; Parkinson et al, 1999), while cytotoxic lesions of the DA substancia nigra pars compacta (SNc) produce parkinsonian motor dysfunctions (Zigmond & Striker, 1989). Clinically, DA dysfunction is implicated, beside Parkinson’s and other extra-pyramidal dyskinesias, in the pathology of psychiatric conditions, which involve attention, memory, emotion regulation and executive control – schizophrenia, OCD, ADHD (Kumar & Clark, 1994; Laviolette, 2007). If we have to generalise, the most fundamental uniting quality of the midbrain DA system, as part of general arousal, is to focus attention, provide motivational drive and facilitate both spontaneous and learnt behaviour expression through action in respect to novel or biologically salient stimuli. The normal function of the DA system is essential for successful interaction with the environment and even slight dysregulation impairs the behaviour-learning-behaviour process and leads to severe consequences – inability to sustain one’s

physiological needs and life.

As the DA system is so important for sustaining life and is a product of evolution, it should be very robust and failure-proof. So why does it then get dysregulated so readily in addiction? And if the effects of drugs of abuse are so pervasive why doesn't consumption of drugs automatically transform into addiction? Questions like these have motivated and continue to drive addiction research. Although there is no definite answer, many of the details of what characterises neuro-biologically the addictive state, as well as some of the underlying mechanisms of the addiction transformation process, are slowly becoming clear. Addiction is a vicious cycle, comprised of three behaviour- and neurobiological-specific stages: binge/intoxication; abstinence/withdrawal and craving/anticipation, which triggers the next cycle of binging (Koob & Volkov, 2010; Koob et al, 1998).

The binging stage is characterised by marked and sustained increase of DA in the shNAc (as discussed above) and sense of 'high' (Volkov et al, 2004), which reflects the acute pharmacological effects of all drugs of abuse. This shNAc increase of DA and its downstream effects is similar to the arousing effects of DA in relation to novel and salient stimuli, which constitutes the initiation of a learning cycle (Ikemoto, 2007). This 'supraphysiological' DA signal is proposed by Volkov and colleagues (2004) to attribute saliency to the drugs/drug taking and form associative links between drugs and reward, so triggering cascades of neuro-adaptive changes of transmitter systems, leading to circuits' reorganisation and ultimately to addiction. In other words, the addiction process begins with impulsive drug taking, associated with pleasurable (reward) experience via the high levels of DA in the meso-limbic VTA system, which through the strital learning mechanisms leads to pattern generation and habit formation – the impulsion-to-compulsion transformation of drug taking (Everitt & Robbins, 2005; Koob & Volkov, 2010).

The abstinence/withdrawal stage is characterised by the emergence of somatic states of varying degrees of physical discomfort and dysfunction, which are accompanied by long-lasting dysphoric negative mood states (Koob, 2009) and readily transforms into the craving/anticipation stage. Understanding the neuro-biological specifics of drug withdrawal is central to the deciphering of the addiction process and the development of successful interventions and strategies, which could help break the vicious cycle of addiction.

Evidence from animal and human studies demonstrates that dysregulation of the

mesolimbic DA system plays a major role in the withdrawal process as well. This dysregulation involves neuroplastic changes of D_2 receptors expression and function in the VTA and prefrontal cortex (PFC), decreased neuro-fillaments and axonal transport of DA neurons, which all contribute to diminished secretion of DA in the VTA-PFC, VTA-limbic (basolateral amigdala, hippocampus) and VTA-extended amygdala (Koob & Volkov, 2010; Kalivas & Volkov, 2005). The extended amygdala (Amg) is a functional concept of structurally and circuitry similar and anatomically close nuclei in the basal forebrain, proposed by Heimer (Heimer & Alheid, 1991) to play a major role as interface between the limbic and motor systems, which influences both approach (reward) and avoidance (punishment) behaviour. The extended Amg includes the medial part of NAc (shell), the central nucleus of the Amg (cAmg) and the bed nucleus of the stria terminalis (BNST). As the extended Amg in concert with CRF, NA and other pro-arousal signalling molecules like orexins, urocortins, vasopressin and glucocorticoids plays a major role in stress (Cornish & Van den Buuse, 1995; Kalivas & Duffy, 1995; Koob, 2008; Koob, 1999), it is tempting to attribute the biasing of arousal - positive (pro-active/approach) vs. negative (freezing/avoidance) to one of the functions of DA (in this respect see the role of the Rostromedial tegmental nucleus in the previous section). In other words, states in which arousal temporarily coincides with sufficient levels of DA in the extended Amg are experienced as rewarding and energising, while arousal with concomitant low DA levels in the extended Amg produces dysphoria, negative affective states and is experienced as stress. Hence the decreased activity of the mesolimbic VTA DA system and the low levels of DA in the PFC and the extended Amg combined with increased levels of dynorphin (Koob, 2008) of abstinent addicts may be the neuro-biological cause for their negative affective and motivational state. This state renders addicted individuals more vulnerable to challenging arousing situations, which are experienced as stressful, and are one of the principle causes of relapse (Koob & Volkov, 2010).

