



## Review

# Impulsivity as a vulnerability marker for substance-use disorders: Review of findings from high-risk research, problem gamblers and genetic association studies

Antonio Verdejo-García<sup>a,\*</sup>, Andrew J. Lawrence<sup>b,c</sup>, Luke Clark<sup>b,c</sup>

<sup>a</sup>Pharmacology Research Unit, Institut Municipal d'Investigació Mèdica, Barcelona Biomedical Research park, Dr. Aiguader 88, 08003 Barcelona, Spain

<sup>b</sup>Behavioural and Clinical Neuroscience Institute, University of Cambridge, Cambridge CB2 3EB, UK

<sup>c</sup>Department of Experimental Psychology, University of Cambridge, Cambridge CB2 3EB, UK

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## Abstract

There is a longstanding association between substance-use disorders (SUDs) and the psychological construct of impulsivity. In the first section of this review, personality and neurocognitive data pertaining to impulsivity will be summarised in regular users of four classes of substance: stimulants, opiates, alcohol and 3,4-methylenedioxymethamphetamine (MDMA). Impulsivity in these groups may arise via two alternative mechanisms, which are not mutually exclusive. By one account, impulsivity may occur as a consequence of chronic exposure to substances causing harmful effects on the brain. By the alternative account, impulsivity pre-dates SUDs and is associated with the vulnerability to addiction. We will review the evidence that impulsivity is associated with addiction vulnerability by considering three lines of evidence: (i) studies of groups at high-risk for development of SUDs; (ii) studies of pathological gamblers, where the harmful consequences of the addiction on brain structure are minimised, and (iii) genetic association studies linking impulsivity to genetic risk factors for addiction. Within each of these three lines of enquiry, there is accumulating evidence that impulsivity is a pre-existing vulnerability marker for SUDs.

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**Keywords:** Impulsivity; Substance-use disorders; Vulnerability; High-risk; Offspring; Pathological gambling; Genetic association studies

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\*Corresponding author.

E-mail address: [averdejo@imim.es](mailto:averdejo@imim.es) (A. Verdejo-García).

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## 1. Introduction

The term impulsivity is used widely within psychology to refer to "behaviour that is performed with little or inadequate forethought" (Evenden, 1999b). Whilst some functional, adaptive aspects of impulsivity have been noted (Dickman, 1990), it is generally regarded to be a dysfunctional trait, associated with actions that may be criminal and/or violent, physically harmful to the self (such as suicide), or inappropriate given accepted social standards. The term has a long history in the study of individual differences, as a trait variable of human personality that is stable within an individual and varies normatively across the healthy population (Barratt, 1959; Patton et al., 1995). Within neuropsychology and cognitive neuroscience, impulsivity is often equated with the term ' disinhibition ', referring to the idea that top-down control mechanisms ordinarily suppress automatic or reward-driven responses that are not appropriate to the current demands (Aron, 2007). These inhibitory control mechanisms may be disrupted following brain injury, or in forms of mental illness, resulting in a predisposition towards impulsive acts.

Defined in this way, impulsivity has clear relevance to substance-use disorders (SUD). Throughout the present article, we will use the term SUD to refer to the abuse of, or dependence upon, illicit substances including stimulants and opiates, as well as alcohol. The early stages of recreational drug taking may be mediated by personality characteristics that influence whether or not the individual will try a substance that is available, and how much of the

substance they will consume. Once dependent, drug users may persist in drug-taking despite awareness that their habit is directly harmful to their health, their finances and their interpersonal relationships. Substance users may repeatedly attempt (but fail) to quit drug-taking or reduce drug intake. Each of these phenomena could plausibly be explained by deficient inhibitory control over a response that provides immediate reinforcement. Further understanding of neurobiological and psychological underpinnings of inhibitory control offers obvious promise for pharmacological treatments and behavioural treatment programs for SUD.

### 1.1. Self-report measures of impulsivity

A wide array of measures exists for measuring impulsive behaviour in human subjects. Within the field of individual differences, well-validated self-report questionnaires exist to quantify the impulsive personality, including the Barratt Impulsivity Scale (BIS; Patton et al., 1995), the Impulsivity-Venturesomeness-Empathy Scale (IVE; Eysenck et al., 1985), or the UPPS Impulsive Behaviour Scale (Whiteside and Lynam, 2001, 2003). Related constructs of Novelty Seeking and Sensation Seeking can be measured with the Tridimensional Personality Questionnaire (TPQ; Cloninger et al., 1991), the Temperament and Character Inventory (TCI; Cloninger et al., 1994) or the Sensation Seeking Scale (SSS) of the Zuckerman-Kuhlman Personality Questionnaire (Zuckerman et al., 1993). As reviewed in Section 2, there is considerable evidence that self-report ratings of

impulsivity, novelty seeking and sensation seeking are increased in SUD populations relative to non-drug using controls. Self-report questionnaires assess general dispositional characteristics of the individual: how the individual would typically behave in a given situation, or to what extent the subject agrees or disagrees with particular statements. This introduces a number of caveats in the context of SUD populations. Primarily, most questionnaires do not explicitly distinguish between those current characteristics of the individual that have become instantiated since the onset of drug-taking from those pre-morbid characteristics that preceded the drug use. Whilst it is easy to assume that an inflated questionnaire score reflects an enduring characteristic of the individual, the methodology is unable to demonstrate this effect empirically. In addition, self-report questionnaires are susceptible to demand characteristics and biases in social desirability that may naturally differ between SUD volunteers and control subjects. Moreover, impulsivity may directly interfere with the completion of the questionnaires themselves, such that the impulsive subject may give less consideration to responses than the non-impulsive subject. Finally, introspective ratings assume that individuals have sufficient insight to rate their personality accurately.

### 1.2. Laboratory measures of impulsivity

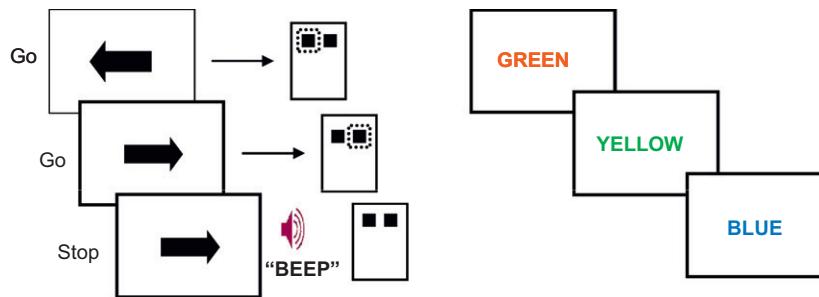
These caveats with self-report measures have led to increased interest in direct measurement of inhibitory control processes using laboratory tasks (Dougherty et al., 2003, 2005; Evenden, 1999b; Moeller et al., 2001a; Reynolds, 2006). Cognitive and behavioural models of impulsivity have enabled the development of objective tests that measure performance in terms of accuracy and reaction time data. For the purposes of the present review, we will focus on three broad classes of neurocognitive test used to measure impulsivity (see also Fig. 1): (i) measures of *response inhibition* based on the suppression of an automatic (prepotent) response, namely the Go–No Go test, the Stop Signal test, the Stroop test, and measures of commission errors on Continuous Performance Tests (CPTs) (Logan et al., 1997); (ii) measures of *delay-discounting*, which define impulsivity in terms of choice preference for a small reward available immediately (or after a short delay) over a larger reward available at some point in the future (Bickel and Marsch, 2001; Reynolds, 2006); and (iii) measures of *cognitive impulsivity*, a broad term that refers to impulsive behaviour in the arena of decision-making. One element of cognitive impulsivity is ‘reflection impulsivity’, which refers to the tendency to gather and evaluate information before making complex decisions (Kagan, 1966). Inadequate reflection at the pre-decisional stage will reduce the accuracy of the eventual decision (Evenden, 1999a). Reflection impulsivity, measured with the Matching Familiar Figures Test (MFFT) (Kagan, 1966) or the Information Sampling Test (Clark et al., 2006), may be related to psychometric constructs of

‘non-planning impulsivity’ (Patton et al., 1995) or ‘lack of premeditation’ (Whiteside and Lynam, 2001). Cognitive impulsivity may also contribute to abnormal decision-making on tasks where the subject may select between a conservative option and a more risky option that offers a ‘superficially seductive’ gain (Bechara, 2003; Knoch and Fehr, 2008). These measures include the Iowa Gambling Task (IGT) (Bechara et al., 1994), the Risky Gains procedure (Paulus et al., 2003), and the Cambridge Gamble Task (CGT) and Risky Gains Task (RGT) (Rogers et al., 1999a, b). Impulsivity can be indexed by selection of the highly rewarding option despite the clear potential for negative outcomes. Whilst performance deficits on these tasks need not necessarily indicate impulsivity (Busemeyer and Stout, 2002), there is substantial overlap between the research literatures on impulsivity and decision-making in SUD, and we believe it is important to consider these tasks under the broad term of ‘cognitive impulsivity’.

### 1.3. Explanations of impulsivity in SUD

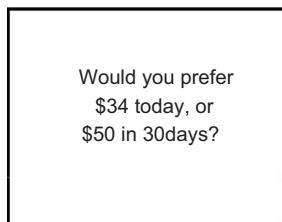
Section 2 of the review provides an intentionally brief overview of the research in SUD groups showing robust deficits on various neurocognitive tests of impulsivity and elevated self-report impulsivity on questionnaire measures. Whilst few researchers would deny this basic observation, when we consider the source of this impulsivity, the field becomes markedly polarised. One possibility is that the chronic neurobiological effects of drug self-administration cause a gradual attrition of behavioural self-control, plausibly mediated by structural changes in the prefrontal cortex (e.g. Bechara, 2003; Goldstein and Volkow, 2002; Porrino and Lyons, 2000). This attrition may occur via direct neurotoxicity (cell death) or tissue shrinkage, and structural brain imaging and post-mortem studies in SUD groups have established reductions in regional brain volumes, and grey- and white-matter densities associated with many substances of abuse (Chanraud et al., 2007; Cowan et al., 2003; Lyoo et al., 2006; Matochik et al., 2003; Thompson et al., 2004). Even in the absence of such macro-cellular changes, a range of micro-cellular alterations including persistent changes in gene expression, and effects on neurogenesis and synaptogenesis, may cause a gradual breakdown of inhibitory control. Animal studies have elegantly demonstrated that cognitive deficits on tests of inhibitory control can be induced by relatively short-term courses of drug administration (Jentsch et al., 2002; Ricaurte et al., 2000; Robinson and Kolb, 2004). Research in experimental animals is able to quantify baseline cognitive function prior to drug initiation, and then precisely regulate drug dosage, frequency of administration, and other critical behavioural parameters. Moreover, the issue of poly-substance abuse that plagues the human clinical literature on SUD groups is obviated in animal research.

By an alternative explanation, deficient inhibitory control may have been present prior to drug initiation.

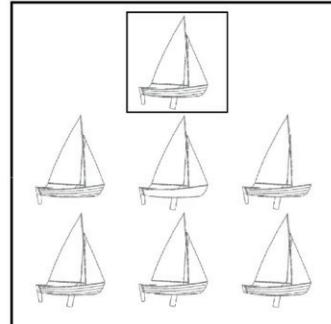


(1) The Stop Signal Task (Logan et al., 1984). This task has two trial types. On Go trials (75%) subjects must make a rapid response in the direction of arrow. On Stop trials (25%; signified by a tone) subjects must withhold the pre-potent Go response. Inhibition is indexed by the stop signal reaction time.

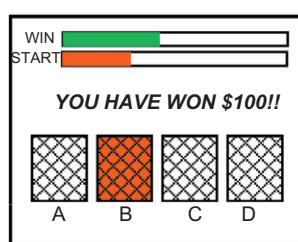
(2) The Stroop Task (MacLeod, 1991). Subjects are required to name the ink colour of colour words that may be incongruent words (trials 1 and 2 above) or congruent trials where the colour and word match (trial 3). The difference in reaction time on incongruent and congruent trials provides an interference score, related in part to the inhibition of an automatic tendency to read the word.



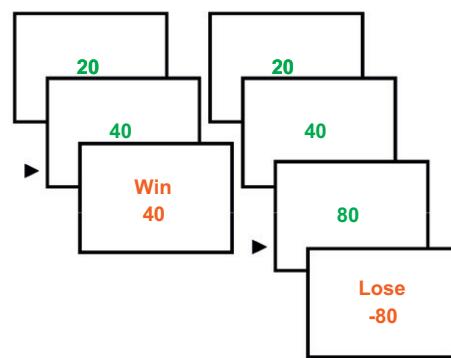
(3) Delay Discounting Task (Kirby, 1999). Subjects are asked to choose between two options: a small reward available immediately (or at a short delay), or a larger delayed reward. Trial by trial manipulation of one parameter (e.g. the long delay) allows estimation of the rate of discounting. Impulsivity is defined as preference for the small reward in order to obtain the reward immediately (i.e. a steeper discount rate).



(4) The Matching Familiar Figures Task (Kagan 1966). Subjects are presented with a template image (top centre) and 6 similar variants; only one of which is identical. The match (bottom left in the example) must be identified each trial. Impulsives respond more rapidly and less accurately than non-impulsives.



(5) The Iowa Gambling Task (Bechara et al., 2000). Subject make 100 card choices from 4 decks. Decks A and B offer high rewards (\$100 per choice) but higher losses. Decks C and D offer only \$50 per choice, but small losses resulting in profit over time. Impulsive groups may prefer the risky decks over the safe decks or may fail to acquire normal preference for the safe decks over the course of the task.



(6) Risky Gains Task (Paulus et al. 2003). Subjects are presented with three potential gains (20, 40 and 80) in sequence. A response when 20 is displayed yields a certain win of 20 points. A response to 40 or 80 may win or lose that number of points, and is therefore 'risky'. Thus, small certain rewards are pitted against uncertain outcomes of potentially higher value.

