Behavioral endophenotypes of drug addiction: etiological insights from neuroimaging studies

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Abstract

This article reviews recent advances in the elucidation of neurobehavioral endophenotypes associated with drug addiction made possible by the translational neuroimaging techniques magnetic resonance imaging (MRI) and positron emission tomography (PET). Increasingly, these non-invasive imaging approaches have been the catalyst for advancing our understanding of the etiology of drug addiction as a brain disorder involving complex interactions between predisposing behavioral traits, environmental influences and neural perturbations arising from the chronic abuse of licit and illicit drugs. In this article we discuss the causal role of trait markers associated with impulsivity and novelty-/sensation-seeking in speeding the development of compulsive drug administration and in facilitating relapse. We also discuss the striking convergence of imaging findings from these behavioural traits and addiction in rats, monkeys and humans with a focus on biomarkers of dopamine neurotransmission, and highlight areas where further research is needed to disambiguate underlying causal mechanisms.

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This article reviews recent advances in the elucidation of neurobehavioral endophenotypes associated with drug addiction made possible by the translational neuroimaging techniques magnetic resonance imaging (MRI) and positron emission tomography (PET). Increasingly, these non-invasive imaging approaches have been the catalyst for advancing our understanding of the etiology of drug addiction as a brain disorder involving complex interactions between pre-disposing behavioral traits, environmental influences and neural perturbations arising from the chronic abuse of licit and illicit drugs. In this article we discuss the causal role of trait markers associated with impulsivity and novelty-/sensation-seeking in speeding the development of compulsive drug administration and in facilitating relapse. We also discuss the striking convergence of imaging findings from these behavioural traits and addiction in rats, monkeys and humans with a focus on biomarkers of dopamine neurotransmission, and highlight areas where further research is needed to disambiguate underlying causal mechanisms.

Keywords: Substance use disorder; impulsivity, sensation/novelty-seeking, PET, MRI, striatum; prefrontal cortex

1.0 Introduction

The worldwide extent of drug use is estimated at 3.4 billion drug users and accounts for over 12% of all deaths each year (WHO, 2012). However, despite the high prevalence of drug use, fewer than 20% of drug users lose control over their drug intake and develop clinical signs of addiction (Waldorf et al., 1991). The intricate interplay of multiple genetic and environmental factors which potentially determine an individual's susceptibility to the development of addiction provides a significant challenge to understanding the etiological mechanisms of this disorder (Kreek et al., 2012; Uhl, 2006; Wong and Schumann, 2008). However, one approach that has proved fruitful in recent years has been the investigation of behavioral traits known to pre-dispose individuals to addiction (reviewed in (Meyer-Lindenberg and Weinberger, 2006; Nader et al., 2012; Robbins et al., 2012). Such traits include impulsivity and novelty/sensation-seeking (Ersche et al., 2012a; Ersche et al., 2010; Kreek et al., 2005; Nigg et al., 2006; Verdejo-Garcia et al., 2008) and likely express causally-relevant neurobiological markers of the addiction syndrome (Dalley et al., 2011; Flagel et al., 2009; Piazza et al., 1998).

Neuroimaging approaches such as magnetic resonance imaging (MRI) and positron emission tomography (PET) have had a major impact on the elucidation of biomarkers associated with addiction, impulsivity, and novelty/sensation-seeking (e.g. (Parvaz et al., 2011; Soloff et al., 2003; Whelan et al., 2012)) and, importantly, have revealed significant overlaps in candidate markers between addiction, sensation-seeking and impulsivity and disorders encompassing these behavioural traits such as attention deficit hyperactivity disorder (ADHD) (e.g. (Frodl, 2010)) a prototypical disorder of impulsivity ((Sonuga-Barke, 2002). However, due to ethical and interpretative constraints, it has not been possible to unambiguously determine causal relationships between impulsivity, novelty/sensation-seeking and addiction in humans (Rogers and Robbins, 2001). Experimental animal models

overcome these limitations by enabling the pre-morbid assessment of behavioral traits and underlying neurobiological mechanisms, together with longitudinal scanning prior to and following drug exposure. Consequently, imaging studies that use clinically-relevant animal models of addiction have the potential to establish causal markers that can be readily translated to human addiction. Here we review converging evidence from pre-clinical and clinical neuroimaging studies on the neurobiological basis of impulsivity and sensation/novelty-seeking and discuss the relevance of these studies for the etiology of addiction.

