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Invited review

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 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.

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1. 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 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, 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 behaivoural 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/

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novelty-seeking and discuss the relevance of these studies for the etiology of addiction.

2. 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, 2012b; 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 interrelate 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