Indeed, deficient inhibitory control may represent a vulnerability marker for SUD, predisposing individuals towards early recreational experiences with drugs, or mediating the transition from recreational use to dependence. It is important to note that the impact of personality and/or neurocognitive variables may differ across various stages of addiction, from initiation, to regular use, to dependence and later on at relapse (Kreek et al., 2005). Critically, the vulnerability and attrition accounts are by no means mutually exclusive: substance users may have impulsive personalities premorbidly, and this impulsivity may be further exacerbated via chronic substance administration. Nonetheless, the characterisation of vulnerability markers for addiction is essential for detecting at-risk individuals, and in order to implement early detection and treatment intervention and thereby avert the devastating effects of long-term use. The vulnerability account of impulsivity in SUD is clearly related to the *endophenotype* concept. Endophenotypes are defined as intermediate variables that lie between the ‘fuzzy’ clinical phenomenology of a disorder and the genetic and neurobiological processes responsible for the manifestation of that disorder (Schumann, 2007). In SUD research, impulsivity variables represent a promising candidate endophenotype to bridge the gap between genetic risk loci and the complex clinical manifestations of SUD. By the criteria proposed by Gottesman and Gould (2003), an endophenotype should: (1) be present in the condition of interest (e.g. in case-control studies), (2) be observable regardless of the state of the illness (i.e. to persist in symptom remission), (3) have evidence of heritability, and (4) be present in individuals at risk of developing the disorder (such as unaffected first-degree relatives) at rates above the general population. One purpose of the article is to consider the current literature on impulsivity in SUD in terms of these criteria. In advance of our conclusions, we will refer to impulsivity with the more general term ‘marker’.

Neuroscientific models of addiction have increasingly recognised the vulnerability pathway. Based on substantial evidence that initiation of drug-taking typically occurs during adolescence, Chambers et al. (2003) proposed that adolescence constitutes a high-risk period for the development of SUD due to the relative maturity of subcortical

systems responsible for reward processing and motivation, coupled with relative immaturity of prefrontal cortical systems responsible for inhibitory control over these responses. In a similar vein, the triadic model of motivated action (Ernst et al., 2006b) explains the risk-taking behaviour of adolescents as result of the greater maturation of the ventral striatum (the reward system), as compared to the amygdala (avoidance system) and the prefrontal cortex (the regulatory system). These theoretical models are supported by the findings of differential trajectories of maturation across different brain regions in the adolescent brain, revealed by longitudinal structural MRI scanning (Lenroot and Giedd, 2006; Toga et al., 2006). Subsequent work has confirmed these developmental trends using risk-taking measures combined with fMRI scanning, in groups of young children, adolescents and young adults (Bjork et al., 2004b; Ernst et al., 2006a; Eshel et al., 2007; Galvan et al., 2006; van Leijenhorst et al., 2006).

A further observation in support of the vulnerability pathway has emerged from PET imaging with dopamine receptor ligands such as raclopride, a dopamine D2 receptor antagonist. A series of studies by Volkow and colleagues have shown that addictions to a range of substances are reliably associated with reduced dopamine D2 receptor density in the striatum (Volkow et al., 1993, 1996, 2001; Wang et al., 1997). Within healthy, drug-naïve individuals, the D2 binding potential was correlated with subjective responses to the psychostimulant methylphenidate, such that individuals with lower D2 density reported pleasurable, hedonic effects of methylphenidate whereas individuals with higher D2 density experienced an anxiogenic response (Volkow et al., 1999). Thus, the healthy individuals who experienced a hedonic response to drug were more similar to the SUD populations in terms of their dopamine transmission. Positive subjective and physiological reactions to initial drug exposure seem likely to influence the risk of developing SUD subsequently, consistent with a number of more recent studies (Brunelle et al., 2004; Fergusson et al., 2003; Grant et al., 2005; Taylor et al., 1999). Whilst these studies demonstrate the importance of pre-morbid characteristics in the development of later addiction, the findings to date have mainly highlighted the role of reward processes, rather than the

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Fig. 1. Some common neuropsychological tests of impulsivity: (1) the Stop Signal Task (Logan et al., 1984). This task has two trial types. On Go trials (75%) subjects must make a rapid response in the direction of arrow. On Stop trials (25%; signified by a tone) subjects must withhold the pre-potent Go response. Inhibition is indexed by the stop signal reaction time. (2) The Stroop Task (Macleod, 1991). Subjects are required to name the ink colour of colour words that may be incongruent words (trials 1 and 2 above) or congruent trials where the colour and word match (trial 3). The difference in reaction time on incongruent and congruent trials provides an interference score, related in part to the inhibition of an automatic tendency to read the word. (3) Delay Discounting Task (Kirby et al., 1999). Subjects are asked to choose between two options: a small reward available immediately (or at a short delay), or a larger delayed reward. Trial by trial manipulation of one parameter (e.g. the long delay) allows estimation of the rate of discounting. Impulsivity is defined as preference for the small reward in order to obtain the reward immediately (i.e. a steeper discount rate). (4) The Matching Familiar Figures Task (Kagan, 1966). Subjects are presented with a template image (top centre) and 6 similar variants; only one of which is identical. The match (bottom left in the example) must be identified each trial. Impulsives respond more rapidly and less accurately than non-impulsives. (5) The Iowa Gambling Task (Bechara et al., 2000). Subject make 100 card choices from 4 decks. Decks A and B offer high rewards (\$100 per choice), but higher losses. Decks C and D offer only \$50 per choice, but small losses resulting in profit over time. Impulsive groups may prefer the risky decks over the safe decks, or may fail to acquire normal preference for the safe decks over the course of the task. (6) Risky Gains Task (Paulus et al., 2003). Subjects are presented with three potential gains (20, 40 and 80) in sequence. A response when 20 is displayed yields a certain win of 20 points. A response to 40 or 80 may win or lose that number of points, and is therefore ‘risky’. Thus, small certain rewards are pitted against uncertain outcomes of potentially higher value.

premorbid impulsivity and inhibitory control, as critical in the development of SUDs.

The issue of impulsivity as a vulnerability marker for substance abuse has been elegantly addressed in some recent animal studies. These studies have divided groups of rodents into high- and low-impulsive subgroups on the basis of behavioural performance, in terms of either discounting preferences (Perry et al., 2005) or premature responses on an attentional task (Dalley et al., 2007). These individual differences remain stable across repeated testing, and can be used to breed strains of more-impulsive animals. The high impulsive subgroup displayed lower levels of striatal dopamine D2 receptor binding (Dalley et al., 2007), mirroring the effect seen in human SUD patients in the studies by Volkow and colleagues. The high impulsive animals also showed more rapid acquisition of drug self-administration and consume more cocaine than rats classified as non-impulsive (Perry et al., 2005; Piazza et al., 1989; Poulos et al., 1995). Considering adolescence as a period of increased risk for drug use, Stansfield and Kirstein (2005) have demonstrated that high impulsive adolescent rats (compared to high impulsive adult animals) also display an enhanced dopamine response to cocaine administration in the nucleus accumbens.

These observations in experimental animals require confirmation in humans and in SUD populations in order for their translational potential to be realised. In Sections 3–5 of this review article, we will review three approaches that have been taken to investigate predisposing markers for addiction in humans. First, it is possible to identify individuals at high-risk of developing SUDs, by virtue of substance dependency in a parent. Second, it has been suggested that pathological gambling (PG) may provide a model of drug-free addiction, sharing genetic vulnerability with SUDs but without the concomitant harmful effects on the brain. Third, it is possible that personality or neurocognitive markers of impulsivity may be associated with particular genetic variants that convey risk for addictive disorders. In the next section, we will briefly review the evidence for increased impulsivity in SUD groups, in reference to four specific groups of substances: opiates, psychostimulants, alcohol and 3,4-methylenedioxymethamphetamine (MDMA). With each substance, we will consider the preliminary indications that this impulsivity may predate substance abuse or arise as an effect of long-term exposure. In the subsequent sections, we will consider the three approaches to vulnerability described above, and highlight the methodological issues that should be considered in future work.

## 2. Increased impulsivity in substance abuse and dependence

### 2.1. Stimulants (cocaine/amphetamine)

#### 2.1.1. Self-report studies

Impulsive behaviour in SUD groups has received the most attention in relation to the psychostimulant drugs,

amphetamine and cocaine. Elevated impulsivity scores on self-report measures (typically the BIS) have been demonstrated in cocaine-dependent outpatients (Coffey et al., 2003; Moeller et al., 2004) and young stimulant users (Leland and Paulus, 2005), even after considering the influence of antisocial personality disorder (Moeller et al., 2002). Elevated BIS scores were correlated negatively with age of first cocaine use (Moeller et al., 2002), consistent with a vulnerability pathway where high impulsivity predispose early recreational drug-taking.

#### 2.1.2. Neuropsychological studies

On neuropsychological measures, robust findings have been reported for response inhibition: cocaine users have increased commission errors on Go–No Go tasks (Hester and Garavan, 2004; Kaufman et al., 2003; Moeller et al., 2004; Verdejo-Garcia, A.J., et al., 2007), increased stop signal reaction time on the Stop Signal task (Fillmore and Rush, 2002; Li et al., 2006), and increased interference scores on the Stroop (Bolla et al., 2000). The Go–No Go, Stroop and Stop Signal findings have all been replicated in amphetamine or methamphetamine users (Monterosso et al., 2005; Salo et al., 2002; Simon et al., 2000). Stimulant users also display overestimation of time intervals, which is mediated by trait non-planning impulsivity (Wittmann et al., 2007). Cocaine and methamphetamine users show steeper rates of delay-discounting on hypothetical tests with delays in the order of weeks to months (Coffey et al., 2003; Hoffman et al., 2006; Kirby and Petry, 2004; Monterosso et al., 2001) as well as on experiential discounting test with delays in the order of seconds (Moeller et al., 2002). The steeper discounting rate in cocaine users was similar in current users and a group who had been abstinent for 30 days (Heil et al., 2005), consistent with a stable alteration in preferences. Notably, delay-discounting performance was shown to correlate with self-report ratings of impulsivity (Coffey et al., 2003; Kirby and Petry, 2004; Moeller et al., 2002). Deficits have also been demonstrated on measures of cognitive inhibition: young stimulant abusers selected more risky choices on the Risky Gains procedure (Leland and Paulus, 2005) and sampled less information than healthy controls on a test of reflection impulsivity (Clark et al., 2006). Performance is reliably deficient on measures of emotional decision-making, including the IGT and the Cambridge Gamble Task (Bechara and Damasio, 2002; Bechara et al., 2001; Rogers et al., 1999a; Stout et al., 2004), although this impairment may be associated with altered processing of rewarding and punishing outcomes on the task, rather than inhibitory control per se (Bechara and Damasio, 2002; Stout et al., 2004).

Unlike long-term effects, acute administration of stimulants (cocaine and d-amphetamine) can facilitate response inhibition in healthy volunteers and chronic stimulant users on the Stop Signal and Go–No Go tasks. These effects are dose-dependent, whereby facilitatory effects at

lower doses are abolished at higher doses (de Wit et al., 2002; Fillmore et al., 2006). In the case of amphetamine, this facilitation was confined to individuals with poorer response inhibition performance at baseline (de Wit et al., 2002). Low dose d-amphetamine also reduced impulsivity in healthy volunteers on the delay-discounting procedure (de Wit et al., 2002). There are also individual differences in the subjective responses to stimulants, which may be predicted by trait impulsivity ratings. In a study by Hutchison et al. (1999), the trait of novelty seeking predicted feelings of 'stimulation' by amphetamine, and the trait of disinhibition (from the Sensation Seeking Scale) predicted feelings of 'elation'. A replication by Kelly et al. (2006) showed that subjects scoring in the lower quartile on the SSS reported no hedonic response to amphetamine, whereas subjects in the highest quartile reported dose-dependent increases in ratings of 'Feel Drug', 'Like Drug' or 'High'. It is likely that these individual differences in the acute drug response in healthy volunteers may predict those individuals who will develop later SUDs.

The neurocognitive deficits associated with stimulants persist with prolonged abstinence from drugs (>1 year) (e.g. Clark et al., 2006), and were unrelated to the duration of abstinence in methamphetamine users who were off drugs for 2–24 weeks (Hoffman et al., 2006). Generally, studies have failed to detect reliable correlations between inhibitory performance and either the duration of stimulant use or the age of onset (Clark et al., 2006; Hoffman et al., 2006; Verdejo-García and Perez-García, 2007). Elevated impulsivity has been associated with unprotected sexual relationships (Semple et al., 2005) and suicidal behaviour (Dougherty et al., 2004a) in stimulant users. Moreover, higher impulsivity in stimulant users is correlated with higher polysubstance involvement (McCown, 1988; Semple et al., 2005), binge use (Semple et al., 2005) and poorer treatment outcomes: lower retention and higher dropout rates (Moeller et al., 2001b; Patkar et al., 2004; Streeter et al., 2007).

## 2.2. Opiates (heroin/methadone)

### 2.2.1. Self-report studies

The relationship between opiate use and impulsivity has received increasing attention in recent years (Ersche et al., 2006; Verdejo-García and Perez-García, 2007). On self-report measures, heroin users have shown increased impulsivity scores on the BIS and Eysenck scales (Kirby et al., 1999; Madden et al., 1997). Heroin users also score lower on personality measures of future time perspective, suggesting decreased ability to plan ahead or a higher focus on immediate as compared to delayed events (Petry et al., 1998).

### 2.2.2. Neuropsychological studies

Whilst relatively few studies have examined neuropsychological performance in opiate addicts, there is emerging

evidence that opiate users may be less impaired in their general neuropsychological function than stimulant or alcohol users. However, performance on tests of cognitive impulsivity is similarly impaired in opiate users compared to other drug classes (Ersche et al., 2006; Verdejo-García and Perez-García, 2007). Studies have reported impaired response inhibition on the Stroop interference score (Mintzer and Stitzer, 2002; Verdejo et al., 2005), although a recent study in relatively pure heroin users failed to support this (Fishbein et al., 2007). On measures of cognitive impulsivity, opiate users showed reduced reflection and higher error rates (Clark et al., 2006; Lee and Pau, 2002), and impaired performance on measures of decision-making including the Iowa Gambling Test (IGT) (Mintzer et al., 2005; Mintzer and Stitzer, 2002; Petry et al., 1998; Pirastu et al., 2006; Verdejo-García, A.J., et al., 2007) and the Cambridge Gamble Task (Ersche et al., 2006). In the study by Fishbein et al. (2007) that tested a group of relatively pure Russian heroin users, increased risk-taking was reported on the Cambridge Risk Task, as well as deficits in executive function (Tower of London) and memory (Delayed Match to Sample, Paired Associates Learning). The profile in heroin users was quantitatively similar to the profile observed in relatively pure alcohol users.