2.0 Impulsivity and novelty/sensation-seeking: behavioral endophenotypes predicting risk for addiction

The behavioral traits of impulsivity and novelty/sensation-seeking have been widely associated with addiction to a broad range of drugs, including stimulants (Moeller et al., 2002; Semple et al., 2005), opiates (Madden et al., 1997; Maremmani et al., 2009), alcohol (Petry, 2001) and tobacco (Bickel et al., 1999). Significantly, the expression of these traits varies throughout the lifespan (e.g. **enhanced impulsivity and sensation-seeking is observed during adolescence** (Arnett, 1992; Spear, 2000) **a period which is also associated with enhanced drug use and addiction**) and during different stages of the addiction cycle (e.g. **drug use increases impulsivity** (Kreek et al., 2005), **which may in turn promote continued use**). Thus, these traits have potential to contribute both to the etiology and ontogenesis of addiction, a notion strongly supported by evidence that novelty/sensation-seeking and impulsivity predict risk for addiction (Belin and Deroche-Gamonet, 2012; Blanchard et al., 2009; Verdejo-Garcia et al., 2008), rates of relapse (Muller et al., 2008) and treatment retention (Moeller et al., 2001; Patkar et al., 2004). However, it is unclear how in neural terms these behavioral traits promote and/or interact with repeated drug use to

accelerate the emergence of compulsive drug seeking and taking in humans. This remains a major challenge for future research.

2.1 Impulsivity

Impulsivity is normally defined as a predisposition for premature, poorly planned, and unduly risky actions (Daruma and Barnes, 1993). Recent theoretical accounts broadly agree that impulsivity consists of at least two major components, motor disinhibition (impulsive action) and impulsive decision-making (impulsive choice), and involve separate but partly overlapping neural mechanisms (Evenden, 1999). Enhanced impulsive action, as defined by laboratory-based measures of performance on the Go/No-Go and stop signal reaction time tasks is often reported in alcoholics (Noel et al., 2007), and long-term abusers of cocaine (Fillmore and Rush, 2002; Hester and Garavan, 2004), and methamphetamine (Monterosso et al., 2005). Additionally, opiate-dependent individuals (Kirby and Petry, 2004), alcoholics (Petry, 2001), stimulant abusers (Kirby and Petry, 2004; Monterosso et al., 2007) and cigarette smokers (Bickel et al., 1999) show increased impulsive choice as indexed by steeper discounting rates for delayed monetary incentives (**known as delay discounting**). However, it is uncertain whether the co-expression of impulsivity in drug addicts reflects a predisposing trait, a consequence of repeated drug use, or both. Thus, whilst drug use has been shown to increase levels of impulsivity in humans (de Wit, 2009) there is evidence that some forms of impulsivity are actually reduced by drug use (Garavan et al., 2008). Prospective studies in children have found that high levels of impulsivity predicts the initiation of smoking in adolescents (Audrain-McGovern et al., 2009) and populations at risk for the development of addiction demonstrate increased levels of impulsivity, including clinical diagnoses of ADHD and pathological gambling (Verdejo-Garcia et al., 2008). Indeed, increased levels of impulsivity are present in non-drug abusing siblings of dependent individuals; thereby

suggesting that impulsivity may be an endophenotypic marker (**i.e. a behavioral phenotype with an underlying genetic basis**) for risk for addiction (Ersche et al., 2012a; Ersche et al., 2012b; Ersche et al., 2010).

Studies in rodents strongly support a causal link between impulsivity and addiction-related behaviors, although this relationship appears to depend on the particular sub-type of impulsivity (impulsive action versus impulsive choice) and drug class. Rats selected for high levels of **impulsive action as measured by enhanced premature responding on the five choice serial reaction time task (Robbins, 2002)** demonstrate increased rates of cocaine (Dalley et al., 2007), nicotine (Diergaarde et al., 2008), alcohol (Radwanska and Kaczmarek, 2012) and methylphenidate (Marusich and Bardo, 2009), but not heroin (McNamara et al., 2010) self-administration. These animals additionally show enhanced conditioned place preference to amphetamine (Yates et al., 2012) and have a higher propensity to develop *compulsive* cocaine self-administration (**i.e. enhanced motivation to self-administer on a progressive ratio schedule, persistent non-reinforced responding, resistance to punishment-induced suppression of responding for drug**) (Belin et al., 2008) and relapse to cocaine (Economidou et al., 2009) and 3,4-methylenedioxymethamphetamine (MDMA) (Bird and Schenk, 2012) seeking. Impulsive choice has been shown to predict increased alcohol (Oberlin and Grahame, 2009; Poulos et al., 1995) and nicotine (Diergaarde et al., 2008) administration, as well as resistance to extinction and enhanced relapse propensity to nicotine (Diergaarde et al., 2008) and cocaine (Broos et al., 2012). However, there are conflicting findings regarding the relationship between impulsive choice and consumption of cocaine and opiates with studies both supporting (Anker et al., 2009; Garcia-Lecumberri et al., 2011) and refuting (Broos et al., 2012; Schippers et al., 2012) this association. While these findings are perhaps surprising given that heroin and cocaine addicts show delay-discounting impulsivity (Kirby and Petry, 2004), it is possible that these clinical observations,

as suggested previously, reflect the effects of chronic drug use on neural substrates underpinning impulse control. Consistent with this hypothesis, both heroin (Schippers et al., 2012) and cocaine (Mendez et al., 2010; Paine et al., 2003; Roesch et al., 2007; Winstanley et al., 2009) exposure increases impulsivity in non-impulsive animals.

