# Impulsivity as a vulnerability factor for poor addiction treatment outcomes:

## A review of neurocognitive findings among individuals with substance use disorders.

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**Abstract**

With the current review, we explore the hypothesis that individual differences in neurocognitive aspects of impulsivity (i.e., cognitive and motor disinhibition, delay discounting and impulsive decision-making) among individuals with a substance use disorder are linked to unfavorable addiction treatment outcomes, including high drop-out rates and difficulties in achieving and maintaining abstinence. A systematic review of the literature was carried out using PubMed, PsycINFO and Web of Knowledge searches. Twenty-five unique empirical papers were identified and findings were considered in relation to the different impulsivity dimensions. Although conceptual/methodological heterogeneity and lack of replication are key limitations of studies in this area, findings speak for a prominent role of cognitive disinhibition, delay discounting and impulsive decision-making in the ability to successfully achieve and maintain abstinence during and following addiction treatment. In contrast, indices of motor disinhibition appear to be unrelated to abstinence levels. Whereas the relationship between impulsivity and treatment retention needs to be examined more extensively, preliminary evidence suggests that impulsive/risky decision-making is unrelated to premature treatment drop-out among individuals with a substance use disorder. The reviewed findings are discussed in terms of their clinical implications.

*Keywords*: Impulsivity; Decision-making; Inhibitory control; Delay discounting; Treatment outcomes.

## 1. Introduction

Akin to memory impairment in Alzheimer or motor control in Parkinson disease, impulsivity lies at the core of the pathogenesis and pathophysiology of substance use disorders (SUDs) (Goldstein & Volkow, 2002; Verdejo-Garcia, Lawrence, & Clark, 2008). Contemporary neurocognitive models posit that both impulsivity and addiction result from an imbalance between the influence of two competing neural systems: an evolutionarily older bottom-up system and a more recently developed top-down system (Bechara, 2005; Bickel & Yi, 2008; Heatherton & Wagner, 2011). The bottom-up system, also referred to as the impulsive or reactive system (Bechara, 2005; Bickel & Yi, 2008), involves subcortical brain areas, including the amygdala and reward-sensitive dopamine-rich areas in the midbrain (Heatherton & Wagner, 2011). This system tends to promote rewarding and habitual behaviors and responds to immediately available (associative) cues, without consideration of long-term consequences. The top-down system by contrast, also referred to as the executive or reflective system (Bechara, 2005; Bickel & Yi, 2008), consists of the prefrontal cortices (particularly the lateral prefrontal cortex), which have been implicated in a wide range of executive and self-control functions (Cohen & Lieberman, 2010; Rubia, Smith, Brammer, & Taylor, 2003). These functions include the ability to plan, attention, working memory, and cognitive control and enable the individual to resist short-term temptations in favor of longer-term goals or benefits (Braver & Bongiolatti, 2002).

When functioning properly, the top-down system is able to override bottom-up influences (e.g., cravings, immediate temptations) through a variety of mechanisms, such as deliberately suppressing undesired thoughts or prepotent action tendencies (response inhibition) or by choosing according to long-term prospects of available options, instead of selecting immediately rewarding outcomes (advantageous decision-making) (Bechara & Van Der Linden, 2005; McClure, Laibson, Loewenstein, & Cohen, 2004; Volkow et al., 2010). In addiction however, the impulsive bottom-up system is believed to overwhelm the top-down executive system (Bechara, 2005; Bickel & Yi, 2008), with corresponding failures in the ability to suppress inappropriate actions or cognitions (impulsive action) or a preference for immediate rewards while disregarding long-term (negative) consequences (impulsive choice) (Winstanley, Eagle, & Robbins, 2006). Both impulsive action and impulsive choice have key complementary roles in different stages of the addiction process, as acknowledged by both animal and human neuroscience studies (Bechara & Van Der Linden, 2005; Diergaarde et al., 2008; Verdejo-Garcia et al., 2008).