Heroin users also show reliable effects on delay-discounting tasks, where there is steeper discounting of both hypothetical and real delayed monetary rewards (Bickel and Marsch, 2001; Kirby and Petry, 2004; Kirby et al., 1999; Madden et al., 1997, 1999). This higher discount rate has shown moderate correlations with self-reported trait impulsivity (Kirby and Petry, 2004; Madden et al., 1997). The rate of delay-discounting may be sensitive to current drug use status. For example, currently injecting drug users have higher discount rates than former injectors (Bretteville-Jensen, 1999), and abstinent heroin users present lower discount rates than former users (Kirby and Petry, 2004).

In addition to the effects of heroin, methadone use seems to additionally impair response inhibition and decision-making (Ersche et al., 2006; Mintzer et al., 2005; Verdejo et al., 2005). However, heroin-related deficits in cognitive inhibition seem to persist beyond the window of acute drug effects; i.e., at least 3 weeks of abstinence (Fishbein et al., 2007). Studies have generally failed to show associations between the dosage or duration of opiate use and measures of impulsivity (Clark et al., 2006; Rogers et al., 1999a), although Kirby and Petry (2004) found a significant correlation between severity of drug use (measured with the Addiction Severity Index) and steeper delay discounting. Rates of delay-discounting have been associated with indices of real-life risky choices such as needle sharing (Odum et al., 2000) and risky sexual behaviour (Lejuez et al., 2005). Performance on the IGT and the Cambridge Gamble Task was also recently found to predict abstinence from opioids at 3 months in opioid-dependent outpatients (Passetti et al., in press).

### 2.3. Alcohol-dependency

#### 2.3.1. Self-report studies

Alcohol use is consistently associated with elevated trait impulsivity. Recent studies have reported that alcohol-dependent subjects have higher scores on the UPPS subscale of urgency, i.e. the tendency to act impulsively in response to negative events (Whiteside and Lynam, 2003), sensation seeking (Bjork et al., 2004a), and more traditional measures such as the BIS (Mitchell et al., 2005).

#### 2.3.2. Neuropsychological studies

Neuropsychological measures indicate that alcohol use is associated with deficiencies in multiple forms of impulsivity. Alcohol-dependent subjects have consistently shown increased rates of commission errors in the CPT and Go–No Go paradigms (Bjork et al., 2004a; Kamarajan et al., 2005a), increased stop signal reaction time (Goudriaan et al., 2006), and higher rates of delay-discounting (Mitchell et al., 2005; Petry, 2001a; Vuchinich and Simpson, 1998). Alcohol users are also impaired on cognitive tasks of reflection-impulsivity (MFIT; Weijers et al., 2001), risk taking (Bjork et al., 2004a), and decision-making modelled by the IGT (Dom et al., 2006b; Fein et al., 2004; Mazas et al., 2000).

Studies on acute effects have also demonstrated that even moderate doses of alcohol (below the legally sanctioned limit) reliably impair response inhibition in the Stop Signal and Go–No Go tasks, and that these effects are dose-dependent (Fillmore and Vogel-Sprott, 1999; Marczinski et al., 2005; Reynolds et al., 2006). In contrast, preliminary evidence suggests that moderate doses of alcohol may foster more cautious decision-making on the IGT (Ramaekers and Kuypers, 2006). Conflicting findings have also been obtained for delay-discounting measures. One study showed reduced discounting of hypothetical rewards after administration of 0.7 mg/kg of alcohol, although the effect was not statistically significant (Ortner et al., 2003). Conversely, a more recent study using real-time rewards (argued to be more sensitive to acute effects) showed that a 0.8 mg/kg dose of alcohol increased discounting parameters in social drinkers (Reynolds et al., 2006).

Impulsivity measures have been correlated with various clinical indices of alcoholism including the age of onset of alcohol use/heavy drinking (Bjork et al., 2004a; Dom et al., 2006a,c; Soloff et al., 2000) and measures of alcohol severity (Mitchell et al., 2005). Furthermore, type 2 alcoholics (characterised by higher family density of alcoholism, earlier onset and antisocial symptoms) display more impaired inhibitory control and higher impulsivity (Bjork et al., 2004a). The relationship between alcohol use and impulsivity is also exacerbated in patients with antisocial personality traits and disorders predating drug use (Mazas et al., 2000; Petry, 2002; Whiteside and Lynam, 2003). Additionally, cognitive impulsivity deficits in alco-

holics are not correlated with abstinence duration, and they persist even 6 years after quitting consumption (Fein et al., 2004). Elevated impulsivity in alcohol users has been correlated with increased risky sexual behaviour (Justus et al., 2000) and higher risk of suicide attempts (Koller et al., 2002). Defective decision-making performance on the IGT and the Cambridge Gamble Task was also associated with relapse at 3-month follow-up in alcoholics attending a residential rehabilitation programme (Bowden-Jones et al., 2005).

### 2.4. MDMA ('Ecstasy')

#### 2.4.1. Self-report studies

The association between Ecstasy use and impulsivity has been subject to considerable research interest given observations in animal studies that MDMA can induce relatively selective serotonin neurotoxicity (McCann et al., 1994; Taffe et al., 2001, 2002): there is a long-standing association between impulsivity and serotonin depletion (Asberg et al., 1976; Linnoila et al., 1983; Soubrie, 1986). For the current review, we refer to human users as Ecstasy users rather than MDMA users as the MDMA content of tablets is variable. Multiple studies have shown increased trait impulsivity in Ecstasy users as measured by several self-report inventories (Butler and Montgomery, 2004; Morgan, 1998; Parrott et al., 2000). In these studies, both recreational and heavy users showed higher scores on impulsiveness, venturesomeness and sensation seeking.

#### 2.4.2. Neuropsychological studies

Ecstasy users also display poor performance on neuropsychological measures of impulsivity. A number of studies have reported impairments in current Ecstasy users on the MFIT measure of reflection impulsivity (Morgan, 1998; Morgan et al., 2006; Quednow et al., 2007). These effects were not reversed by prolonged abstinence (Morgan et al., 2002). Neurocognitive deficits were also evident on risk taking and decision-making tasks: Ecstasy users selected more risky choices on the Bets-16 and the Rogers decision-making tasks (Butler and Montgomery, 2004; Morgan et al., 2006) and more disadvantageous choices on the IGT (Quednow et al., 2007). In these studies, the poor performance of Ecstasy users was not generally observed in polysubstance (non-Ecstasy) using control subjects, who are typically regular cannabis users. Ecstasy users seem to be largely preserved on measures of response inhibition including the Stroop, Stop-signal and Go–No Go tasks (Lamers et al., 2006; Quednow et al., 2007; von Geusau et al., 2004). Most previous studies were conducted on samples of current or short-term abstinent Ecstasy users; however, a recent study used abstinent Ecstasy users to assess durability of effects (Halpern et al., 2004). Their results showed a dose-dependent effect of Ecstasy use on Stroop interference scores, with heavy users showing poorer inhibitory control.

When administered acutely in recreational users, moderate (75 mg) but not higher (100 mg) doses of MDMA improved stop signal reaction time in the Stop Signal task, although it had no effect on Go–No Go performance (Ramaekers and Kuypers, 2006). This finding resembles the U-shaped effects of stimulants dose on response inhibition, but more studies are needed to replicate this effect with MDMA. MDMA had no effect on cognitive inhibition performance measured with the IGT. The study of the acute effects of MDMA is particularly interesting in light of recent findings showing that single doses of ecstasy can modulate trait impulsivity and induce long-term changes in brain regions putatively involved in inhibitory control (de Win et al., 2007).

Two lines of evidence suggest a relationship between trait impulsivity and the severity of Ecstasy use. First, heavy Ecstasy users (more than 20 occasions) but not lower users have been shown to present with higher impulsiveness scores on the Eysenck IVE (Parrott et al., 2000) compared to non-drug using controls. Second, some studies have shown a significant correlation between dose-related measures of Ecstasy use and self-report and neurocognitive indices of impulsivity (Butler and Montgomery, 2004; Quednow et al., 2007). The direction of causality here is unclear: it is possible that more-impulsive individuals tend to use Ecstasy more heavily than less impulsive individuals, or alternatively, that higher exposure to Ecstasy may induce changes in trait impulsiveness, perhaps via serotonin neurotoxicity. In support of the neurotoxicity hypothesis, a recent prospective study targeting individuals at high-risk of using Ecstasy in the following year showed that premorbid impulsivity levels were not significant predictors of subsequent Ecstasy use (de Win et al., 2006); whereas impulsivity scores (BIS) did increase following first Ecstasy use (de Win et al., 2007).

## 2.5. Other drugs

Impulsive behaviour has been most widely studied in relation to the four substances reviewed above, but in addition, there are preliminary findings with regard to several other substances. Cannabis impairs response inhibition and increases cognitive impulsivity when administered acutely (Lane et al., 2005; McDonald et al., 2003; Ramaekers et al., 2006); and is associated with decision-making deficits in chronic heavy users (Verdejo-García, A., et al., 2007; Whitlow et al., 2004). With regard to nicotine and cigarette smoking, there are a number of papers showing higher rates of delay-discounting in current smokers compared to non-smoking controls (Bickel et al., 1999; Mitchell, 1999; see Reynolds, 2006 for review). This effect has been shown with both hypothetical (Bickel et al., 1999) and experienced delays (Reynolds et al., 2004), and with both monetary rewards and cigarette rewards (Baker et al., 2003). Discounting of delayed rewards in smokers was also increased further by short-term nicotine deprivation (Field et al., 2006). Subtle elevations in trait

impulsivity have also been reported in tobacco smokers (Dinn et al., 2004), as well as evidence for deficits in Go–No Go response inhibition and reflection impulsivity (MFFT) in female smokers (Yakir et al., 2007). With regard to one less frequently abused substance, ketamine has also been shown to have detrimental effects on response inhibition when administered acutely (Morgan et al., 2004), but little is known about its long-term effects on impulsivity among habitual users, or about the role of impulsivity in ketamine use initiation. The link between impulsivity and other emerging club drugs such as GHB or MDA also warrants future research.

## 2.6. Summary

The available evidence shows a highly consistent increase in self-report questionnaire impulsivity and neurocognitive measures of impulsivity across multiple substances of abuse. There is little evidence for disproportionate effects associated with any specific substances, although few studies have directly compared groups of users dependent upon different substances (for exceptions, see Bechara and Damasio, 2002; Fishbein et al., 2007). There is no consistent association between the duration of drug use and impulsivity, and studies of abstinent drug users typically detect comparable effects to current users, and minimal correlations between impulsivity and the duration of abstinence. This is consistent with the hypothesis that impulsivity is a pre-existing characteristic in drug users, which does not change radically with the development of the addiction or with long-term abstinence. However, there are some specific effects that are not immediately consistent with this position, and some remarks are necessary. First, whilst alcohol and stimulant users are reliably impaired on measures of response inhibition, these effects have not been observed in several studies of Ecstasy users, and there remains relatively little research on these measures in opiate users. Thus, varieties of impulsivity relevant to cognitive inhibition and risk-taking may be more closely related to vulnerability mechanisms than measures of response inhibition. Second, impulsivity in substance users may be modulated by acute drug administration. Opiate users are more impulsive while they are using the drug or receiving methadone (Kirby and Petry, 2004; Verdejo et al., 2005), whereas in contrast, acute administration of cocaine and MDMA to regular users of those substances may improve inhibitory control at low doses (Fillmore et al., 2006; Ramaekers and Kuypers, 2006). However, these effects should be treated as independent of the vulnerability hypothesis. Third, in the case of Ecstasy, there is emerging evidence that impulsivity may be exacerbated chronically, and irreversibly, by Ecstasy exposure. This may putatively occur via the neurotoxic effects of MDMA on the serotonergic system, and this progressive effect may mask pre-existing abnormalities. Notably, cross-sectional case-control studies in current or abstinent substance users are

clearly insufficient to disentangle the aetiology of impulsivity deficits in SUDs.

### 3. Models of vulnerability I: impulsivity in high-risk populations

This section will review a number of studies that have attempted to address the role of impulsivity in the pre-existing vulnerability to SUDs by virtue of examining populations at known high-risk for drug use. These high-risk populations comprise three basic groups: (i) adolescent populations who are considered vulnerable to drug use by virtue of their age; (ii) clinical groups with externalising behavioural disorders (ADHD and Conduct Disorder) who are known to display high rates of subsequent drug use; (iii) children and adolescents with parents diagnosed as SUD, who are at increased risk of developing SUD themselves by virtue of either genetic or environmental factors.

#### 3.1. Impulsivity during adolescence

Adolescence is a critical period for the development of SUDs. Retrospective studies in adult SUD groups report that the initiation of use of the substance of later dependence invariably starts before age 18 (Helzer et al., 1991; Wagner and Anthony, 2002). Cross-sectional surveys also demonstrate widespread recreational substance use in adolescence: by age 18, around 90% of youths report having tried alcohol, and around 20–25% of 18-year olds display abuse or dependence to at least one substance (Young et al., 2002). In addition to recreational use and initiation, the risk of actually developing SUD is also elevated during the teenage years. For example, the risk of alcohol use disorder is twice as high for youths aged 14–18 years as compared to young adults aged 22–26 years, and the risk of cannabis use disorders is seven times higher for youth aged 15–16 years as compared to young adults aged 22–26 years (Winters and Lee, 2008).