2.2 Novelty/sensation-seeking

Novelty/sensation-seeking is defined as a tendency to pursue novel and intense emotional experiences (Zukerman, 1979). Like impulsivity, novelty/sensation-seeking represents a multifaceted behavioral construct and can be divided into a number of dimensions related to novelty-seeking, novelty-preference and other behavioral facets including risk-taking, harm avoidance and thrill-seeking, and are reflected as such in the various questionnaire based assays of this behavior (Arnett, 1994; Whohlwill, 1984). Throughout this review, we have chosen to refer to sensation-seeking and novelty-seeking interchangeably to more easily inter-relate basic and clinical research. Work over many years has yielded unequivocal evidence that these personality traits co-exist in individuals with substance dependence (Gerra et al., 2004; Hittner and Swickert, 2006; Noel et al., 2011). Further, novelty/sensation-seeking predicts risk for the initiation of drug use (Nees et al., 2012; Sargent et al., 2010; Spillane et al., 2012; Stephenson and Helme, 2006) and is present in individuals at risk for developing substance dependence, including problem gamblers (Fortune and Goodie, 2010) and those with genetic polymorphisms known to confer addiction risk (e.g. the serotonin transporter (Pascual et al., 2007)).

There is some debate, however, whether novelty/sensation-seeking truly represents an endophenotype of addiction risk. Recent studies by Ersche and colleagues found that sensation-seeking was not present in the non-affected siblings of drug addicts (Ersche et al., 2010). However, sensation-seeking was present in individuals who regularly used drugs but

were able to maintain control over their drug use (Ersche et al., 2012a). These findings suggest that the relationship between sensation-seeking and dependence may not lie in a shared genetic risk for the development of drug addiction, but instead may reflect the consequences of repeated drug use and/or predisposition to drug use and experimentation. The latter possibility is consistent with findings from the primary animal model of sensation-seeking, namely enhanced locomotor activity in a novel, inescapable environment (high responders, 'HR', (Piazza et al., 1989) reviewed in (Blanchard et al., 2009)). HR animals typically show an enhanced propensity to self-administer stimulant drugs (Belin et al., 2008; Marinelli and White, 2000; Piazza et al., 1989) but are less likely to develop compulsive cocaine self-administration than highly impulsive rats (Belin et al., 2008). Selectively-bred HR rats are also more likely to assign salience to reward predictive cues, known as 'sign tracking' behavior (Flagel et al., 2010), which has also been shown to motivate cocaine self-administration (Saunders and Robinson, 2010). Further, sign-tracking behavior has been demonstrated to relate to enhanced novelty preference and in turn to elevated levels of cocaine self-administration (Beckmann et al., 2011).

Sensation-seekers also exhibit impaired reward processing, expressed as an enhanced sensitivity to the reinforcing effects of psychostimulant drugs (Hutchison et al., 1999; Stoops et al., 2007) and physiological reactions to alcohol (Brunelle et al., 2004). Similarly, HR rats show enhanced locomotor reactivity to cocaine (Hooks et al., 1991), self-administer psychostimulants at doses that are not reinforcing in low responder rats (Marinelli and White, 2000; Piazza et al., 1990) and maintain higher levels of operant responding for alcohol (Nadal et al., 2002), cocaine (Piazza et al., 2000) and opiates (Ambrosio et al., 1995). HR rats also exhibit enhanced striatal dopamine (DA) release following exposure to reward predictive cues (Flagel et al., 2011). Such behavior suggests common underlying impairments in

reward processing, which may underlie the increased propensity of sensation-seekers to initiate and maintain drug use.

The contribution of sensation/novelty-seeking to risk for drug addiction is unclear but may depend, in part on interactions with impulsivity. A recent study found that individuals demonstrating high levels of drug intake, but nevertheless were able to maintain control over their drug use, were sensation-seekers but were not impulsive. However, by contrast, both sensation-seeking and impulsivity traits were present in addicts (Ersche et al., 2012a). Further, non-drug using siblings of addicts were found to be impulsive but were not sensation-seekers (Ersche et al., 2010). These findings suggest that both impulsivity and sensation-seeking traits may interact to drive risk for addiction. In keeping with this, rats impulsive on the five-choice serial reaction time task, which demonstrate drug use modeling addiction (Jupp et al., 2013), fail to show a heightened response to novelty (Dalley et al., 2007; Molander et al., 2011). However, there is evidence for enhanced levels of novelty *preference* in these (Molander et al., 2011) and other strains of impulsive rats (e.g. the Roman High Avoidance rat (Giorgi et al., 2007). Interestingly, animals showing enhanced levels of novelty preference also developed compulsive cocaine self-administration, indicative of a key aspect of addiction (Belin et al., 2011), although levels of impulsivity prior to drug exposure were not assessed in these animals.

3.0 Neuroimaging studies of impulsivity and novelty/sensation-seeking

The evidence reviewed above indicates a clear link between the behavioral traits of impulsivity and novelty/sensation-seeking, the initiation and maintenance of drug intake, and the development of addiction. On the basis of these relationships, an understanding of the neurobiological mechanisms underlying these behavioral traits might inform how these in turn confer risk for addiction. Neuroimaging studies provide a powerful approach to

investigate the neurobiological substrates mediating such behavioral traits as they offer a means to directly correlate individual variation in behavior with markers of neuronal structure and function. These markers often reflect individual differences in genetic, molecular and cellular processes, and thus can provide valuable insight into the biological origin of complex behavioral traits (Hariri, 2009).