Beside the DA system, other neurotransmitter systems' dysregulation like glutamate, GABA, serotonin (5-HT) (Torregrossa & Kalivas, 2008; Koob & Volkov, 2010; Volkov et al, 2004) and especially the opioid one (Zubieta et al, 1996) have also been implicated in addiction. Brain imaging studies have further confirmed these findings and have helped to correlate brain structure and activity with behaviour in addiction (Volkov et al, 2004; Verdejo-Garcia & Bechara, 2009). Structural brain imaging studies using MRI have demonstrated two principle abnormalities associated with addiction: *first*, reduction of grey matter of ventro-medial prefrontal cortex (VMPFC), insula (Ins), temporal cortices and right

anterior cingulate cortex (ACC) (Franklin et al, 2002) and more especially the lateral PFC, medial and lateral orbitofrontal cortex (OBFC) (Matochik et al, 2003), as well as Amg (Makris et al, 2004); and *second*, white matter lesions within the Ins, inferior frontal cortex and anterior corpus callosum (Bartzokis et al, 1999; Lim et al, 2002), which connect VMPFC with paralimbic areas (Lyoo et al, 2004) and are associated with impulsivity (Moeller et al, 2005). PET and fMRI functional brain imaging studies, which have employed visual stimuli (pictures, or video) to study brain activation patterns, have yielded interesting results, clearly distinguishing drug users from control subjects. Drug-addicted individuals (DAI) responded with stronger activation of the PFC and OBFC, Ins, ACC to drug-related cues, which correlated with the experienced craving (Sell et al, 1999; Childress et al, 1999). In comparison, healthy controls had similar activation patterns to natural reinforcing cues, but not drug induced cues (Garavan et al, 2000). Furthermore, control subjects responded stronger to pleasant pictures with activation of PFC and basal ganglia (BG) compared to DAI, who had strong activation of the limbic region, Hippocampus, VTA and subthalamic nucleus (STN) to drug cues (Zijlstra et al, 2009). The altered salience of drug cues compared to natural reinforcers in DAI was poignantly illustrated by the results of Childress and colleagues' (2008) study. Drug cues, even viewed at a subliminal level (33 milliseconds) were able to produce significant activation in the Amg and ventral pallidium (vPal), areas associated with impulse generation and reward. As drug-associated cues can produce a potent impulse drive and strongly bias goal-directed behaviour, it is not surprising the prominent role they play in the mechanisms of drug relapse.

Few studies have examined the emotional responding of drug-addicted individuals (DAI) using emotive picture viewing – the International Picture Viewing System (IAPS). In brief, IAPS is a set of more than 600 emotionally calibrated pictures (in respect to their valence and arousal intensity), which are used to test the emotional, motivational and physiological responses in humans (Lang et al, 1997). Results from emotive picture viewing of DAI further illustrated the altered salience of natural reinforcers, which manifested as flattened emotional and physiological responsiveness to both pleasant and unpleasant pictures, but increased arousal to drug-related pictures (Gerra et al, 2003; Arguilar de Arcos et al, 2005). Other studies have examined emotional perception and experience in DAI by analysing facial expressions. Although there are some variations, according to type of drug, all DAI demonstrated diminished capability of recognition of facial expressions (Kemmis et al, 2007; Kornreich et al,2003; Martin et al, 2006; Salloum et al, 2007). As

emotion recognition and expression are fundamental for appropriate responding to social environmental cues, the results of these studies shed further light on the dysfunctional and anti-social nature of DAI's behaviour, caused by the alteration of their motivation-drive.

In terms of behavioural dysfunction, what is most striking in respect to DAI's behaviour is their inability to make choices according to long-term outcomes of their actions – inability to stop drug taking, despite its' detrimental consequences. This cognitive 'myopia' is well illustrated in studies, which examine the decision-making process in DAI using task performance paradigms like the Iowa Gambling Task (IGT), Cambridge Gambling Task (CGT) and other delayed discounting and probabilistic tasks (Vardejo-Garcia & Bechara, 2009). The IGT is a good example of these paradigms. In brief, participants have to choose from different decks of cards that yield high immediate reward, but larger future loss, and small immediate gain, but a smaller future loss (Bechara et al, 2000). In a series of studies Bechara and Damasio (2002), Bechara and colleagues (2002) combined the IGT with a physiological marker of arousal (skin conductance response – SCR) to study the decision-making process of DAI in respect to their emotional regulation in comparison to healthy controls and patients with ventro-medial prefrontal cortex (VMPFC) lesions. The results of these studies highlighted that the majority of the DAI performed similar to the VMPFC patients on the task and made more disadvantageous choices (chose cards from the disadvantageous decks) compared to the healthy controls. At the same time these DAI also displayed abnormal emotional anticipatory response (no increase of the SCR) before choosing from the disadvantageous decks, but increased emotional response to immediate reward. In other words DAI failed to recognise the consequences of their choices (no development of SCR when choosing from the riskier, disadvantageous decks) and failed to adjust their behaviour accordingly. As this decision-making was similar to the VMPFC lesion group, the Bechara team (2002) concluded that the deficits in DAI's behaviour are caused by alteration in executive function due to hyperactivity of the 'impulsive' (limbic) system in relation to the 'reflective' (frontal) system.