Neuroscientific models have emphasised how the major neurodevelopmental trajectories during the adolescent period may convey vulnerability to high-risk behaviours like drug-taking, via the relative immaturity of frontal cortical control systems coupled with the relative maturity of striatal systems responsible for reward processing and motivation (Chambers et al., 2003). This imbalance makes adolescence a period during which the activity of the reward system prevails over that of the systems governing avoidance or self-control (Ernst et al., 2006a). This hypothesis has been supported by functional imaging studies, which have demonstrated increased ventral striatum, diminished amygdala, and less-efficient frontal cortex activation in adolescents compared to young adults, during the performance of tasks assessing response inhibition and cognitive impulsivity (Ernst et al., 2006a; Eshel et al., 2007). Studies of neurocognitive performance in adolescent groups are broadly consistent with these functional

imaging data, demonstrating inferior decision-making abilities on the IGT in adolescents aged 9–18 years (Hooper et al., 2004; Overman et al., 2004). The study by Overman et al. (2004) reported a progressive increase in the total number of ‘safe’ card selections from age 11 to 18. Notably, there was a modest association between poor IGT performance and polydrug use. However, even the youngest age group (aged 11) preferred the safe decks over the risky decks overall, as also shown by Hooper et al. (2004). Thus, the adolescent subjects, on average, do not resemble the ventromedial prefrontal cortex patients described by Bechara et al. (1994) who significantly preferred the risky decks over the safe decks. It is possible that the age-related changes in the adolescent groups reflect developmental trajectories of *learning* mechanisms rather than risk-taking/impulse control mechanisms. Consistent with this, in the Overman et al. (2004) study, there was no association between the IGT and questionnaire measures of impulsivity and excitement seeking.

These findings show that the adolescent period is accompanied by relative deficiencies in inhibitory capacity. These deficiencies may predispose individuals towards drug experimentation and subsequent development of SUD. The link between adolescent impulsivity and SUD development is illustrated in a study where children rated by their teachers as more inattentive and impulsive at age 11 were more likely to have tried alcohol for first time before age 14 (McGue et al., 2001). Cross-sectional studies in adolescent samples have shown that elevated trait impulsivity (e.g., sensation seeking) and higher rates of delay-discounting were associated with earlier age of alcohol and drug experimentation (Kollins, 2003; Martin et al., 2002, 2004). Elevated impulsivity was also demonstrated in adolescents who have recently initiated drug use: adolescents (aged 14–16) who reported recently trying cigarette smoking for the first time showed steeper rates of delay discounting than both current and never smokers (Reynolds et al., 2003). Sensation seeking scores were elevated in both recreational and habitual users of alcohol in a similar age group (14–16) (Gerra et al., 2004a). These studies indicate that increased impulsivity could play a major role in substance-use initiation. In a study of response inhibition where adult social drinkers were classified by their age at first use (before vs. after 18), Dougherty et al. (2004b) showed that initiation of alcohol use during adolescence (before 18) was associated with higher rates of commission errors in a CPT.

Longitudinal studies have also begun to explore these maturational trajectories in inhibitory control performance, and their association with subsequent drug use development. Wong et al. (2006) assessed a sample of 514 children of alcoholics and matched controls to analyse the impact of neurodevelopmental patterns of impulsivity (as measured by clinicians' ratings of behavioural self-control) and resiliency on subsequent experimentation with drug use and SUD. Impulsivity and resiliency were assessed at 3 years intervals using five waves of children from 2- to

14-year old. Their results elegantly show that slower rates of development of behavioural self-control strongly and specifically predict early initiation of drug use at 14-year old and higher number of drug-related problems at 17-year old. These effects were still present after controlling for parental alcohol use and children internalising/externalising problems. Clearly, more studies addressing the neurocognitive developmental trajectories of different forms of impulsivity across adolescents and their influence on subsequent SUD are necessary.

### 3.2. Impulsivity in groups with ADHD and externalising behavioural problems

There is a higher prevalence of SUDs in adolescents and adults who were previously diagnosed with ADHD and other externalising behavioural problems during their childhood (Biederman et al., 1997; Molina et al., 2007; Wilens et al., 1997). Consequently, children with these behavioural problems may be considered at high-risk for later drug use. ADHD is robustly associated with impulsivity and neurocognitive deficits in behavioural inhibition. There are robust deficits on measures of response inhibition like the Stop Signal test, with a moderate effect size of (Cohen's  $d = 0.58$ ) through meta-analysis of 17 studies (Lijffijt et al., 2005). There are also reliable changes in delayed reward processing and temporal discounting functions (Scheres et al., 2006; Sonuga-Barke, 2002). In addition, there are similar profiles of risk-preference on the IGT in adolescents diagnosed with ADHD or conduct disorder (Ernst et al., 2003) to that seen in adult SUD groups. Several of these deficits have been associated with structural and functional abnormalities in prefrontal cortex, particularly in the right frontal cortex (Clark et al., 2007). These deficits are also associated with alterations in dopamine neurotransmission: ADHD is widely treated with psychostimulant drugs that increase dopamine (and noradrenaline) function, and is associated with genetic polymorphisms involved in dopamine regulation, including the DAT1 gene (Aron and Poldrack, 2005).

The link between behavioural disinhibition in ADHD groups and subsequent risk of developing SUDs has received somewhat less attention. Empirical studies have consistently found no evidence that treatment of ADHD with psychostimulant medication increases the risk of developing SUDs later in life (Barkley, 1997). Whilst the inattentive and impulsive subtypes of ADHD are equally associated with development of alcohol/substance abuse (Murphy et al., 2002), children with ADHD and comorbid conduct disorder seem to be at higher risk of developing SUDs than ADHD children without conduct disorder (Burke et al., 2001; Chilcoat and Breslau, 1999; Pliszka, 2003; Sartor et al., 2007). A recent prospective study examined behavioural predictors of drug-taking in adolescents with ( $n = 50$ ) and without ( $n = 28$ ) ADHD diagnoses (Ernst et al., 2006a). Aged 12–14, the participants completed a behavioural assessment including the BIS

and an aggression rating scale, and at 4-year follow-up, participants were screened for the initiation of substance use. In this study, ADHD diagnosis did not significantly predict later use of alcohol, tobacco or marijuana. However, specific facets of the ADHD syndrome were associated with drug initiation: BIS impulsivity was a significant predictor of alcohol use, and aggression ratings were associated with tobacco and marijuana use. In another recent longitudinal study, Elkins et al. (2007) assessed a large sample of 11-year-old twins (760 female and 752 male twins) for categorical ADHD diagnosis, as well as dimensional measures of Inattention vs. Impulsive/Hyperactive symptoms. They used these assessments to prospectively predict drug use initiation and SUD. Follow-up assessment of outcome variables at ages 14 and 18 showed that dimensional symptoms of Impulsivity/Hyperactivity were stronger predictors than Inattention or ADHD diagnosis for initiation of tobacco, alcohol and illicit drugs use at 14. This effect was evident even after controlling for conduct disorder. Impulsivity symptoms were also stronger predictors than Inattention or ADHD diagnosis for SUD at 18 (nicotine, alcohol and cannabis abuse/dependence). These two experiments both indicate that the impulsive symptoms of the ADHD syndrome may offer superior prediction of drug use initiation and SUD than the ADHD diagnosis per se. Further research is needed with prospective designs, incorporating neurocognitive measures of impulsivity into the baseline assessment.

### 3.3. Impulsivity in adolescent offspring of SUD parents

The prevalence of SUDs is elevated in the offspring of parents with SUDs including alcohol-dependency and stimulant use (Kendler et al., 2003; Sher et al., 1991). Thus, the investigation of children and adolescents with SUD parents may provide insights into the vulnerability mechanisms of drug use and dependence: we would hypothesise that impulsivity should be elevated in the offspring of SUD parents (high-risk children) compared to offspring of non-SUD parents (low-risk children). These effects have been shown in several cross-sectional studies. For example, Martin et al. (1994) found that young boys (10–12-year old) with a paternal history of substance abuse had higher levels of impulsivity than boys without family history. In this study, impulsivity was measured using a combination of several trait indices reported by parents and teachers, as well as a number of laboratory tasks (the Porteus Maze and a vigilance task). Adults with a family history of alcoholism also display poorer performance on tasks of reflection and motor impulsivity (Stevens et al., 2003), and children of alcoholics (aged 10–12) presented impaired ability to inhibit oculomotor responses in an antisaccade task (Blekher et al., 2002; Habeych et al., 2006). However, interpretation of these results is constrained by the co-occurrence of externalising disorders. In the studies of Martin et al. (1994) and Stevens et al. (2003) a significant proportion of high-risk individuals also had a

history of ADHD, conduct disorder or antisocial behaviour, and ADHD comorbidity may be associated with inhibitory deficits (Habeych et al., 2006). Thus, whilst cross-sectional studies support the role of impulsivity as a vulnerability marker for SUD, longitudinal studies provide a superior design for identifying the consequential effects of behavioural characteristics of later drug use. That is, to demonstrate that impulse control deficits constitute a vulnerability marker for the development of SUD it must be shown that (1) high-risk individuals present impulsivity related deficits before the onset of drug use and (2) impulsivity deficits predict later onset of drug use. Table 1 presents a summary of these studies.

In a series of longitudinal studies, Tarter and colleagues have examined performance of children (aged 10–12) of fathers with SUD on a cluster of measures related to inhibitory control, and they have followed up these

children to assess development of drug use disorders. Principal components analysis was used to extract a latent variable associated with behavioural disinhibition, which includes measures of inattention, impulsivity, hyperactivity and aggression (Dawes et al., 1997). The high-risk children presented with increased levels of behavioural disinhibition compared to demographically matched low-risk children, and at 2-year follow-up, this construct significantly predicted a prodromal indicators of SUD, including deviant peer affiliation, family dysfunction and poor school performance. A subsequent study incorporated affective measures of difficult temperament and externalising behavioural symptoms into the *behavioural disinhibition* latent variable. At baseline and aged 16 follow-up, the construct clearly discriminated high-risk from low-risk children, and higher behavioural disinhibition predicted substance use frequency after 4–6 years (ca. age 16), and

Table 1  
Longitudinal studies of individuals at high-risk (HR) of developing Substance Use Disorders (SUD) based on parental SUD

Study	Design	Participants	Measures	Main results
Dawes et al. (1997)	Cross-sectional and longitudinal (2-year follow-up)	<ul style="list-style-type: none"> <li>● HR group: 10–12-year-old sons of fathers with SUD (<math>n = 180</math> baseline/<math>n = 117</math> follow-up).</li> <li>● Control group: 10–12-year-old sons of fathers without SUD (<math>n = 200</math> baseline/<math>n = 124</math> follow-up).</li> </ul>	<ul style="list-style-type: none"> <li>● Behavioural Self-Regulation (BSR): Composite measure of: (1) inattention, (2) impulsivity/hyperactivity, and (3) aggressivity as measured by mother, child and teacher.</li> </ul>	<ul style="list-style-type: none"> <li>● HR: higher BSR at baseline.</li> <li>● BSR in HR group prospectively predicted peer affiliation, family dysfunction and poorer school performance at 2-year follow-up.</li> </ul>
Tarter et al. (2003)	Cross-sectional and longitudinal. (Follow-up at 16 and 19 years old.)	<ul style="list-style-type: none"> <li>● HR group: 10–12-year-old male offspring of fathers who met criteria for SUD (<math>n = 47</math> baseline).</li> <li>● Control group: 10–12-year-old sons of fathers without SUD (<math>n = 65</math> baseline).</li> </ul>	<ul style="list-style-type: none"> <li>● Neurobehavioral Disinhibition (NBD): composite measure of: (1) affective (revised dimensions of temperament survey), (2) behavioural (K-SADS-E externalizing symptoms and Disruptive Behaviour Disorder Rating Scale), and (3) cognitive (battery of tests measuring executive functions).</li> </ul>	<ul style="list-style-type: none"> <li>● HR: higher NBD at baseline.</li> <li>● NBD at baseline prospectively predicted SUD 7–9 years later (at age 16).</li> </ul>
Tarter et al. (2004a)	Cross-sectional and longitudinal. (Follow-up at 16 and 19 years old.)	<ul style="list-style-type: none"> <li>● HR group: 10–12-year-old male offspring of fathers who met criteria for SUD (<math>n = 66</math>).</li> <li>● Control group: 10–12-year-old sons of fathers without SUD (<math>n = 104</math>).</li> </ul>	<ul style="list-style-type: none"> <li>● Neurobehavioral Disinhibition (NBD): defined as in Tarter et al. (2003).</li> <li>● Social maladjustment.</li> <li>● Child neglect (parents).</li> </ul>	<ul style="list-style-type: none"> <li>● HR: higher NBD at baseline and age 16.</li> <li>● NBD (along with social maladjustment and drug use frequency) mediated the link between parental SUD and offspring SUD.</li> </ul>
Tarter et al. (2004b)	Longitudinal: assessments at ages 11 (baseline), 16 and 19 years	<ul style="list-style-type: none"> <li>● HR group: 10–12-year-old male offspring of fathers who met criteria for SUD (<math>n = 232</math>).</li> </ul>	<ul style="list-style-type: none"> <li>● Neurobehavioral Disinhibition (NBD): defined as in Tarter et al. (2003).</li> <li>● Suicide propensity (Beck Suicide Assessment Inventory).</li> </ul>	<ul style="list-style-type: none"> <li>● NBD (baseline and age 16) predicted SUD at age 19.</li> <li>● NBD at age 16 predicted suicide propensity at 19.</li> </ul>
King and Chassin (2004)	Longitudinal: three annual interviews during adolescence and a	<ul style="list-style-type: none"> <li>● HR group: 11–15-year-old offspring of fathers who met criteria for alcohol abuse or</li> </ul>	<ul style="list-style-type: none"> <li>● Behavioural Undercontrol (BU): Revele Impulsivity Scale and Sensation Seeking Scale.</li> <li>● Parental support (PS) (Network</li> </ul>	<ul style="list-style-type: none"> <li>● Parental alcoholism predicted BU.</li> <li>● BU prospectively predicted SUD.</li> </ul>

Table 1 (continued)