3.1 Neural correlates of impulsivity

MRI studies have revealed striking regional variations in brain structure, connectivity, and task-related activation in individuals expressing high levels of impulsivity. In general this research has shown high concordance with findings in animal models of impulsivity (Dalley et al., 2008), and in individuals with specific brain lesions that show enhanced measures of impulsivity (Aron, 2007). This work has consistently highlighted reduced grey matter volume and cortical thickness of the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) as markers of impulsivity in humans (Cho et al., 2012; Matsuo et al., 2009; Schilling et al., 2012). In other studies, delay-discounting impulsivity was coupled with morphological abnormalities in the hippocampus and prefrontal cortex (Yu, 2012), and with reduced integrity of fronto-striatal fiber tracts (Konrad et al., 2010; Peper et al., 2012). Notably, impulsivity was also associated with volumetric changes in the frontal lobes of individuals with borderline personality disorder (Sala et al., 2011), bipolar disorder (Matsuo et al., 2009), Parkinson's disease (O'Callaghan et al., 2012) and schizophrenia (Kumari et al., 2009). Additionally, ventral striatal volume negatively correlated with measures of impulsivity in healthy subjects (Cho et al., 2012), suicide attempters (Dombrovski et al., 2012), and individuals with ADHD (Carmona et al., 2009).

Other studies indicate that impulsivity is associated with reduced functional connectivity between medial and lateral regions of the prefrontal cortex and subcortical

reward structures including the ventral striatum and amygdala (Davis et al., 2012; Schmaal et al., 2012). Further, prefrontal cortical metabolism has been shown to negatively correlate with measures of impulsivity in suicide attempters and patients with borderline personality disorder (Oquendo et al., 2003; Soloff et al., 2003). Impulsive individuals further show reduced activation in the anterior insula and middle frontal cortex during active response inhibition (Farr et al., 2012). Similarly, activation in the ACC was found to correlate inversely with measures of impulsivity in a Go/No-Go task (Liu et al., 2012).

Much previous research indicates that reward-related activity in cortico-striatal circuitry is impaired in impulsive individuals. Questionnaire-based measures of delay-discounting impulsivity correlated positively with activation in dorsal and ventro-lateral regions of the prefrontal cortex (Hinvest et al., 2011; Sripada et al., 2011), consistent with a postulated role of these regions in salience encoding (Ernst and Paulus, 2005). Impulsive individuals also showed increased ventral striatal activity during performance of a monetary delay-discounting task (Hariri et al., 2006), a finding that may be relevant to divergent patterns of activation within the ventral striatum and amygdala reported in impulsive subjects following win and near-win outcomes during a gambling task (Shao et al., 2013). Thus, the subjective value of wins and emotional responses to near-wins may be enhanced in impulsive individuals. Impulsive individuals also show altered reactivity related to reward value following delays. Specifically, impulsivity correlated with a reduction in ventral striatal activation in relation to the magnitude of future rewards during the delay period (Ballard and Knutson, 2009; Ripke et al., 2012). This prominent effect may underlie the preference of impulsive individuals for immediate, small-magnitude rewards. Interestingly, the relationship between ventral striatal reward reactivity and delay discounting was opposite in individuals with ADHD (Hommer et al., 2011; Strohle et al., 2008; Wilbertz et al., 2012), a difference

postulated to reflect abnormal reward processing by the OFC in ADHD patients (Wilbertz et al., 2012).

3.2 Neurochemical correlates of impulsivity

Given the prominent role of DA in modulating the striatal networks (reviewed in (Onn et al., 2000)) and the central role of this neurotransmitter in addiction and ADHD (e.g. (Kalivas and Volkow, 2005; Solanto, 2002; Volkow et al., 2009)), the majority of PET and SPECT studies have unsurprisingly focused on the brain DA systems. Indeed, substantial evidence points to a key role of DA in the expression of impulsivity (Dalley and Roiser, 2012; Pattij and Vanderschuren, 2008). For example, binding of ligands for DA D2/D3 receptors in the ventral striatum (predominantly [¹⁸F]-fallypride, [¹¹C]-raclopride) correlated negatively with questionnaire-based measures of impulsivity in healthy individuals (Reeves et al., 2012), pathological gamblers (Clark et al., 2012) and methamphetamine abusers (Lee et al., 2009). Similarly, rats with high levels of impulsive responding on the five choice serial reaction time task exhibited **lower** D2/D3 receptor availability in the ventral striatum (Dalley et al., 2007). D2/D3 receptor binding was also found to be **lower** in the dorsal striatum (Ghahremani et al., 2012), substantia nigra/ventral tegmental area (Buckholtz et al., 2010) and extra-striatal regions, including temporal cortex and thalamus (Bernow et al., 2011) of impulsive individuals. In one study, striatal D2/D3 receptor availability was found to correlate with neuronal activation, as measured by fMRI in the striatum and prefrontal cortex during performance of a Go/NoGo task (Ghahremani et al., 2012), suggesting a putative involvement of DA in response inhibition. This key finding is consistent with the reported correlation between striatal D2/D3 receptor binding and glucose metabolism in the OFC of stimulant abusers (Volkow et al., 2001).