Growing recognition of the centrality of neurocognitive impairments related to impulsivity in addiction should bring with it more attempts to examine the effects of these deficits on treatment outcomes, as this may result in an increased emphasis on top-down and bottom-up rehabilitation (Bates, Buckman, & Nguyen, 2013; Garavan & Weierstall, 2012). Indeed, different from the chronicity of memory loss in Alzheimer or motor dysfunction in Parkinson disease, aspects of impulsive action and impulsive choice are amenable to treatment and may – at least partially – recover by targeting top-down and bottom-up processes (Alfonso, Caracuel, Delgado-Pastor, & Verdejo-García, 2011; Bickel, Yi, Landes, Hill, & Baxter, 2011). In fact, heightened prefrontally-mediated cognitive control over subcortical bottom-up processes is increasingly being recognized as a key characteristic of successful abstinence (Garavan & Weierstall, 2012). Corroborating this notion, addiction treatment services with documented efficacy routinely employ therapeutic paradigms that (indirectly) target aspects of prefrontal cortical and/or bottom-up functioning. Contingency Management (CM) for example, might decrease drug or alcohol use by working via impulsive bottom-up brain regions, whereas cognitive behavioral therapy (CBT) may operate by strengthening top-down brain functions (Bickel et al., 2007; DeVito et al., 2012; Potenza, Sofuoglu, Carroll, & Rounsaville, 2011).

Whereas an emphasis on top-down and bottom-up approaches might be specifically indicated in addicted individuals with higher levels of impulsive action or choice, many existing empirically-supported treatment programs (e.g., CBT, relapse prevention) assume a certain level of cognitive ability needed to acquire skills or to successfully engage in treatment. Indeed, many programs not only target but also rely (heavily) on executive top-down processes (i.e., the ability to plan, exert cognitive control, postpone immediate gratification or consider the long-term consequences of available options), which may be particularly challenging for substance abusers with higher levels of impulsive action and choice. With the current review, we aim to examine whether individual differences in aspects of impulsive action and choice at treatment onset (negatively) affect the ability to benefit from addiction treatment. In order to frame the literature, we first discuss the main dimensions and measures of impulsivity as described in neurocognitive studies, followed by an intentionally brief overview of the addiction treatment outcome indicators selected for this review.

## 1.1. Impulsivity

### 1.1.1. General introduction

To date, there is a broad agreement that impulsivity is a multifaceted construct comprised of several related components which are influenced by different neurobiological mechanisms (Reynolds, Ortengren, Richards, & De Wit, 2006; Whiteside & Lynam, 2001). Historically, impulsivity has been studied by different research disciplines, with personality researchers viewing facets of impulsivity as *traits* that are fairly stable over time and evident across a range of situations, whereas neurocognitive researchers approach facets of impulsivity as transitory *states*, sensitive to environmental influences (Verdejo-Garcia et al., 2008). In accordance with these different conceptualizations of impulsivity, different measures have been developed to assess trait or state dimensions of impulsive behavior. As a personality trait, impulsivity is typically measured using self-report questionnaires, which assess the subjective views on impulsive behavior, including the Barratt Impulsiveness Scale (BIS-11; Patton, Stanford, & Barratt, 1995), the Temperament and Character Inventory (TCI; Cloninger, Przybeck, Svrakic, & Wetzel, 1994) and the Zuckerman's Sensation Seeking Scale (Zuckerman, Eysenck, & Eysenck, 1978). These instruments include questions that cover broad periods of time, making them appropriate for assessing stable or trait aspects of impulsivity. As a neurocognitive state by contrast, impulsivity is typically measured using neurocognitive tasks, which are considered to be a more objective method of measuring impulsivity (Verdejo-Garcia et al., 2008). Indeed, these measures do not require introspection or self-assessment of behavior but instead, examine spontaneous reactions to (with some notable exceptions) motivationally relevant stimuli (e.g., drug-related cues, monetary rewards). As proximate measures of the neurobiology underlying impulsive behavior, neurocognitive instruments serve as indicators of endophenotypes, which may represent particularly attractive therapeutic targets (Gottesman & Gould, 2003). Although a number of studies suggest some degree of correspondence between self-report and neurocognitive tasks of impulsivity (Christiansen, Cole, Goudie, & Field, 2012), there are more data to suggest that these disparate measures should not be referred to under the same rubric (Aichert et al., 2012; Christiansen et al., 2012; Cyders & Coskunpinar, 2011; Dom, De Wilde, Hulstijn, & Sabbe, 2007; Meda et al., 2009; Reynolds et al., 2006). Indeed, the small magnitude of the observed effect sizes indicates that largely, there is more variability in what is being assessed via self-report and neurocognitive tasks of impulsivity than there is overlapping content domain (Cyders & Coskunpinar, 2011).