Study	Design	Participants	Measures	Main results
	fourth interview at emerging adulthood	dependence ( $n = 175$ ). ● Control group: matched sons of fathers without SUD ( $n = 190$ ).	of Relationships Inventory) and Paternal discipline (PD) (Children's Report of Parental Behaviour Inventory).	● The relation of BU to drug diagnosis was buffered by PS, but at high levels of BU this buffering effect disappeared.
Clark et al. (2005)	Longitudinal: assessments at ages 11 (baseline), 13, 16 and 19 years	● HR group: 10–12-year-old offspring of fathers with SUD ( $n = 266$ ). ● Control group: 10–12-year-old sons of fathers without SUD ( $n = 294$ ). ● Participants were further classified into five “at-risk subgroups” by cluster analyses using parental SUD, childhood alcohol/tobacco use and impulsivity.	● Neurobehavioral Disinhibition (NBD): defined as in Tarter et al. (2003). ● Parental SUD. ● Childhood alcohol/tobacco use. ● Risk clusters: lowest, intermediate-low, intermediate, intermediate high, highest.	● Parental SUD, childhood drug use and NBD predicted accelerated onset of tobacco, cannabis and cocaine regular use, problems and disorders. ● NBD was the most important predictor of accelerated onset of cocaine use disorders. ● Risk clusters (the highest risk cluster) predicted accelerated onset of all drugs regular use, problems and disorders.
Kirisci et al. (2005)	Longitudinal: assessments at ages 12–14, 16, 19 and 22 years	● HR group: 10–12-year-old offspring of fathers with SUD ( $n = 167$ ). ● Control group: 10–12-year-old sons of fathers without SUD ( $n = 184$ ).	● Neurobehavioral Disinhibition (NBD): defined as in Tarter et al. (2003). ● Drug use overall problem density: drug use screening Inventory, measuring several problem domains linked to SUD.	● Baseline NBD was associated with a latent class variable defining individuals at highest risk of increasing drug use problem density between early and mid-adolescence (age 16) and SUD at age 22.
Kirisci et al. (2006)	Longitudinal: Assessments at ages 11 (baseline), 13 and 16 years	● HR group: 10–12-year-old offspring of fathers with SUD ( $n = 119$ ). ● Control group: 10–12-year-old sons of fathers without SUD ( $n = 183$ ).	● Neurobehavioral Disinhibition (NBD): defined as in Tarter et al. (2003). ● Decision to desist substance use: Prevention Exposure Survey.	● Severity of NBD negatively predicted decision to desist drug use at age 19. ● NBD predicted initial level of drug use and acceleration of drug use between 12 and 19 years old.
Nigg et al. (2006)	Longitudinal (ongoing prospective)	● 498 children aged 12–14 at baseline, 15–17 at follow-up: HR group—alcoholic father ( $n = 146$ ); intermediate HR group ( $n = 61$ ); non-HR group ( $n = 95$ ).	● Parental alcoholism and ASPD. ● Child ADHD and CD: Child behavioural checklist. ● Child neurocognitive tests: stop-signal task; Wisconsin Card Sorting Test.	● Response inhibition (Stop-Signal), CD and parental alcoholism were significant independent predictors of onset of drug use. ● Poor response inhibition had a stronger effect on the HR families.
Ohannessian and Hesselbrock (2007)	Longitudinal (follow-up at 5 years)	● 249 15–19-year-old adolescents and their fathers, of whom 56% had SUD (diagnosed with the Semi-structured assessment for the genetics of alcoholism).	● NEO-Five Factor Inventory: Agreeableness. ● Sensation Seeking Scale: Disinhibition and Boredom susceptibility. ● Risk Taking Questionnaire. ● Adolescent Substance Use: frequency last 6 months, age first drinking/marijuana use.	● Parental SUD had direct effects on age first use of marijuana. ● HR adolescents had higher disinhibition that predicted earlier onset of alcohol and marijuana use and higher frequency of alcohol use to get high. ● HR adolescents had higher risk taking that predicted earlier onset of alcohol and marijuana use.

Note: CD, conduct disorder, ADHD, attention deficit and hyperactivity disorder, ASPD, antisocial personality disorder, K-SADS, kiddie-schedule for affective disorders and schizophrenia.

SUD diagnoses after 7–9 years (ca. age 19; Tarter et al., 2003). Subsequent studies have shown that neurobehavioral disinhibition during childhood is associated with earlier age of onset and rapid progression of SUDs across a variety of drugs (Clark, D.B., et al., 2005; Kirisci et al., 2005, 2006; Tarter et al., 2004a), and remains predictive of SUDs after controlling for parental drug and alcohol use (Clark, D.B., et al., 2005; Nigg et al., 2006).

These findings have been supported in longitudinal designs from other research groups. Nigg et al. (2006) have examined neurocognitive predictors of drug taking and problem of alcohol use in a large sample of high- and low-risk adolescents. Stop signal reaction time at baseline assessment (age 12–17) was found to predict the number of illicit drugs used, and alcohol use problems, at a follow-up assessment. The associations were significant after controlling for high-risk status, but the effect of poor response inhibition was strongest in families with paternal alcoholism and antisocial personality disorder. The Wisconsin Card Sorting Test did not enter the multivariate models as a significant predictor of drug or alcohol use, demonstrating some specificity of these relationships to response inhibition. In a similar design using questionnaire measures, by Ohannessian and Hesselbrock (2007), structural equation modeling was used to show that the high-risk adolescents displayed higher sensation seeking scores than the low-risk adolescents. Sensation seeking predicted scores on the risk-taking scale, and these scores in turn predicted younger age of regular alcohol use, younger age of first marijuana use, and frequent drinking to get drunk. Thus, the indirect effects of paternal substance dependence on subsequent offspring drug use were mediated via impulsivity and risk-taking self-report constructs.

High-risk studies in children of SUD parents have also examined neurophysiological correlates of impulsivity and disinhibition, which are putatively linked to prefrontal cortical dysfunction (Begleiter and Porjesz, 1999; Chambers et al., 2003; Jentsch and Taylor, 1999). Electrophysiological studies of evoked potentials have demonstrated decreased anterior P3 amplitude and deficient brain oscillatory activity during performance on inhibition tasks in individuals with a family history of SUD (Kamarajan et al., 2005b, 2006). Two prospective studies with an Event-related potentials (ERP) oddball task showed that reduced anterior P3 amplitude in adolescence predicted subsequent SUD onset (Habeych et al., 2005; Iacono et al., 2002). The oddball paradigm provides a coarse index of attentional processing and it is important to extend this research to investigate P3 alterations during pure inhibition tasks (e.g., the Go–No Go or Stop-Signal paradigms) as predictors of SUD development. ERP studies could also extend to other relevant electrophysiological indices, such as the error-related negativities (ERN, a brain potential emerging 50–150 ms after erroneous responses; Nieuwenhuis et al., 2004) and paradigms of cognitive impulsivity. For example, a recent study showed that alcoholics with higher familiar density of alcohol problems had smaller ERN

amplitude than alcoholics with lower familiar density when losing reward in a risk-taking task (i.e., the Balloon Analogue Risk Task; Fein and Chang, 2008). There is also a limited number of brain imaging studies in high-risk individuals. Using structural brain imaging, there is evidence that adolescents with a family history of alcoholism displayed smaller volumes of the hippocampus and the amygdala (De Bellis et al., 2000; Hill et al., 2001). These regions are densely interconnected with the prefrontal cortex, and the amygdala is also reduced in volume in cocaine users (Makris et al., 2004). Of more relevance to the impulsivity hypothesis, one functional MRI study measured brain activity during performance of a Go–No Go task in children aged 12–14 years with and without a family history of alcoholism (Schweinsburg et al., 2004). The high-risk group displayed reduced activity in the left middle frontal gyrus and other parts of the prefrontal cortex in the contrast of No Go trials against Go trials.

### 3.4. Challenge studies

A further possibility is that high-risk individuals with a family history of SUDs may possess basically intact inhibitory capabilities when tested under normal conditions, but may be highly sensitive to particular challenges. Neurochemical probes such as alcohol administration or dietary serotonin (tryptophan) depletion may reveal disproportionate deficits in impulse control in high-risk individuals. Previous studies using these designs are reviewed in Table 2. Two studies have looked at the effects of serotonin challenge in high-risk subjects, using the tryptophan depletion procedure where serotonin availability is reduced by dietary depletion of its amino acid precursor (Crean et al., 2002; LeMarquand et al., 1999). LeMarquand et al. (1999) found that acute tryptophan depletion selectively increased commission errors on the Go–No Go task in participants with a multigenerational history of alcohol use. Similarly, Crean et al. (2002) showed that tryptophan depletion impaired stop signal response inhibition in individuals with a family history of alcoholism, although there was no effect on a delay-discounting measure. Thus, both studies suggest that high-risk vulnerability status may be associated with response inhibition deficits that may be uncovered by mild perturbations of serotonin transmission, perhaps related to genetic vulnerability (see below). This is a promising avenue of research that could be usefully extended with comparable studies challenging the dopamine and noradrenaline systems, which are also implicated in addiction and inhibitory control.

With a slightly different rationale, other studies have examined the effects of acute alcohol administration. Compared to placebo, alcohol increased premature responses and decreased task persistence on a measure of impulsivity in young adults with a family history of alcohol abuse (Baer et al., 1995). However, those findings were challenged by Finn et al. (1999), who failed to find an

**Table 2**  
Pharmacological challenge studies in subjects at high-risk of developing an SUD

Study	Design	Participants	Measures	Main results
Baer et al. (1995)	Within subjects, two studies: (1) participants were tested sober and 50 min after 0.8 ml/kg dose of ethanol; (2) participants were tested 3 times 50 min after 0.8 ml/kg dose of ethanol	(1) 294 heavy drinking college seniors: 150 men and 144 women (mean age 22.7 years). High-risk: children of alcoholics ( $n = 49$ ). (2) 149 moderate to heavy drinking volunteers: 75 men and 74 women (mean age 23.8 years). High-risk: children of alcoholics ( $n = 17$ ).	(1) Matching Familiar Figures Test (MFFT). (2) Circle Tracking Task (CTT).	(1) Children of alcoholics had higher acceleration of response latencies after alcohol in the MFFT. (2) Children of alcoholics showed poorer persistence on the second and third administration of the CTT.
Finn et al. (1999)	Within subjects; participants consumed one of two doses of alcohol: (1) a dose targeting a blood alcohol level (BAL) of 0.07% or (2) a dose targeting BAL of 0.09%	● High risk group (HR): 34 men and 37 women (mean age 23.1 years) who had alcoholism in two generations (including father) ● Low risk group (LR): 35 men and 43 women (mean age 22.2 years) who had no family history of alcoholism	● Go/No-Go learning task ● Digits backward ● Conditional association task	● Alcohol increased Go/No Go false alarms rate on low working memory (WM) participants but not on high WM participants. ● There were no significant effects of family history in the effects of alcohol on Go/No-Go
LeMarquand et al. (1999)	Double-blind placebo-comparison between subjects design using acute dietary tryptophan depletion	● High risk group (HR): 13 men aged 18–25 years with a multigenerational family history of alcoholism ● Low risk group (LR): 15 matched men with no family history of alcoholism	● Modified Taylor aggression task ● Go/No-Go learning task	● Acute tryptophan depletion increased Go/No Go commission errors only in the HR group ● Acute tryptophan depletion did not affect aggression
Crean et al. (2002)	Double-blind placebo-comparison between subjects design using acute dietary tryptophan depletion	● High risk group (HR): 20 men aged 18–25 years sons of an alcoholic father ● Low risk group (LR): 20 matched men with no family history of alcoholism	● Stop task ● Delay discounting task (DDT) ● BIS-11	● HR but not LR: longer Stop reaction times after tryptophan depletion ● No differences between HR and LR groups on DDT after tryptophan depletion

overall detrimental effect of alcohol administration on impulsivity in individuals at high-risk for alcoholism. In contrast, they found that alcohol administration selectively increased commission errors in participants with lower baseline working memory ability. These findings indicate that increased vulnerability to drug abuse may as well be modulated by factors other than family history, including (impaired) executive functioning, inhibitory control, and personality (Finn and Hall, 2004; Nigg et al., 2006; Stout et al., 2005).

### 3.5. Summary

A number of groups can be identified as being at high-risk of developing SUDs, and there is a growing body of evidence that these groups display poor inhibitory control, primarily on neurocognitive indices. By one approach, adolescence can itself be considered a ‘high-risk’ period of development, given that SUDs are typically initiated at this time. Prefrontal cortical development and associated

neurocognitive functions (e.g. emotional decision-making) continue to develop throughout adolescence, and developmental delays in this period may be associated with SUD risk. In a second approach, it is well-established that children and adolescents with externalising disorders including ADHD are at increased risk of developing SUDs later in life. Whilst ADHD is itself robustly associated with impaired inhibitory control, it is currently unclear whether this impulsivity mediates the later risk of SUDs. More consistent evidence in favour of impulsivity as a vulnerability marker for SUD comes from cross-sectional and longitudinal studies of children with SUD parents. These studies have elegantly demonstrated that (1) children of SUD parents have elevated impulsivity *before* drug exposure and (2) impulsivity indices are strong and reliable predictors of later drug initiation and drug and alcohol problems. In addition, pharmacological challenge designs indicate that the offspring of SUD parents may be disproportionately sensitive to serotonin and alcohol challenges, whereby perturbation of neurochemical

systems has a pronounced effect upon impulse control ability.