To summarise, all the examples from the above studies demonstrate that drug addiction is characterised by maladaptive emotional and decision-making deficits, rather than neural circuits' dysfunction. Although drug addiction was associated with structural abnormalities of grey and white matter in the MRI scan studies, none of these changes correlated with either severity or length of the drug problem, raising the question of the causal connection between addiction and brain deterioration. The general dysfunctions of addiction behaviour

were closely linked with the function of the meso-limbic DA system and the motivation-drive that it is instrument of. So if motivation that drives addiction behaviour is expressed via DA, what really drives motivation and where does motivation reside?

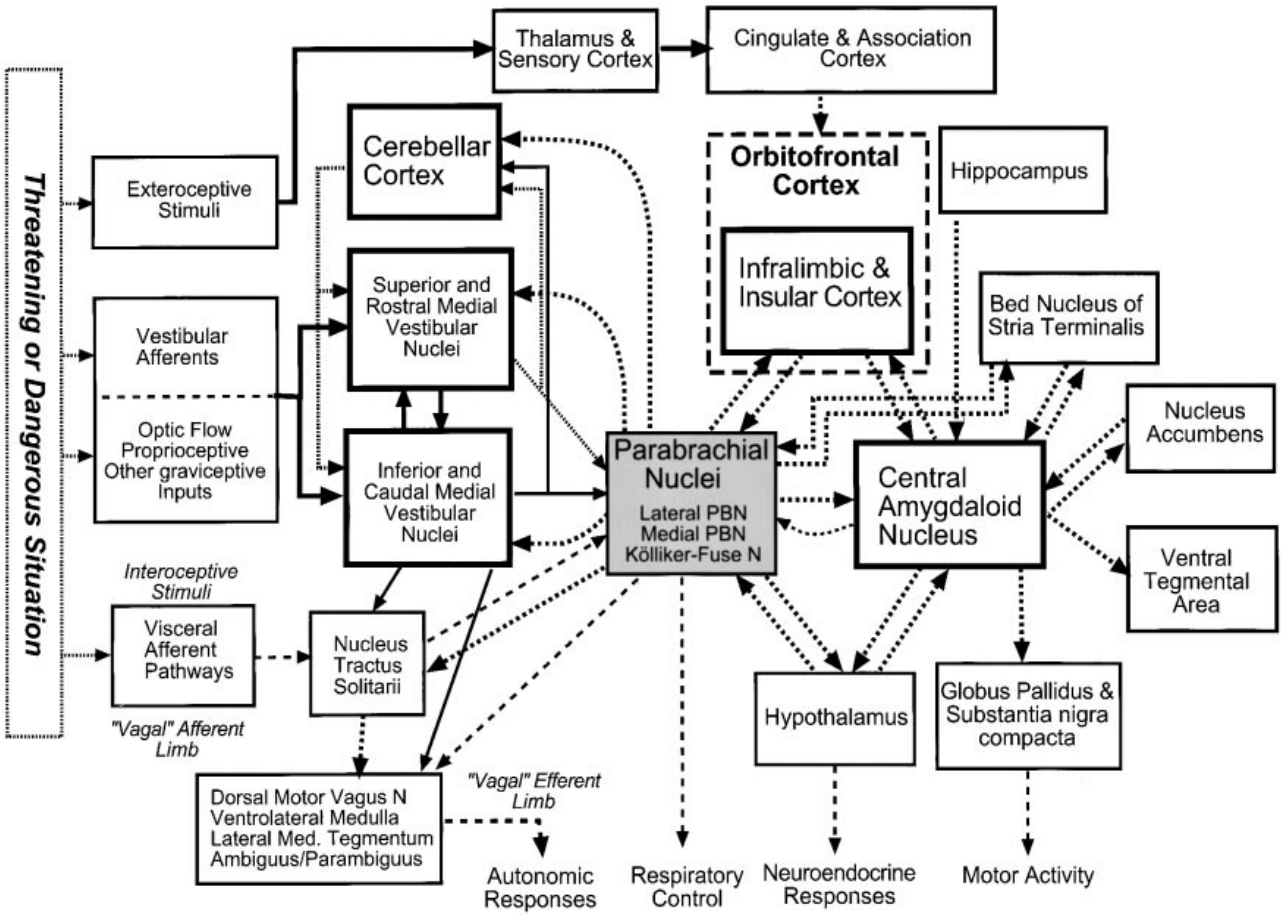

Figure 3. The Parabrachial nuclear complex (Balaban & Thayer, 2001)