### 1.1.2. Neurocognitive aspects of impulsivity

Historically, impulsivity has been predominantly approached from a personality perspective. Indeed, aspects of impulsivity are evident in almost every major personality model and include traits such as

venturesomeness, sensation and novelty seeking (Cloninger, Svrakic, & Przybeck, 1993; Eysenck & Eysenck, 1985; Tellegen, 1982). Elevated impulsivity scores on personality-based self-report measures have consistently been found across various groups of alcohol and drug dependent subjects (Coffey, Gudleski, Saladin, & Brady, 2003; Kirby, Petry, & Bickel, 1999; Mitchell, Fields, D'Esposito, & Boettiger, 2005; Moeller et al., 2004).

During the past decades, there has been a growing scientific interest for impulsivity within neuropsychological and neurocognitive research. At a neuropsychological level, impulsivity is thought to arise from an impairment in cognitive control or an imbalance between the strength of the "top-down" cognitive control system provided by the frontal cortices and the influence of "bottom-up" drives or habits triggered by striatal and limbic regions (Bechara, 2005). Consistent with findings stemming from personality research, neuropsychological studies suggest that impulsivity is a multifaceted construct comprised of several components which are influenced by different neurobiological mechanisms (Reynolds et al., 2006). During the past decade, numerous attempts have been made to clarify the factorial nature of neurocognitive aspects/measures of impulsivity (Christiansen et al., 2012; Dom et al., 2007; Reynolds, et al., 2006). Based on the results of these studies, most current neuropsychological models agree that on a conceptual and experimental level, impulsivity can be divided into impulsive action (being characterized by deficits in response inhibition) and impulsive choice (being associated with difficulties to curb the "lure" of reward in order to optimize decision-making processes) (Dalley, Everitt, & Robbins, 2011; Lane, Cherek, Rhodes, & Pietras, 2003; Reynolds et al., 2006). These constructs are typically measured using (computerized) neurocognitive tasks. An overview illustrating the distinct neurocognitive aspects of impulsivity and some of the neurocognitive tasks that can be used to measure these is provided in Fig. 1.

**Impulsive action** or response disinhibition may involve different mechanisms, including compromised cognitive (interference control) and motor inhibition (Kertzman et al., 2006; Nigg, 2000). *Interference control* represents a cognitive form of inhibition in that it involves the suppression of competing, distracting information in order to maintain response performance (Nigg, 2000). Interference control is commonly measured with tasks that elicit conflict between an automatic response and a more controlled response, such as the Stroop Color Word Test (Stroop, 1935). In the Stroop test, interference is expressed as the difference in reaction times between incongruent and congruent trials. Impulsive individuals may be impaired in their ability to inhibit interference and accordingly, show greater Stroop

interference effects (Kertzman et al., 2006). In “drug versions” of the Stroop test, color words are replaced with words that are relevant to the respective substance of abuse (e.g., “needle” for heroin dependent individuals or “beer” for alcoholics). Longer interference scores on this test are induced by the drug-related meaning of words, which capture attention more automatically due to motivational significance. This preoccupation with drug-associated words has been proposed to reflect a form of attentional bias that underlies relapse (Streeter et al., 2008). It should be noted however, that alternative explanations have been proposed to account for Stroop effects on drug-versions of the task (Christiansen & Field, 2013; Waters, Sayette, Franken, & Schwartz, 2005). *Motor inhibition* on the other hand, is measured with tasks that assess an individual’s ability to inhibit in a controlled way the production of an initial prepotent or ongoing response, such as the Stop Signal Task (SST; Logan, Cowan, & Davis, 1984), the Go/No-Go task (Donders, 1969; see also Luce, 1986), the Continuous Performance Test (CPT; Mackworth & Taylor, 1963) and the Immediate and Delayed Memory Task (IMT/DMT; Dougherty, Marsh, & Mathias, 2002). Although in all of these paradigms, the subject is required to withhold from making a prepotent motor response, there are some subtle, yet structurally significant differences between them. In the Go/No-Go task, a not-yet-initiated action has to be restrained, whereas in the SST, an already-initiated response has to be cancelled (Schachar, Logan, Robaey, Chen, Ickowicz, & Barr, 2007). Accordingly, the Go/No-Go task has been argued to index action restraint (i.e., inhibition before the response has been started), whereas the SST is believed to measure action cancellation (i.e., inhibition of an already-initiated behavior at later stages of motor output) (Schachar et al., 2007). Further supporting this distinction, both types of inhibition have been found to be mediated by subtly dissociable fronto-parietal cortical networks and can be dissociated in terms of the neurochemistry of their regulation (Dambacher, Sack, Lobbestael, Arntz, Brugman & Schuhmann, 2013; Eagle, Bari, & Robbins, 2008; Rubia et al., 2001).