#### **4. Models of vulnerability II: impulsivity in problem gambling**

Gambling is a widespread and socially acceptable form of entertainment that is known to become problematic or ‘compulsive’ in a minority (around 1–3%) of the population in the US and UK (Shaffer et al., 1999; Sproston et al., 2000). Prevalence estimates vary according to the threshold used in diagnosis: strict ‘pathological gambling’ (where symptoms resemble those of DSM dependence) was reported to have a prevalence of between 0.5% and 1.5% (Petry et al., 2005; Welte et al., 2002), whereas the prevalence estimates rise considerably for ‘problem gambling’ (based on social consequences, similar to DSM abuse) to 3.5% (Welte et al., 2002). Recent approaches consider problem gambling as a form of ‘behavioural addiction’, which shares vulnerability and aetiological mechanisms with SUDs, but where—critically—there is no administration of an exogenous substance to cause harmful effects in the brain (Bechara, 2003; Potenza, 2001). Common to all varieties of gambling, participants risk a stake on the uncertain prospect of receiving a monetary reward. Money is a powerful reinforcer that can drive behaviour in a manner comparable to primary rewards like food and water. The potential for gambling to elicit addictive behaviour in some individuals has led to the suggestion that PG may be a prototypical form of addiction (Bechara, 2003). Thus, clinical and neuropsychological examination of problem gamblers may afford unique insights into the vulnerability mechanisms underlying addictive behaviour, without the confounding effects of drug administration.

PG is recognised as an impulse control disorder in the DSM-IV, and several of the core symptoms overlap with characteristics of SUDs. In addition to functional impairments in occupational, financial and interpersonal capacity as a result of continued gambling, there is empirical evidence that PG individuals also display cravings (Tavares et al., 2005), withdrawal symptoms (Wray and Dickerson, 1981), tolerance (Griffiths, 1993), and frequent relapse (Ledgerwood and Petry, 2006). PG is also highly comorbid with drug use: rates of SUDs are increased in PG individuals seeking treatment (e.g. Ramirez et al., 1983) and conversely, rates of PG are increased in clinical SUD populations like cocaine users (Hall et al., 2000). Beyond these phenomenological similarities to drug addiction, there is accumulating evidence for shared genetic and neurobiological mechanisms, which particularly implicate the dopamine system. Dopamine metabolites are reduced in PG (Bergh et al., 1997), and physiological and psychological responses to gambling play are promoted by prior administration of alcohol (Stewart et al., 2006) and amphetamine (Zack and Poulos, 2004). Dopamine polymorphisms (e.g. the DRD2 polymorphism, see

Section 5.1) associated with the risk of SUDs are also present at elevated levels in PG (Comings et al., 1996) and twin data indicate that 12–20% of the genetic vulnerability to PG is shared with alcohol dependency (Slutske et al., 2000). A recent fMRI study using a monetary reward task in PG and non-gambling controls reported a blunted response in the ventral striatum in PG during monetary wins (Reuter et al., 2005). This is consistent with a reward deficiency hypothesis, that these individuals are driven towards exciting activities like gambling (and drug use) by virtue of a developmentally under-stimulated brain reward system. By viewing PG as a behavioural addiction with shared vulnerability to SUDs, whether an ‘at-risk’ individual develops problem gambling, alcohol-dependency, or stimulant use (or indeed no addiction), is thought to depend predominantly on environmental factors including parental behaviour and peer influences.

Studies of PG may be able to provide insights into the pre-morbid characteristics of substance abusers, given the shared vulnerability without the confounding effects of drug use. Below, we review the evidence for impulsivity in PG groups, using self-reported questionnaires and neurocognitive indices. In these studies, PG individuals are predominantly identified in one of two ways. First, they may be treatment-seeking gamblers at a specialist addiction centre or self-help group (e.g. Gamblers Anonymous), and these individuals typically meet DSM criteria for pathological gambling. The alternative approach is to recruit gamblers through community advertising and to assess PG with the South Oaks Gambling Screen (Lesieur and Blume, 1987), using a widely accepted threshold of  $\geq 5$  as a cut-off for ‘probable’ PG.

##### *4.1. Questionnaire measures*

Case-control studies comparing self-reported impulsivity in PG and non-gambling controls have demonstrated elevated scores on the BIS (Carlton and Manowitz, 1994; Fuentes et al., 2006; Petry, 2001c; Rodriguez-Jimenez et al., 2006a), the Eysenck Impulsivity Questionnaire (Blaszczynski et al., 1997), the California Personality Inventory Ego Control Scale (McCormick et al., 1987), and the Zuckerman SSS (Potenza et al., 2003). In the only negative report in the area, Allcock and Grace (1988) failed to find a significant difference between 10 problem gamblers and 25 healthy controls, although the effect size was comparable to other reports (e.g. Blaszczynski et al., 1997) and their study was presumably under-powered. Impulsivity scores predicted symptom severity in a study of 115 treatment-seeking gamblers (Blaszczynski et al., 1997) and was the only variable to predict disordered gambling in both male and female youths in a survey of 1339 adolescents (Nower et al., 2004). Impulsivity ratings in PG were comparable to scores in SUD groups (Castellani and Rugle, 1995; McCormick et al., 1987). In studies looking at PG with and without comorbid SUDs, as well as other comorbidities like childhood ADHD, the comorbid group showed

the highest scores on the Barratt Impulsivity Scale, but in these studies, significantly elevated scores were uniformly present in the group without comorbidity (Fuentes et al., 2006; Petry, 2001b; Rodriguez-Jimenez et al., 2006a).

Two further studies have demonstrated that personality measures of impulsivity during adolescence significantly predict problem gambling behaviour at a follow-up assessment (Slutske et al., 2005; Vitaro et al., 1999). The Vitaro et al. study is considered below (Section 4.2) as this study also employed neurocognitive measures. In the Slutske et al. study, a birth cohort of 939 individuals completed the Multidimensional Personality Questionnaire (MPQ) at age 18, and aged 21, participants were reassessed for past-year problem gambling using an 8-item version of the SOGS. Later problem gambling behaviour was predicted by a low score on the MPQ superfactor of 'constraint' (associated with risk-taking and impulsivity) and a high score on 'negative emotionality' (associated with aggression). Similar relationships were observed for prediction of alcohol, cannabis and nicotine dependence, but the association between problem gambling and (lack of) constraint remained significant in a sub-group of 'pure' problem gamblers without any comorbidities. This study convincingly supports the hypothesis that impulsivity is associated with a shared vulnerability to gambling and SUDs.

#### 4.2. Neurocognitive measures

Neuropsychological investigations of PG is a burgeoning area of research, and for the purposes of the present review, we will focus on studies that have employed measures of inhibitory control and decision-making. For a thorough review of broad neuropsychological function (e.g. attention, memory) in PG, the reader is referred to Goudriaan et al. (2004). Regarding response inhibition, recent case-control studies in PG have reported deficient performance on various tests including Go-No Go (Fuentes et al., 2006), the Stop Signal Test (Goudriaan et al., 2006) and the Stroop test (Goudriaan et al., 2006; Kertzman et al., 2006; Regard et al., 2003; Rugle and Melamed, 1993). One of the stronger studies, by Goudriaan et al. (2006), compared a group of treatment-seeking PG outpatients ( $n = 49$ ) against groups of alcohol-dependent subjects and subjects with Tourette's Syndrome, in addition to healthy controls. Stop Signal and Stroop impairments were present in both the PG and alcohol-dependent groups, as well as deficits in time estimation and planning that may also be related to impulsivity. These findings are consistent with shared vulnerability to addictions. Impaired stop signal reaction time was also reported by Rodriguez-Jimenez et al. (2006a), although only in PG subjects with a childhood history of ADHD. Slower stop signal reaction time was also predictive of relapse at 1-year naturalistic follow-up in a later examination of the Goudriaan patients (Goudriaan et al., 2008). Also of note, Fuentes et al. (2006) found an increased rate of commission errors on both auditory and

verbal versions of a Go-No Go task in a large group ( $n = 214$ ) of consecutive admissions to a PG outpatient facility. This impairment was present in patients with and without psychiatric comorbidities, and commission errors and the BIS both made significant independent contributions to a discriminant function analysis distinguishing the PG subjects from controls.

Similar effects were reported in studies of delay-discounting in PG groups, as reviewed by Reynolds (2006). In two studies comparing PG patients referred to an addiction treatment centre against healthy controls, Petry and Casarella (1999) and Petry (2001b) reported significantly steeper discounting rates in the PG group, with additive effects of comorbid substance abuse and PG on discounting rates. A further study from this group showed that discounting rates were associated with severity of gambling behaviour, when PG subjects were separated into more severe ( $SOGS > 13$ ) and less severe ( $SOGS < 13$ ) subgroups (Alessi and Petry, 2003). The basic case-control difference was replicated by Dixon et al. (2003) in horse-racing gamblers recruited from a betting facility. A single negative result reported by Holt et al. (2003) may be explained by the reasonably small sample size ( $n = 19$ ), and the use of a less-stringent criteria for problem gambling ( $SOGS \geq 4$ ). These studies have all employed self-report questionnaires of delay-discounting where the rewards and delays are both hypothetical. Further research may fruitfully examine discounting behaviour of different commodities (e.g. health or food) or experiential discounting with real rewards and/or delays.

Further studies have examined performance on laboratory tasks of decision-making and risk-taking, which model some elements of gambling decisions. Using the IGT, case-control differences were reported in treatment-seeking PG subjects by Cavedini et al. (2002) and Petry (2001c). In the study by Cavedini et al. the PG group selected significantly more cards from the risky decks than from the safe decks, and showed increasing preference for the risky decks over the course of the task. The study by Petry compared substance users with and without PG, and healthy controls. The IGT deficit in the gamblers was more subtle: they made fewer safe card choices than the controls, but they did not actually prefer the risky decks over the safe decks, on average. Thus, whilst PG subjects are impaired on the IGT, it is unclear whether their profile actually resembles that of ventromedial PFC lesion patients (Bechara et al., 2000) who fail to overcome their initial preference for the risky decks. Goudriaan et al. (2005) conducted a more thorough analysis of IGT performance variables in her group of PG patients. In this study, PG made fewer choices from the safe decks and had slower learning of the advantageous strategy on the IGT. In addition, the PG group were faster to select their card decks, and were less likely to switch decks following a losing outcome. These latter effects were actually specific to the PG group, compared to alcohol-dependent individuals and subjects with Tourette syndrome, suggesting that rapid unplanned

responding and a disregard for negative outcomes may be particularly relevant to PG behaviour. Brand et al. (2005) measured performance in 25 PG subjects on the ‘game of dice’ task, a risk-taking task that differs from the IGT in clearly displaying the potential win values and outcome probabilities. PG subjects made significantly more risky decisions than controls, and the number of risky decisions correlated with measures of executive function including the Stroop test.

Further studies have used a card-playing task that requires a repeated decision to quit or continue playing, and therefore may capture the loss-chasing tendency that is characteristic of PG behaviour. The task is based on the Newman et al. (1987) passive avoidance task, and the subject must decide on a trial by trial basis whether to continue to play, or to quit the task. The rate of reward is high (e.g. 70%) at the beginning of the task, but decreases by 10% in successive block of 10 trials, such that there is an optimal point at which to quit play. Studies by Goudriaan and colleagues have shown that PG subjects are less likely to quit the task during the optimal window (Goudriaan et al., 2005) and that low scores are predictive of gambling relapse at 1-year follow-up (Goudriaan et al., 2008). Breen and Zuckerman (1999) recruited students who reported gambling at least occasionally, and subjects were provided with a \$10 stake at the start of the session. Self-reported impulsivity on Zuckerman–Kuhlman Personality Questionnaire accurately discriminated ‘chasers’—who played until they lost all their \$10 stake—from ‘non-chasers’, who quit whilst still in profit. A prospective study by Vitaro et al. (1999) used the same task (although without the initial stake), in a baseline assessment of impulsivity in 154 adolescents males aged 12–14. At a 4-year follow-up session aged 17, subjects were screened for gambling involvement. Problematic gambling behaviour was predicted by excessive responding on the card-playing task, and also by self-reported impulsivity on a 5-item version of the Eysenck Impulsivity Questionnaire, after controlling for aggressiveness, anxiety levels, and gambling engagement at age 13.

#### 4.3. Summary

The studies reviewed in this section form a consistent body of research demonstrating that problem gambling is associated with increases in self-reported impulsivity as well as deficient performance on neurocognitive measures of inhibitory control, including tests of response inhibition, delay-discounting and risky decision-making. Whilst many studies find only limited convergence between self-reported ‘trait’ measures and behavioural neurocognitive measures of impulsivity (e.g. Fuentes et al., 2006), there is some evidence that questionnaire ratings may predict gambling tendencies on more ecological valid tasks, like the Breen and Zuckerman (1999) study that involved an actual monetary stake. The rationale for studying problem gamblers is that the vulnerability mechanisms appear to

overlap extensively with those for SUDs, but in PG there is no exogenous drug administration to cause harmful effects in the brain. The robust evidence of impulsivity in PG therefore supports the hypothesis that impulsivity predates drug-taking in SUD subjects, and is associated with the vulnerability for addiction.

This conclusion does make some assumptions that require more careful scrutiny. Many PG subjects have comorbid drug and alcohol problems, and therefore without careful screening, it is difficult to disentangle the predisposition to gambling versus SUD in practice. This also creates some difficulty in identifying appropriate control groups. For example, even in PG subjects who do not meet criteria for alcohol dependence, we may still expect to see elevated rates of social alcohol consumption and binge drinking above the general population. By carefully selecting PG subjects with no comorbid diagnoses, we also run the risk of creating a super-selected sample and ‘throwing the baby out with the bathwater’. Whilst this represents an important caveat, a number of studies have demonstrated increased impulsivity in PG subjects without SUD comorbidity (Petry, 2001b,c; Petry and Casarella, 1999; Slutske et al., 2005), with additive effects of PG and SUD features. There is less work examining the impact of other comorbidities like ADHD (Rodriguez-Jimenez et al., 2006a), depression or obsessive-compulsive disorder, and clearly, the underlying features that predispose PG may contribute to the development of a spectrum of disorders associated with poor impulse control and/or compulsion.