In addition to alterations in the regulation of D2/D3 receptors, impulsive individuals exhibit abnormalities in the release of DA in striatal regions. Thus, impulsivity in humans predicted enhanced amphetamine-induced DA release in the striatum, as indexed by the increased displacement of a D2/D3 receptor radioligand in this region (Buckholtz et al., 2010). Curiously, however, this positive relationship between impulsivity and striatal DA release did not extend to ADHD where DA release was decreased relative to healthy unaffected controls (Rosa-Neto et al., 2005).

3.3 Neural correlates of novelty/sensation-seeking

MRI investigations have consistently reported morphometric changes in cingulate cortex, inferior frontal gyrus, and hippocampus that correlate with questionnaire-based measures of novelty/sensation-seeking (Gardini et al., 2009; Martin et al., 2007; Van Schuerbeek et al., 2011). There is also evidence for enhanced connectivity, as measured by the number of fibers, from the hippocampus and amygdala to the striatum, in individuals with enhanced self-reported levels of novelty-seeking (Cohen et al., 2009). These structural differences are accompanied by alterations in baseline levels of neuronal activity, specifically enhanced [¹⁸F]-flurodeoxyglucose uptake and relative cerebral blood flow in the frontal and parietal cortical regions, including the ACC and insula (Hakamata et al., 2006; O'Gorman et al., 2006; Sugiura et al., 2000; Youn et al., 2002).

Unsurprisingly, novelty/sensation-seeking is associated with enhanced neuronal responses to novelty. In general, this trait appears to correlate with novelty-induced activation in the ventral tegmental area and ventral striatum (Krebs et al., 2009; Wittmann et al., 2008), as well as the hippocampus (Naghavi et al., 2009) and OFC (Lawson et al., 2012). In addition, neural responses to emotional or arousing pictures are enhanced in the prefrontal cortex (Berpohl et al., 2008), insula and OFC (Joseph et al., 2009) of novelty/sensation-

seekers. This pattern of activation most parsimoniously reflects an increased reactivity of these individuals to reward (e.g. (Stoops et al., 2007)). Thus, sensation-seekers showed increased activity following receipt of monetary reward in regions related to reward processing including the insula, prefrontal gyrus and ventral striatum (Cservenka et al., 2012; Kruschwitz et al., 2012). The same individuals showed reduced activity in these regions when confronted with a loss, or no-win situation, suggesting that sensation-seekers may be less sensitive to negative outcomes.

3.4 Neurochemical correlates of novelty/sensation-seeking

Like impulsivity, sensation/novelty-seeking is associated with dopaminergic dysfunction. Rats exhibiting high trait-like levels of novelty reactivity (i.e. HR rats) demonstrate enhanced basal and psychostimulant-induced DA release in the ventral striatum compared with their low novelty-reactive counterparts (Hooks et al., 1991; Piazza et al., 1989) and further show reduced D2/D3 receptor density in the dorsal and ventral striatum (Hooks et al., 1994). PET studies have broadly confirmed these findings. For example, novelty-reactive Gottingen minipigs showed enhanced amphetamine-induced DA release in the striatum (as measured by the change in binding of [¹¹C]-raclopride), similar to an analogous PET study in humans (Leyton et al., 2002). Moreover, sensation-seeking in humans was predicted by reduced D2/D3 receptor availability in the ventral tegmental area and substantia nigra (Zald et al., 2008) as well as the insular cortex (Suhara et al., 2001). Novelty reactivity was also found to correlate negatively with D2/D3 receptor availability in the caudate nucleus of cynomolgus monkeys (Czoty et al., 2010). Interestingly, novelty-reactive animals were found to be socially submissive. This finding fits well with studies demonstrating that reduced social rank is associated with reduced striatal D2/D3 receptor binding in healthy volunteers (Martinez et al., 2010). However, the relationship between striatal D2/D3 receptor availability and

sensation-seeking in humans is apparently non-linear and best described by a quadratic, inverted U-shaped function (Gjedde et al., 2010). This complex relationship is thought to reflect the influence of elevated levels of endogenous DA (providing competition for radioligand binding) accompanied by reduced DA receptor availability in sensation-seeking individuals. Taken as a whole, these findings indicate that sensation-seeking is associated with hyper-dopaminergic function (**in terms of DA release**) in the striatum and midbrain, which may in turn contribute to the heightened reactivity to novelty and reward observed in these individuals (Krebs et al., 2009).

4.0 Implications for the etiological basis of addiction

Convergent findings from neuroimaging studies on the neurobiological basis of impulsivity and sensation-seeking have enabled a greater understanding of the causal role played by these traits in addiction. These studies have revealed a significant degree of overlap in markers of addiction and those relating to striatal DA function, the frontal cortical systems, and perturbations in reward processing in impulsivity and novelty/sensation-seeking.