Evidence from various sources supports a close relationship between motor inhibition and the ability to resist interference from distracting (cognitive and affective) information (Friedman & Miyake, 2004; Verbruggen, Liefooghe, & Vandierendonck, 2005). In the case of addiction, it has been suggested that addicted individuals with impairments in motor inhibition may be less able to engage strategic processes to override the attentional bias towards drug-related stimuli (Field & Cox, 2008; Liu, Lane, Schmitz, Waters, Cunningham, & Moeller, 2011). Whereas preliminary evidence supports a positive correlation between attentional bias and motor disinhibition in drug dependent individuals (Liu et al., 2011), drug-

related attentional biases cannot merely be seen as a function of poor inhibitory control. Therefore, further research is needed to delineate the precise nature of this relationship. Additional support for a close relationship between motor and cognitive inhibition comes from neuroimaging studies pointing to common areas of neural activation, although regional functional specialization exists for suppression of motor versus cognitive and affective responses (Aron & Poldrack, 2005; Blasi et al., 2006).

**Impulsive choice** is measured with tasks that assess decisional patterns when individuals are confronted with rewards that differ in their magnitude and the time to be obtained, or with options that differ in their probability to yield rewarding or punishing outcomes (Bechara, Damasio, Damasio, & Anderson, 1994; Paulus, Rogalsky, Simmons, Feinstein, & Stein, 2003). To provide a clearer map of the underlying processes involved, Verdejo-García and colleagues (2008) subdivide this dimension of impulsive choice into two separate components, labeled delay discounting and impulsive decision-making. *Delay discounting* is typically indexed by an individual's preference for smaller immediate rewards relative to larger delayed rewards in delay-discounting paradigms, including the Delay Discounting Task (DDT; Richards, Zhang, Mitchell, & De Wit, 1999), the Kirby Delay Discounting Measure (DDM; Kirby et al., 1999) and the Experiential Discounting Task (EDT; Reynolds & Schiffbauer, 2004). *Impulsive decision-making* on the other hand, would be indexed by tasks in which the individual can choose between a conservative option and a more risky option that offers a superficially attractive gain (Bechara, 2003), including the Iowa Gambling Task (IGT; Bechara et al., 1994), the Cambridge Gamble Task (CGT; Rogers et al., 1999) and the Balloon Analogue Risk Task (BART; Lejeuz et al., 2002). On decision-making tasks, impulsivity can be expressed as a tendency to select the more risky options (e.g., choosing cards from the bad decks or increased betting), with choices being driven more by immediate reward than delayed punishment. However, it should be noted that different cognitive and neural mechanisms may underlie this choice pattern, including risk preference, a myopia for the future and deficits in the ability to withhold responding from previously reward-paired stimuli (Dunn, Dalgleish, & Lawrence, 2006; Fellows & Farah, 2005). In contrast to response inhibition, which has been considered to represent a "cold" cognitive system largely dependent on lateral prefrontal and dorsal striatal functioning, impulsive decision-making and delay discounting can be viewed as feedback-sensitive "hot" affective systems which depend on medial prefrontal and ventral striatal functioning (Aron et al., 2007; Hare, O'Doherty, Camerer, Schultz, & Rangel, 2008).