Few recent studies have highlighted the importance of the Insula (Ins) in the addiction process. The Ins is hypothesised to be the interface between the subconscious and the conscious brain, bringing somato- and viscero-ceptive information from the body via the sub-cortical brain (Craig, 2003) into conscious awareness. The Ins holds the mind image of who we are and how we are. The Ins is reciprocally connected to the parabrachial nuclei (PBN) (Figure 3 above), which are a crucial integrative centre of somatic interoceptive and proprioceptive information with sensory input, as well as potent modulator of the limbic, autonomic and motor systems (Balaban & Thayer, 2001; Craig, 2003). The Ins is one of the principle brain regions activated during craving and urge-arousal, as illustrated in all of the functional brain imaging studies above. What is fascinating is that Ins lesions are able to wipe out withdrawal urges in human smokers (Naqvi et al, 2007) as well as

amphetamine-habituated rats and to also reduce the rats' lithium-induced malaise (Contreras et al, 2007).

The fact that the Ins is essential for the expression of drug withdrawal urges, as well as other chemical and somatic reactions, which are generated in the sub-cortical brainstem and midbrain regions and reflect homeostatic body needs, posits the possibility that motivational drive is a 'bottom-up' process in which body needs are assessed and motivational priorities set. Once set, these priorities in turn drive the rest of the CNS into executing appropriate behaviour to fulfil these needs. Changing homeostatic needs changes motivational drive and determines the valence of stimuli. An example of this is provided by an animal (rat) study, in which by dietary manipulation, the rats' sodium balance was altered, which changed their reactions to the force-fed sodium solution (Tindell et al, 2006). The change of the rats reaction to the sodium solution was expressed by changes of the firing of the ventral pallidium neurons, a principle link in the reward circuitry, which connects the meso-limbic DA system, NAc, limbic structures, thalamus-cortex, as well as Hypothalamic and sub-cortical brain regions involved in homeostatic and autonomic regulation (Groenewegen et al 1993; Haber, 2003).

Final remarks

The midbrain DA system, trough its targets-specific functions, is instrumental in both generation and execution of goal-directed behaviour. The DA system plays a crucial role in the functioning of the striatal information flow, allowing for limbic and cognitive associative learning to influence pattern generation and motor-action expression. The meso-limbic and meso-cortical projections of the VTA, with their unique structural and electrophysiological properties, are essential for the adequate functioning of the PFC, limbic areas, as well as Hypothalamus and other motor output structures of the CNS. Bearing in mind the paramount importance of the DA system in both behaviour and learning (higher CNS functions), it is ever more surprising that majority of its regulation is derived from lower brainstem and midbrain structures, connected to autonomic regulation.

Dysfunctions of the DA system are one of the principle characteristics of the drug addiction process. Drug addiction is a maladaptive behaviour caused by altered motivation-drive from natural, life-sustaining reinforcers to drug reinforcers. Although many of the underlying molecular, cellular and transmitter systems' mechanisms involved in the

addiction process have been identified, the questions to why the motivation-drive is so dramatically altered and even more importantly, which CNS structure are in control of motivation, are still left unanswered.

The recent discovery that lesions to the Insula (Ins), a cortical region implicated in feelings of drug craving and 'urge', abolishes withdrawal symptoms in human smokers and amphetamine-habituated rats, sheds a new light on the nature of the motivation-drive in addiction. The Ins has close functional connections with the PBN, which are a major multi-modal somatosensory integrative centre, well positioned to assess the homeostatic somatic 'needs' and influence autonomic and motor output of limbic, diencephalic, as well as midbrain and brainstem effector structures. This raises the interesting possibility that motivation-drive is a 'bottom-up' generated process.

More experimental research is needed to clarify the precise functions of the Ins, PBN and the general RF (which forms the isodendric core of the CNS - Ramon-Molinier & Nauta, 1966; Saper, 2002) in determining behavioural motivation-drive. Evolutionary, the CNS has become gradually more and more complex in 'bottom-up' fashion. Even so, it has preserved its fundamental functions – to serve the body in its constant strife to fulfil its biological needs, adapt through learning and optimise its relationship with the environment. Viewed in this light, addiction is a process of slow alteration of the motivational function of 'bottom' core CNS regions through evolutionary adaptation mechanisms, which explains the limited responsiveness of addiction to available treatment regiments. How these mechanisms work is another fascinating avenue for future research, which will hopefully lead to the development of successful therapeutic interventions for this horrendous human condition.

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