Reduced striatal D2/D3 receptor binding is a highly conserved marker of impulsivity and sensation-seeking. D2/D3 receptor availability is also reduced in the striatum of cocaine (Volkow et al., 1993), methamphetamine (Volkow et al., 2001), heroin (Wang et al., 1997), cannabis (Sevy et al., 2008) and nicotine (Fehr et al., 2008) users, and further predicts enhanced relapse propensity in methamphetamine addicts (Wang et al., 2012). It is therefore possible that reduced striatal D2/D3 receptor binding in addicts represents, in part, a pre-existing deficit and biological risk factor for the development of addiction. Evidence from studies in experimental animals provides some support for this notion. Subordinate cynomolgous monkeys with a lowered baseline (i.e. pre-drug) availability of D2/D3 receptors in the striatum subsequently self-administered more cocaine than their dominant cage-mates

(Morgan et al., 2002). Reduced striatal D2/D3 binding has also been associated with enhanced cocaine preference in rats and monkeys (Michaelides et al., 2012; Nader et al., 2006), and biased decision making in a rodent model of gambling (Cocker et al., 2012). Some or all of these consequences of reduced D2/D3 receptor availability may be amenable to computationally-derived models, for example, as a way of predicting drug self-administration (Piray et al., 2010).

However, notwithstanding the importance of individual variation in D2/D3 receptor availability as a trait risk marker for addiction, there is unequivocal evidence that chronic self-administration of stimulants is sufficient to decrease D2/D3 receptor availability in the striatum (e.g. (Ginovart et al., 1999; Nader et al., 2006)). Indeed, this view is supported by evidence that D2/D3 receptor availability correlates inversely with the duration of cocaine use in humans (Volkow et al., 1993). Thus, pre-existing reductions in DA receptor density, as found in impulsive individuals, for example, may be further compromised by chronic drug exposure. Recently, we tested this hypothesis by scanning highly impulsive rats on the five-choice serial reaction time task on two occasions; initially to establish pre-drug [¹⁸F]-fallypride binding potentials in the ventral and dorsal striatum and then again after a 2-week period of long-access cocaine self-administration (Caprioli et al., 2013). We predicted that impulsivity would be exacerbated in highly impulsive rats if cocaine had the expected effects of further diminishing D2/D3 receptors in the ventral striatum. Our results indicated that prior cocaine exposure not only remediated impulsivity in trait impulsive rats it also *increased* D2/D3 receptor availability in both the ventral and dorsal striatum. Intriguingly, the direction of this effect (increase or decrease) depended on pre-drug D2/D3 receptor availability in the ventral and dorsal striatum. These results suggest that a key determinant of the behavioral outcome of stimulants in addiction-prone impulsive animals involves an interaction between baseline D2/3 receptor availability and the effects of extended access to cocaine and

potentially other stimulant drugs as well. This interaction may be relevant to the observed ventral to dorsal shift in dopaminergic dysfunction that results from prolonged cocaine self-administration (Porrino et al., 2004), postulated to underlie the development of maladaptive habit learning and ultimately compulsive drug seeking (Belin and Everitt, 2008; Everitt and Robbins, 2005, 2013).

The fact that impulsivity was normalized in highly impulsive rats by prior extended exposure to cocaine provides some validity to the idea that drug use in impulsive individuals reflects a form of 'self-medication'. Thus, medicating impulsive individuals may prevent the development of compulsive drug use and/or the occurrence of relapse in susceptible individuals, although clinical and pre-clinical studies confirming this therapeutic intervention are needed. Atomoxetine, a selective norepinephrine reuptake inhibitor, has been shown to decrease both impulsive responding (Fernando et al., 2012) and relapse to cocaine seeking (Economidou et al., 2009) in highly impulsive rats. Indeed, evidence from clinical trials indicates enhanced rates of abstinence following treatment with the related drug reboxetine in cocaine-dependent patients (Szerman et al., 2005), **although studies using atomoxetine have failed to replicate these findings (Walsh et al., 2012).**

Further shared findings between novelty/sensation-seeking and impulsivity include increased reward and stimulant-induced activity together with increased DA release in the ventral striatum (Buckholtz et al., 2010; Leyton et al., 2002). Enhanced DA release in this region has been suggested to reflect underlying reductions in **midbrain** D2/D3 receptors (Buckholtz et al., 2010). However, these findings do not resonate with observations made in addicts. Thus, while there is conflicting evidence regarding drug- and reward-induced striatal activity in addicts (reviewed in (Hommer et al., 2011)), a consensus has emerged that reward reactivity, and associated DA release, is reduced in the ventral striatum of addicts (e.g. (Narendran and Martinez, 2008)). This dichotomous set of findings may lie in the dissociable