**Insert Figure 1.**

1.2. Treatment outcome indicators

Two indicators that are frequently used for evaluating addiction treatment outcomes are: (1) the length of time spent in and completion of the treatment program (retention and drop-out), and more directly, (2) the level of alcohol and/or drug use during and after treatment (abstinence vs. relapse). In the past decade, variables associated with *treatment retention* (e.g., drop-out, completion) have become increasingly important, as one of the most consistent findings in addiction research is the positive association between the length of time spent in treatment and post-treatment outcomes (Laudet, Stanick, & Sands, 2009; Simpson, 2004; Vanderplasschen et al., 2013; Zhang, Friedmann, & Gerstein, 2003). Conversely, premature treatment drop-out has been found to predict relapse and increased legal and employment difficulties (Gossop, Marsden, Stewart, & Rolfe, 1999; Lang & Belenko, 2000; Siegal, Li, & Rapp, 2002). Importantly, this relationship between treatment retention and post-treatment outcomes has been found across all the major types of both residential and outpatient programs (Simpson, 2004).

Traditionally, the level of alcohol/drug use and *relapse* following treatment have been the most commonly reported outcome indicators in addiction treatment studies (McLellan, McKay, Forman, Cacciola, & Kemp, 2005). However, the degree of alcohol/drug use during treatment has also been recognized as an important outcome indicator, as it is significantly related to post-treatment *abstinence* (Higgins, Badger, & Budney, 2000). In cocaine users for example, the ability to achieve a period of continuous abstinence during treatment is associated with greater odds of being abstinent at 12-month post-treatment follow-up (Higgins et al., 2000). Further, the time or latency to relapse following periods of abstinence is increasingly being recognized as a potentially relevant outcome indicator, as it has been consistently implicated as a key variable in accounting for long-term outcomes (Mueller et al., 2009; Westman, Behm, Simel, & Rose, 1997). For example, early relapses in nicotine dependent individuals are highly correlated with the return to regular smoking (Westman et al., 1997).

**The current review**

During the past decades, a wide range of baseline client characteristics have been examined and identified as potentially relevant to addiction treatment outcomes, including socio-demographic (e.g., ethnicity, gender), drug-related (e.g., drug use severity, poly-drug use) and psychosocial (e.g., personality, stress, coping, self-efficacy) factors (Frawley & Smith, 1992; Hawkins, Baer, & Kivlahan, 2008; King & Canada, 2004; Laudet et al., 2009; McMahon, 2001). Recently however, growing

recognition of the centrality of neurocognitive impairments in addiction has led to a new generation of research in which measures of neurocognitive functioning are being applied to the task of predicting treatment outcomes (Passetti, Clark, Mehta, Joyce, & King, 2008). As some of the neurocognitive deficits associated with addiction have been proven to be malleable (Alfonso et al., 2011; Bickel et al., 2011), these studies have the potential to identify important targets for manipulation.

As recently suggested by Bates and colleagues (2013), neurocognitive deficits related to impulsivity (e.g., lack of inhibitory control and impulsive decision-making) may be more directly related to addiction treatment outcomes as compared to classic aspects of neurocognitive functioning (e.g., working memory, attention). However, whereas previous review articles have focused on the relationship between neurocognitive impairment, cognitive rehabilitation and addiction treatment outcomes (Bates et al., 2013) and on the neurobiology of cognitive control/reward processes and their role in recovery (Garavan & Weierstall, 2012), none of these studies were systematic reviews nor focused specifically on the role of impulsivity.

Given the key role of impulsivity in the pathophysiology of SUDs and the malleability of impulsive action and choice in addiction (Alfonso et al., 2011; Bickel et al., 2011), this manuscript systematically reviews all published articles examining the relationship between neurocognitive aspects of impulsivity and addiction treatment outcomes in individuals with a SUD.