It may also be naïve to assume that the transitional process that occurs between social gambling and problem gambling leaves the brain unchanged. The problem gambler has extensive experience in making complex financial decisions involving variable wins, losses and probabilities. This experience is likely to shape their cognitive approach to laboratory tests of risky decision-making like the IGT. At a very simple level, they may find such tasks (with hypothetical wins and no wagers) trivial and uninteresting compared to healthy controls. Somewhat ironically, experimental tasks with less ‘ecological validity’ to the gambling situation, like the Go–No Go or Stop Signal tests, may be easier to interpret at a neuropsychological level. More speculatively, whilst PG does not entail exogenous drug administration, neural systems that process reinforcement and choice may nonetheless undergo neuroadaptive change as the PG individual experiences a chronic regime of winning and losing, coupled with the changes in arousal that are induced by those events. Psychological experience can clearly affect brain function and even brain structure. For example, there is accumulating evidence that increased cortisol levels during periods of depressed mood may have direct effects on hippocampal structure, with progressive cell loss and volume reduction associated with the duration of depression (MacQueen et al., 2003; Sapolsky et al., 1985). Increased cortisol levels are also seen during gambling sessions (Meyer et al., 2004).

These changes could affect neurocognitive performance on any measures of impulsivity, not just those that aim to model the gambling situation. This substantial caveat applies to case-control studies comparing PG and non-PG subjects. However, a small number of carefully conducted prospective studies in PG have also demonstrated that impulsivity and ‘loss-chasing’ tendencies measured during adolescence predict the later involvement in gambling over follow-up periods of 3–4 years. These prospective studies begin to establish a causal connection between impulsivity and the development of PG, which may be extrapolated to the vulnerability mechanisms in SUD.

### **5. Models of vulnerability III: genetic association studies of impulsivity with risk factors for addiction**

Family and twin designs indicate a genetic contribution to SUDs in the range of 30–60% (Kreek et al., 2005), and much of this variance is non-specifically associated with multiple drugs of abuse as well as behavioural addictions including PG (Comings et al., 2001; Kendler et al., 2003; Slutske et al., 2000; Tsuang et al., 1998). In the past 15 years, genetic association studies have begun to identify a number of specific gene variants that are implicated in the risk of developing SUDs. Single nucleotide polymorphisms (SNPs) exist in multiple variants across the population and may convey differing degrees of functionality in that gene. As an example, one of the most widely studied SNPs in the field of addiction is the Taq1 polymorphism of the dopamine D2 receptor gene. This gene occurs in two alleles—A1 and A2—and hence individuals can be classified as one of three possible genotypes: A1/A1, A1/A2, or A2/A2. The A1 allele (present in ~28% of the population; Noble, 2000) is functionally significant, as it is associated with reduced D2 binding in the striatum (see below). If a genetic variant such as DRD2 can be reliably associated with the risk of developing an SUD, then we can begin to assess whether this vulnerability is mediated via a psychological characteristic such as questionnaire impulsivity or neurocognitive disinhibition. Study designs may usefully examine the association between genotype and impulsivity in diagnosed SUD populations, but here, it is important to bear in mind that the polymorphism may be additionally associated with the severity of the addiction, or the harmful consequences of the drug on brain structure or function, and this could again confound or mask an association with vulnerability. The ideal study design is to investigate genetic associations with impulsivity in high-risk groups prior to initiation of drug-taking. Clearly, the research field investigating genetic associations with SUDs is vast and beyond the scope of the present review. In the following section, we have restricted our review to polymorphisms that meet two criteria: first, there should be a recognised link to addiction vulnerability, and second, where that polymorphism has been examined in relation to either self-report or neurocognitive measures of impulsivity in SUD or high-risk groups. The genetic data reviewed

below refer to polymorphisms clearly linked to brain monoamine function, and for reviews of the psychopharmacology of impulsivity, we refer the reader to Evenden (1999b), Chamberlain et al. (2006), and Robbins et al. (2006). There are a number of other promising candidate genotypes that are implicated in addictive behaviour from genome-wide scans or family-based linkage studies, but which are yet to be explored in relation to impulsivity. For reviews of these studies, the reader is referred to Uhl et al. (2008) and Kreek et al. (2005).

#### *5.1. DRD2 polymorphism*

The Taq A1 allele of the DRD2 polymorphism was first associated with alcohol dependency by Blum et al. (1990), and subsequent work has demonstrated similar associations with cocaine use (Noble et al., 1993), opiate dependence (Perez de Los Cobos et al., 2007; Xu et al., 2004) and PG (Comings et al., 2001). Its association with alcohol dependency has been confirmed in a number of meta-analyses and large-scale studies (Berggren et al., 2006; Noble, 2003; Young et al., 2004). Moreover, A1 carriers in the healthy population show reduced dopamine activity and decreased D2-receptor binding in the striatum, as measured with PET radioligand imaging (Jonsson et al., 1999; Noble et al., 1991; Pohjalainen et al., 1998). This latter effect is consistent with the widely observed reduction in striatal D2-receptor binding in SUD groups including cocaine addicts (Volkow et al., 1993) and alcohol-dependent patients (Volkow et al., 1996).

There is currently little evidence to support a link between DRD2 genotype and questionnaire trait impulsivity. One study in alcohol-dependent males reported significantly *reduced* scores on the BIS in A1/A1 homozygotes compared to both A1/A2 and A2/A2 groups (Limosin et al., 2003), which cannot be obviously reconciled with the basic genetic association. Another study found no association between DRD2 genotype and TCI Novelty Seeking in adolescent male offspring of alcohol-dependent parents (Conner et al., 2005), although there was an association with the Psychoticism scale of the Junior Eysenck Personality Questionnaire.

Preliminary neurocognitive studies suggest that moment-to-moment inhibitory control may be impaired in A1 carriers, however. An early study in 182 adolescent male offspring of alcohol-dependent fathers and non-alcoholic fathers reported poorer performance on the Benton Judgement of Line Orientation Test (JLOT) in the A1 carriers, and this effect was most pronounced in the high-risk adolescents (Berman and Noble, 1995). In the JLOT, the subject is briefly presented with two template lines, and they must identify the orientations of the 2 lines from 11 displayed alternatives. Whilst this task is generally used to measure visuospatial ability, it bears resemblance to the MFFT, and DRD2-related performance differences could indicate inadequate reflection at the pre-decisional stage. However, JLOT performance failed to enter a multivariate

regression model as a significant predictor of substance use severity in the follow-up study by Conner et al. (2005). A recent study in alcohol-dependent males ( $n = 50$ ), found that response inhibition was more impaired in A1 carriers on both the Stop Signal Task (stop signal reaction times) and a CPT (commission errors) (Rodriguez-Jimenez et al., 2006b). A further study in a healthy student population ( $n = 195$ ) found that A1 homozygotes displayed steeper delay-discounting functions than subjects without the A1 allele (Eisenberg et al., 2007), whilst there were no differences by genotype on the BIS, the Eysenck IVE or the Zuckerman SSS.

### 5.2. Other dopamine polymorphisms

There are a number of other SNPs on genes that affect dopamine transmission. In two of the first published findings in the field of personality genetics, the 7 repeat of the dopamine DRD4 polymorphism was associated with the trait of Novelty Seeking (on Cloninger's TPQ) (Ebstein et al., 1996) and Extraversion (Benjamin et al., 1996). Whilst impulsivity is a clearly related to the higher-order trait of Novelty Seeking, the relationship between impulsivity and Extraversion is more controversial. Eysenck's 3 factor model considered impulsivity to load on the higher-order trait of extraversion, but in Costa and McCrae's NEO 5-factor model, impulsivity was actually related to the neuroticism factor. Subsequent meta-analytic reviews of DRD4-Novelty Seeking have suggested that any association is likely to be of small effect (Kluger et al., 2002; Schinka et al., 2002). However, this polymorphism was also linked to recreational substance use in male adolescents, in the form of cigarette smoking and heavy alcohol use, and there is accumulating evidence that this relationship may be mediated via increased Novelty Seeking scores (Laucht et al., 2005, 2007). There are few studies investigating this polymorphism in relation to more specific indices of impulsivity. A recent study in a sample of 119 healthy individuals has shown that carriers of the 7 repeat allele have poorer inhibitory control on the Stop-Signal task (Congdon et al., 2008), and again, these effects did not generalise to the BIS questionnaire. In the study of healthy volunteers by Eisenberg et al. (2007) discussed above, the effect of the DRD2 A1 allele on delay-discounting was also most pronounced in DRD4 long-repeat subjects, constituting a gene by gene interaction effect. However, these results need to be extended to other indices of neurocognitive impulsivity, and replicated in groups diagnosed with SUDs, or at high-risk of developing SUDs.

Preliminary data have implicated a polymorphism of the DRD3 receptor gene in impulsivity. In alcohol-dependent subjects, subjects who were heterozygous for the Ball polymorphism were more likely to score above the median on the cognitive subscale of the BIS (Limosin et al., 2005), and scored highly on Novelty Seeking (Thome et al., 1999). However, this heterozygous genotype appears to be less

prevalent in SUD patients (Comings et al., 1999; Duaux et al., 1998). There is current a priori interest in the dopamine D3 receptor in addictions, given evidence that selective D3 blockade can reduce cocaine seeking behaviour in rodent models (Pilla et al., 1999) and, conversely, that D3-preferrent drugs used in the treatment of Parkinson's disease may inadvertently induce compulsive gambling behaviour (Dodd et al., 2005). There is, however, limited evidence that the DRD3 polymorphism has actual functional significance on DA transmission in human subjects.

Other polymorphisms exist in genes coding for enzymes involved in the metabolic degradation of extra-cellular dopamine. The enzyme catechol *O*-methyltransferase (COMT) plays a critical role in the breakdown of dopamine in prefrontal cortex, where dopamine transporters are scarce. The val116met polymorphism of the COMT gene is currently one of the more widely studied SNPs in relation to neurocognitive functioning, with the val genotype associated with higher enzyme activity and inferior working memory and behavioural flexibility in healthy subjects (Egan et al., 2001; Goldberg et al., 2003). Whilst there is some evidence that the high-activity genotype may be over-represented among SUD populations (e.g. Horowitz et al., 2000; Vandenberghe et al., 1997), this genotype has not been studied in relation to self-reported impulsivity or neurocognitive measures of inhibitory control at the current time.

### 5.3. Serotonin transporter (5-HTTLPR) polymorphism

The gene encoding the serotonin transporter (SLC6A4) contains a functional polymorphism, a variable repeat sequence in the promoter region (5-HTTLPR). This polymorphism produces two alleles: the short (s) and long (l) variants and hence individuals can be classified as one of three possible genotypes: s/s, s/l, or l/l. The short allele has been most widely studied in relation to the risk of developing anxiety and mood disorders, possibly mediated by the personality trait of neuroticism (Caspi et al., 2003; Lesch et al., 1996; Sen et al., 2004). The polymorphism has clear functional significance, as carriers of the less-efficient short allele have inferior serotonin neurotransmission in terms of antidepressant response rates (Smeraldi et al., 1998) and neuroendocrine responses to serotonin challenge (Whale et al., 2000). Several studies have explored the relationship between this polymorphism and impulsivity. This has been driven in part by the hypothesis that behavioural impulsivity is associated with reduced serotonin function (Soubrie, 1986), as evidenced by animal models of impulsivity as well as observations of reduced 5-HT metabolites in the cerebrospinal fluid of violent offenders (Linnoila et al., 1983) and suicide victims (Asberg et al., 1976). PET radioligand studies (e.g. with 3H-citalopram or 11C-DASB) have also reported lower SERT density in SUD groups, particularly in alcohol-dependency

(Heinz et al., 1998; Storvik et al., 2006) and Ecstasy users (McCann et al., 2005).

The 5-HTTLPR polymorphism has been widely studied in relation to SUDs but the findings are inconsistent. A number of studies have shown increased frequency of the short allele in SUD groups; for example, in alcohol-dependency (Lichtermann et al., 2000; Sander et al., 1997) and heroin addiction (Gerra et al., 2004b). However, a large study also failed to find any relation in alcoholism (Edenberg et al., 1998), and some features of alcoholism are more associated with the long allele, including early age of onset (Ishiguro et al., 1999) and low response to alcohol administration (Schuckit et al., 1999). In the study of heroin addicts ( $n = 101$ ) by Gerra et al. (2004b), subjects who were homozygous for the short allele (s/s) had higher aggression scores on the Buss–Durkee Hostility Scale than the long–long heroin users. However, a similar study in African-American cocaine-dependent subjects ( $n = 105$ ) did not report a similar genetic association (Patkar et al., 2002). Whilst impulsivity and aggression scores (BIS and Buss–Durkee Hostility Scale) were elevated in the cocaine users, these ratings did not vary significantly with genotype, and there was no difference in genotypic frequencies between the drug users and controls. One of the few studies to examine genetic associations with impulsivity in high-risk children with paternal alcoholism ( $n = 64$ ), higher ratings of behavioural disinhibition on an aggression scale were reported in the long–long genotype subjects compared to the short carrier subjects (Twitchell et al., 2001).

Recent studies have also begun to examine this polymorphism in relation to neurocognitive measures of impulsivity. Clark, L., et al. (2005) examined the effects of serotonin depletion (dietary tryptophan depletion) on the Stop Signal test in a group of healthy volunteers stratified by 5-HTTLPR genotype. There was no main effect of either tryptophan depletion or 5-HTTLPR genotype, nor any gene by depletion interaction effect on the Stop Signal task. An unusual study in recreational Ecstasy users ( $n = 66$ ) and healthy controls indicated that Ecstasy use may uncover impulsive tendencies as a function of 5-HTTLPR genotype. This study reported increased Eysenck IVE impulsivity in the Ecstasy users, which did not vary with 5-HTTLPR genotype. However, the study also employed the Affective Go–No Go task, and found that Ecstasy users who possessed the ss or sl genotype were unable to reduce their impulsive (commission) errors when the go/no-go relationships were repeated (Roiser et al., 2005).