functions of D2 and D3 receptors to mediate DA responses at both pre- and post-synaptic membranes, as well as the differing anatomical distributions of these two receptor subtypes. **Indeed it has been suggested that D3 receptors are increased in addicts.** Thus, a recent study found that [¹¹C](+)-PHNO binding, a PET ligand exhibiting 25-48 fold greater selectivity for D3 receptors over D2 receptors (Gallezot et al., 2012), was increased in the substantia nigra of methamphetamine poly-drug users (Boileau et al., 2012). **Acting pre-synaptically, an increase in these receptors may drive the decrease in DA release observed in addicts.** However, while [¹¹C](+) PHNO is a useful radioligand for the investigation of D3 receptors, it lacks absolute specificity and consequently the significance of these data must be interpreted with caution. Further, it is not possible to dissect the effect of chronic drug exposure on DA release in the ventral striatum and D2/D3 receptor availability in addicts. Thus, the observed reduction in ventral striatal reactivity observed in addicts may reflect the outcome of repeated drug use. **Indeed chronic cocaine exposure has been found to reduce both basal and cocaine-evoked DA release in experimental animals (Kirkland Henry et al., 2009; Lee et al., 2011; Willuhn et al., 2012) and further has been found to correlate with the duration of drug use in cannabis addicts (Urban et al., 2012). Interestingly, cocaine-induced DA release in the ventral striatum has been shown to be critical for the later development of drug induced alterations in activity in the dorsal striatum thought to underlie the development of compulsive drug use in rats (Willuhn et al., 2012). Thus, enhanced ventral striatal activity associated with natural and drug rewards may preferentially recruit the circuitry required for the expression of compulsive drug use and in this way enhance risk for addiction in vulnerable individuals.**

Beyond striatal dopaminergic mechanisms, individuals exhibiting enhanced levels of impulsivity and novelty/sensation-seeking also demonstrate significant, albeit contrasting

alterations in functioning of the prefrontal cortex. Specifically, sensation-seeking has been associated with increased basal metabolic activity in this region and enhanced reactivity to emotionally-arousing stimuli (e.g. (Berpohl et al., 2008; Youn et al., 2002)). By contrast, impulsivity is generally associated with hypofunctioning of the prefrontal cortex leading to deficiencies in cognitive control (Dalley et al., 2011). Thus, increased metabolic activity of prefrontal cortical regions observed in sensation-seekers contrasts distinctly with findings in impulsive individuals (e.g. (Oquendo et al., 2003)), as well as in drug addiction, where hypofrontality is generally reported (Goldstein and Volkow, 2011; Moreno-Lopez et al., 2012). Indeed, regional glucose metabolism is reduced in the dorsolateral prefrontal cortex of methamphetamine addicts (Kim et al., 2009) and was found to correlate inversely with the severity of heroin, alcohol, cannabis, cocaine and MDMA abuse (Moreno-Lopez et al., 2012). Nevertheless, there are reports suggesting that brain metabolism may be increased in metamphetamine addicts, although this may reflect inflammatory cascades within the brain related to neurotoxicity (e.g. (Berman et al., 2008)).

It is not clear whether alterations in brain metabolism reflects the neurotoxic effects of chronic drug use since grey matter volume is also generally decreased in drug addicts (Fein et al., 2002; Liu et al., 2009). In addition, OFC volume depends on the duration of drug use (Ersche et al., 2012a), whilst also being affected in impulsive individuals (Matsuo et al., 2009). Thus, OFC volume may be a risk marker for addiction that is subsequently exacerbated by chronic drug use. Previously, it was shown that hypometabolism in frontal cortex was linked to reduced striatal D2/D3 receptor availability in detoxified alcoholics (Volkow et al., 2006), as well as abusers of methamphetamine (Volkow et al., 2007) and cocaine (Volkow et al., 1993). This reduction in frontal metabolism may underlie deficits in inhibitory control observed in both impulsive individuals and addicts (Fu et al., 2008; Kaufman et al., 2003).

Remarkably, there is no evidence (at least in animal models) to suggest that sensation-seeking is associated with deficits in response inhibition (Marusich et al., 2011), which may go some way to explaining why this behavioral trait is not associated with reductions in the activity of the prefrontal cortex. Indeed, the dissociation in deficits in response inhibitory control between sensation-seeking and impulsivity may relate to the apparent differential contribution of these two behavioral traits to addiction vulnerability (Belin et al., 2008; Ersche et al., 2010). It is also possible that enhanced activity in the prefrontal cortex observed in sensation-seekers (e.g. (Hakamata et al., 2006)) may contribute to the increased rates of drug use observed in these individuals (Ersche et al., 2012a) and in animal models of this trait, namely the HR rat (Belin et al., 2008).

Collectively, the findings reviewed above suggest the presence of several robust neurobehavioral makers associated with impulsivity and sensation/novelty-seeking that localize to cortico-striatal circuitry and which putatively underlie individual vulnerability for addiction (see **Figure 1**). These findings indicate a common involvement of diminished striatal D2/D3 receptor availability both in relation to predisposing traits and as a marker of prior drug abuse. However, this analysis also reveals important dissociations between frontal and striatal volume, as well as frontal metabolism, linked to impulsivity, sensation/novelty-seeking, and addiction. Such differences may reflect the increased propensity of sensation/novelty-seekers to initiate and maintain drug use but not develop diagnostically-relevant signs of addiction, unlike impulsive or impulsive/sensation-seeking individuals (Belin et al., 2011; Belin et al., 2008; Ersche et al., 2012a; Ersche et al., 2010). Clearly, in addition to these predisposing factors, repeated cycles of drug bingeing and withdrawal are likely to modify and hasten this transition, putatively through effects on the reactivity of the striatal systems to reward and OFC under-activity. How, and to what extent, each of these

specific alterations in brain structure and function contribute to the development of compulsive drug seeking remains an important area for future research.

5.0 Conclusions and future directions

It is now generally accepted that the transition to addiction must entail pre-existing individual neurobiological risk factors, modified and exacerbated by both drug exposure and environmental variables. **As reviewed here, the behavioural traits of impulsivity and sensation-seeking** critically influence disease progression and show remarkable overlap with addiction with respect to DA dysfunction, altered brain metabolism and structure, **as detected by neuroimaging studies in both humans and animal models. These shared mechanisms may represent underlying neurobiological risk factors for the development of drug addiction which may in turn be modulated by repeated bouts of drug bingeing and withdrawal (Nader et al., 2008) to hasten addiction. The effect of drug use to modify this neural background may account for some of the differences observed between the neuroimaging findings between addiction and impulsivity/sensation-seeking. The cascade of molecular mechanisms driving the shift from initial drug use to habitual and eventually compulsive drug seeking are unknown but are, without doubt, critically influenced by these predisposing behavioral endophenotypes and importantly therefore represent promising targets for developing new therapies in addiction.**

Despite evidence for these shared mechanisms, particularly relating to DA dysfunction, there have been surprisingly few therapies developed for stimulant addiction based on pharmacological interventions of the brain DA systems (Christopher Pierce et al., 2012). In hindsight, this challenging failure in rational drug design is perhaps not surprising given current conceptualization of addiction as a progressive disorder characterized by pervasive

and long-lasting disturbances in a complex myriad of neurotransmitter systems which includes glutamate, GABA, serotonin, noradrenaline and endogenous opioids, as well as DA (Kalivas and Volkow, 2011).

In turning to the future, it is clear that a more complete understanding of risk for addiction requires the non-invasive imaging of neurotransmitter systems other than the biogenic amines. In this regard promising PET ligands have been developed for the metabotropic glutamate receptors, mGluR1 and mGluR5 (Hostetler et al., 2011; Simeon et al., 2012), GABA_A and GABA_B receptors (Moran et al., 2012), and the noradrenergic transporter, the latter with promising results in cocaine addicts (Ding et al., 2010). As reviewed above, animal models have provided valuable insight into the neural and psychological mechanisms of compulsive drug self-administration, which implicate a broad network of brain structures and neurotransmitter systems (Everitt and Robbins, 2013), including the brain serotonin systems (Pelloux et al., 2012), for which excellent PET radioligands are available (e.g. [¹⁸F]altanserin and [¹¹C]DASB). Other promising leads include investigations of the endogenous opioid and cannabinoid systems, which powerfully modulate impulsivity (Wiskerke et al., 2011) and sensation/novelty-seeking (Van Laere et al., 2009).

The continued development of novel PET tracers and complementary structural and functional MRI approaches is expected to lead to further major discoveries in the field of addiction research. Central to this progress, and thereby the rationale development of new therapies, will be a greater understanding of brain mechanisms that confer individual vulnerability to the emergence of harmful drug use.

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Figure 1: Summary of the key imaging biomarkers associated with impulsivity, sensation/novelty-seeking and drug addiction. For all images red/yellow indicates **higher**, while blue indicates **lower values** compared with healthy controls. For simplicity, regions of interest combine (i) dorsal and ventral striatum (D/VS), and (ii) medial and lateral regions of prefrontal cortex (M/LPFC). Impulsivity and sensation-seeking are associated with increased reward reactivity in the D/VS. However, in addicts, reward reactivity is reduced in these regions. Sensation-seekers demonstrate enhanced activity in M/LPFC. However, both impulsive individuals and drug addicts show broad-ranging abnormalities in structural integrity and volume of M/LPFC, anterior cingulate cortex (ACC), and orbitofrontal cortex (OFC). These markers closely associate with reduced metabolism in these regions with the exception of the OFC in impulsive individuals. By contrast, sensation-seekers show increased volume in posterior cingulate cortex (PCC) and increased metabolism in M/LPFC but not the OFC. D2/D3 receptor availability is decreased in the D/VS of all three groups. Collectively, these results suggest an involvement of reduced striatal D2/D3 availability in the general risk for addiction. However, dissociable alterations are observed in brain morphology and metabolism for impulsivity, sensation/novelty-seeking, and addiction, and these may reflect differential contributions of impulsivity and sensation/novelty-seeking to different stages of addiction. By contrast, findings in addicts of reduced striatal reward reactivity and orbitofrontal metabolism compared with impulsive and sensation-seeking individuals appear to reflect the impact of repeated drug bingeing and withdrawal.

Figure 1

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