#### 5.4. Monoamine oxidase A polymorphisms

The monoamine oxidase A (MAO-A) polymorphism has also received particular attention. Whilst monoamine oxidase is involved in the degradation of all monoamines, the MAO-A isoform has particularly high affinity for serotonin. A genetic mutation affecting the MAO-A gene

can give rise to Brunner Syndrome, an X-linked condition associated with mental retardation but also with extreme violence and aggression (Brunner et al., 1993). The gene presents with a number of polymorphisms, including a 30-base pair variable nucleotide tandem repeat (VNTR) in the promoter region, which has been widely studied in relation to psychiatric disorders and impulsivity. The short (3) repeat allele is associated with lower activity of the MAO-A enzyme than the longer (3.5 and 4) repeat alleles. The short repeat allele is more prevalent in alcohol-dependency (Contini et al., 2006; Guindalini et al., 2005; Parsian et al., 2003; Saito et al., 2002) and other SUDs (Vanyukov et al., 2004). As with Brunner syndrome, these effects are predominantly found in male subjects, and may be mediated in interaction with childhood adverse experience (Caspi et al., 2002; Huang et al., 2004). However, in non-SUD populations, increased impulsivity is predominantly associated with the longer-repeat alleles. Manuck et al. (2000) found that long-repeat subjects scored significantly higher on a composite measure of aggression and impulsivity based on the BIS and two widely used aggression questionnaires. A recent functional imaging study measured brain responses during the Go–No Go task in a small group of healthy volunteers stratified by MAO-A genotype (Passamonti et al., 2006). The rate of commission errors and the BIS showed non-significant effects in the same direction as Manuck et al. and the imaging analysis showed significantly greater activity of frontal regions (right ventrolateral prefrontal cortex) associated with inhibitory control in the long-repeat subjects. Frontal activation was significantly predicted by Barratt score in the long-repeat subjects. The long-repeat allele has also been associated with diminished sustained attention in children with ADHD (Manor et al., 2002), plausibly as a result of increased impulsivity. In summary, there is accumulating evidence for a relationship between SUD, MAO-A genotype, and both state and trait measures of impulsivity. It is as yet unclear how the large number of alleles arising from this polymorphism relates to the functional status of brain monoamine systems. Deficient cognition may arise from excess monoamine levels as well as insufficient transmission, and this may explain the apparently conflicting effects between MAO-A studies in SUD groups and healthy populations.

#### 5.5. Other serotonin polymorphisms

Associations have been reported between measures of impulsivity and other polymorphisms putatively affecting serotonin function. There has been some interest in two polymorphisms in the promoter region of the 5-HT2A gene. Preuss et al. (2001) reported an increased prevalence of the A-1498G A alleles in alcohol-dependent patients, who were categorised as high impulsive by a median split on the BIS. This genotype was also shown to make more commission errors on a Go–No Go task in a reasonably small group of Japanese healthy volunteers (Nomura et al.,

2006). Another SNP on the same gene (the T102C polymorphism) was also related to increased commission errors on a variant of the CPT in community-recruited volunteers (Bjork et al., 2002). In a large student sample, poor response inhibition on the Stop Signal task was linked to T/T genotype of the tryptophan hydroxylase-2 polymorphism (Stoltenberg et al., 2006), although this was only present in male volunteers and other aspects of task performance (e.g. Go reaction time) were not adequately reported. In these studies, the functional significance of the polymorphism in the human brain is unclear, as is the frequency in SUD groups.

### 5.6. Summary

Studies of genetic associations with impulsivity are currently at an early stage, and the preliminary observations reviewed above are summarised in Table 3. Whilst there are a number of interesting leads, it is difficult to draw consensus across studies and there are a number of confusing—and possibly paradoxical—results. It should also be noted that the large majority of studies have been undertaken in groups of SUD patients or in the healthy population, and both approaches are problematic. Studies in the healthy population, particularly in student samples, may be unable to capture the high levels of impulsive behaviour associated with clinical disorders, and it is likely that these designs will require very large sample sizes to detect robust effects. Genetic associations with impulsivity in SUD subjects cannot conclusively implicate impulsivity as a vulnerability marker, as the polymorphism may be alternatively predispose patients to more severe substance abuse (which can be statistically covaried for), or to the

harmful effects of substance administration (which cannot be controlled for). The optimal study design is to examine genetic associations with impulsivity in high-risk and low-risk subjects, in order to demonstrate that (i) impulsive variable is increased in high-risk subjects relative to low-risk subjects, prior to onset of drug-taking, and (ii) that this index varies as a function of genotype, either in the high-risk group alone, or in the collapsed group of high-risk and low-risk subjects. There is currently a paucity of studies examining genetic associations with impulsivity in high-risk subjects (for exceptions, see Berman and Noble, 1995; Conner et al., 2005; Twitchell et al., 2001). A complementary approach is to collect genetic longitudinal data during childhood, and to analyse the relative contributions of genotype and impulsivity in relation to the trajectory from initial drug taking through to dependence. However, here again is difficult to disentangle the relative influence of genes on two temporally closed phenomena: predisposition to first drug use vs. predisposition to the harmful effects of drug intake (de la Torre and Farre, 2004). Other methodological concerns in this area include (i) the frequent failure to replicate basic association studies that link a polymorphism to psychiatric diagnoses, (ii) many studies are underpowered and report effects that were not predicted *a priori*, (iii) many of the widely studied polymorphisms lack evidence for functional significance on the system of interest, and even when data exist for functional significance, the consequences of those effects in the adult human brain may be far from clear.

The DRD2 polymorphism is arguably most clearly associated with addiction vulnerability, with the A1 allele at increased prevalence across multiple substances of abuse as well as behavioural addictions like PG. Whilst there is

Table 3

Summary of genetic association studies linking polymorphisms affecting monoamine transmission with self-report and neurocognitive measures of impulsivity

Genotype	Risk allele for addiction	Functional significance	Link to impulsivity
DRD2 (TaqI)	A1 allele	Decreased D2 receptor binding	<i>Lower</i> BIS scores <i>Impaired</i> JLOT, SST, CPT, DDT
DRD3 (Ser9Gly)	Ser/Ser or Gly/Gly homozygosity	–	<i>Lower</i> BIS/Novelty Seeking scores
DRD4	7 repeat	Blunted dopamine response	Increased Novelty Seeking Impaired SST Interaction with DRD2 to impair DDT
5-HTLPR	Short allele	Decreased serotonin function	Higher BDHS <i>Lower</i> disinhibition scores
MAO-A	Short (3) allele	Lower MAO enzyme activity	Higher BDHS and Barratt scores <i>Higher</i> GNG brain activity <i>Superior</i> CPT performance
5-HT2A	A1498G: A allele	–	Increased BIS scores Increased GNG commission errors Increased CPT commission errors
	T102C: C allele		

Italicised findings refer to higher impulsivity scores in the low-risk genotype group (i.e. opposite to hypothesised direction).

BIS: Barratt Impulsivity Scale (Limosin et al., 2003, 2005; Manuck et al., 2000; Preuss et al., 2001); JLOT: Judgment of Line Orientation Test (Berman & Noble 1995); SST: Stop Signal Test (Rodriguez-Jimenez et al., 2006a, b; Congdon et al., 2008); CPT: Continuous Performance Test (Rodriguez-Jimenez et al., 2006a, b; Bjork et al., 2002; Manor et al., 2002); DDT: Delay Discounting Test (Eisenberg et al., 2007); BDHS: Buss-Durkee Hostility Scale (Gerra et al., 2004b); GNG: Go-No Go test (Nomura et al., 2006; Passamonti et al., 2006).

little evidence that this polymorphism is associated with questionnaire measures of impulsivity, there is accumulating data supporting a relationship with neurocognitive measures including response inhibition and delay-discounting, as well as two studies in high-risk subjects (Berman and Noble, 1995; Conner et al., 2005). The genotype that has the clearest effect on impulsivity in healthy subjects (the MAO-A long-repeat allele) is paradoxically at *reduced* prevalence in SUD groups. The polymorphisms with the greatest functional impact on monoamine transmission (5-HTTLPR and COMT) are not clearly linked to prevalence of addictions, or to any measures of impulsivity. Other polymorphisms that are very interesting in the context of addiction (e.g. DRD3, DRD4) lack clear evidence for functional significance.

## 6. Conclusion

The diverse lines of evidence reviewed in the preceding sections supports our overall thesis that impulsive behaviour exists in SUD populations prior to the onset of drug taking, and is associated with the vulnerability to drug use and dependence. The case-control studies reviewed in Section 2 convincingly demonstrate that increased impulsivity is a robust phenomenon across SUD groups dependent upon a range of different substances including stimulants (cocaine or amphetamines), opiates, alcohol or MDMA (Ecstasy). Moreover, there is little evidence to indicate disproportionate effects associated with any specific substances on impulsivity measures. These case-control studies in current or abstinent drug users are insufficient to address the aetiology of impulsivity in SUDs, as there is clear evidence that the long-term self-administration of these substances can affect brain function and structure in its own right, and thereby mask any pre-existing markers. The putative presence of both pre-existing vulnerability markers and active harmful effects of drug use in SUD groups raises the need for novel “models of vulnerability” to elucidate the role of impulsivity in SUDs. In this review, we have addressed three approaches that have been proposed to identify vulnerability markers. The high-risk research (reviewed in Section 3) has provided persuasive evidence of increased impulsivity in high-risk children of SUD parents prior to onset of drug use. These findings are generally supported by other high-risk approaches, namely the study of adolescent groups compared to young adults and the study of children and adolescents with externalising disorders including ADHD and conduct disorder. Critically, behavioural disinhibition in high-risk populations is a strong and reliable predictor of subsequent SUDs in longitudinal designs, predicting the recreational use of several substances and substance-related problems. One caveat of this approach is that impulsivity is often not a specific predictor of SUDs, but a shared risk factor for multiple clinical manifestations and disorders. Thus, more research using neuropsychological, electrophysiological and imaging tools

is needed to gain insights into facets of impulsivity that predate SUDs.

The evidence for pre-existing impulsivity is further supported by studies of gambling behaviour, based upon the premise that there are overlapping aetiological mechanisms in problem (or pathological) gambling and SUDs. Critically, in PG without comorbid drug use, the lack of exogenous drug administration may allow researchers to exclude the potential harmful effects, and isolate the vulnerability markers. The available research in PG groups shows convincing evidence of impulsivity on both questionnaire self-report measures and a variety of neurocognitive tasks of inhibitory control. However, the assumptions made in this approach are constrained by a number of caveats, including the frequent comorbidity of PG with SUD, the familiarity of PG subjects with complex tests requiring monetary reward processing and risk assessment, and the possibility that gambling experiences may cause gradual neuroadaptive changes in the brain reward system, which may actually alter the premorbid status of these individuals. Nonetheless, these caveats are circumvented in a limited number of prospective studies looking at personality and neurocognitive predictors of problem gambling behaviour, which are highly supportive of the vulnerability model (Slutske et al., 2005; Vitaro et al., 1999).

In the third approach, a rapidly developing area of pharmacogenetic research has begun to investigate the relationship between putative genetic risk factors for SUDs and behavioural measures of impulsivity. It is likely this area will expand considerably over future years, and the next generation of studies are presented with a number of challenges. First, there is a clear need for larger sample sizes in order to limit the widespread failures of replication that plague the current literature. Second, further pre-clinical evidence is required in order to demonstrate whether many of the widely studied polymorphisms in the field of addiction research actually have a significant functional impact on the neurochemical systems of interest. Without detailed understanding of how these genetic variants affect neurotransmitter function in the adolescent and adult brain, there are substantial ‘missing links’ in our aetiological models of SUD development. Third, the strongest design in this area entails the examination of genetic influences on impulsivity in high-risk populations prior to the onset of drug taking. Preliminary evidence suggests the altered prevalence of DRD2 and MAO-A polymorphisms in SUD populations may be mediated by premorbid elevations in impulsivity associated with the ‘at-risk’ gene variants.

These data suggest that the construct of impulsivity may meet the core criteria proposed for an endophenotype variable (Gottesman and Gould, 2003). Certainly, measures of impulsivity are elevated in SUD populations (Section 2), and this impulsivity can be detected despite fluctuations in clinical state, for example, in long-term abstinence. In addition, impulsivity is elevated in

individuals at high risk for SUD, like the children of alcoholic parents (Section 3). At the present time, the heritability of impulsivity has received less attention, but there is evidence for moderate heritability (in excess of 50%) for questionnaire measures including Eysenck impulsivity and Sensation Seeking (Eysenck, 1993). Thus, impulsivity may represent an intermediary between risk genotypes for addiction, and the complex psychiatric description of these disorders. Future research will be required to identify the precise mapping between genetic risk factors and dimensions of the impulsivity construct.

Impulsivity itself is a highly complex behavioural phenotype that appears to be multifactorial in nature (e.g. Evenden, 1999b). The use of self-report questionnaires like the BIS and the SSS remains the most common method of impulsivity assessment. Questionnaire ratings are assumed to reflect enduring ‘trait’ dispositions that were present prior to drug initiation, although this assumption is rarely tested, and recent prospective data indicate increases in self-report ratings of impulsivity after initiation of Ecstasy use (de Win et al., 2006). Neurocognitive measures of impulsivity are now used increasingly in both cross-sectional and longitudinal designs, and these tests provide a rigorous ‘state’ assessment of subjects’ capacity to control impulsive responses. Functional imaging and human lesion studies can be used to link these measures more readily to underlying neurobiological mechanisms. A number of tests are widely used in this area, although the measures can be classified into three basic paradigms: response inhibition, delay-discounting, and cognitive impulsivity (including reflection impulsivity and tests of risky decision-making). Whilst there is emerging evidence that these components are dissociable at the neural level (e.g. response inhibition versus delay-discounting), it is an unresolved issue whether SUDs and SUD risk are specifically associated with certain facets of impulsivity. Current data suggest, perhaps surprisingly, that SUD groups show consistent elevations in impulsivity and deficits in inhibitory control across the various measures that have been applied. In pathological gamblers, for example, there is robust evidence for increases in questionnaire trait impulsivity, poor response inhibition, steeper rates of delay-discounting, and increases in risky decision-making. Nonetheless, these different measures of impulsivity frequently do not correlate (or correlate only weakly) with another, even in large samples (e.g. Lijffijt et al., 2004). A description of the relationships between these operational models of impulsivity remains a fundamental task for research in this area. This task will also clarify the neurobiological underpinnings of the different constructs of impulsivity, to make headway in the search of neurocognitive factors conferring risk to SUD.

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