## 2. Methods

### 2.1. Search Strategy

A literature search was performed in the databases PubMed, PsycINFO and Web of Knowledge, based on publication title, abstract or keywords. Search terms related to substance use disorders (e.g., addict* or drug use or substance or substance abus* or alcohol* or smokers or dependen* or users) were combined with terms related to impulsivity (impulsiv* or inhibit* or interference or reward or delay discounting or decision-making or attentional bias or exec* function* or exec* control or cognitive or neurocognit* or neuropsychol*) and with search terms referring to treatment outcomes (outcome or abstinence or relapse or cessation or retention or attrition or drop-out or complet* or success). The databases were searched for studies published between January 2000 and May 2013, encompassing the period during which neuroscientific models began to recognize the crucial role of impulsivity in the pathophysiology of addiction (Goldstein & Volkow, 2002; Jentsch & Taylor, 1999). In order to select

methodologically sound studies, only manuscripts published in peer-reviewed English language journals were considered for inclusion. Cross references of studies and review articles identified during the search process were also checked to detect relevant additional papers.

### 2.2. Study selection

The combination of the afore-mentioned search terms led to the identification of 372 articles. To be included for this review, studies had to examine at least one neurocognitive measure of impulsive action or impulsive choice (see section 1.1. and Fig.1. for the domains of interest). In addition, the association between impulsivity and treatment outcomes had to be studied longitudinally. The search was further limited to studies among human subjects (i.e., adolescent and adult populations). After inspection of titles and abstracts, 287 studies were immediately excluded because they did not meet the above-mentioned criteria. The most common reason for exclusion was the absence of a neurocognitive measure of impulsivity. The remaining 85 articles were inspected by two independent reviewers. Studies were retained for the present review, if they met the following cumulative inclusion criteria:

a. study participants underwent some form of in- or outpatient substance abuse treatment;
b. an impulsivity assessment was conducted before, at the start of or shortly following treatment entry;
c. at least one outcome indicator was reported that was related to treatment retention or drop-out or to abstinence or relapse during or after the treatment episode.

In case it was unclear whether a study met all eligibility criteria, the paper was forwarded for assessment to at least one other study author. In total, twenty-five studies fulfilled the criteria for inclusion.

### 2.3. Data-extraction, analysis and presentation

For each study, relevant data were extracted by the first author using a coding form, which addressed methodological characteristics and findings of the selected studies (see Table 1). The following study characteristics were extracted: 1) author and publication year; 2) sample characteristics (i.e., the number and type of substance users, the setting in which study participants were assessed (treatment or laboratory), and whether participants were abstinent or not at the time of the assessment); 3) type of study design (controlled study design (with or without random group allocation) or follow-up of one single study cohort); 4) type of impulsivity measure(s) used; 5) study findings regarding measures of treatment retention and abstinence. Given the exploratory nature of this systematic review, the different assessment

instruments and the variety of study designs and statistical analyses in the selected studies, the findings are presented as a narrative review. The presentation of the findings is organized according to the neurocognitive dimensions of impulsivity outlined in section 1.1. and Fig.1. Since most studies on impulsivity among substance abusers have focused on users of specific substances and since treatment interventions typically target specific groups of users, the findings for each impulsivity dimension are discussed separately for each substance. Unless otherwise specified, only significant findings are reported.

## 3. Results

### 3.1. Description of studies

#### *3.1.1. Study design and sample*

In total, 25 unique empirical papers were identified from the search criteria. Sixteen studies were secondary analyses of data collected from a larger Randomized Clinical Trial (RCT), whereas nine used a prospective cohort design (Bowden-Jones, McPhillips, Rogers, Hutton, & Joyce, 2005; Cox, Hogan, Kristian, & Race, 2002; De Wilde, Verdejo-Garcia, Sabbe, Hulstijn, & Dom, 2013; Krishnan-Sarin et al., 2007; Mueller et al., 2009; Passetti et al., 2008, 2011; Sheffer et al., 2012; Verdejo-Garcia et al., 2012). Sample sizes ranged from 10 to 182. Six of the 25 selected studies were conducted among primary cocaine users (Black & Rosen, 2011; Brewer, Worhunsky, Carroll, Rounsaville, & Potenza, 2008; Schmitz et al., 2009; Streeter et al., 2008; Verdejo-Garcia et al., 2012; Washio et al., 2011), three among primary opiate users (Marissen et al., 2006; Passetti et al., 2008, 2011), three among primary alcohol users (Bowden-Jones et al., 2005; Cox et al., 2002; De Wilde et al., 2013), eight among primary nicotine users (Dallery & Raiff, 2007; Janes et al., 2010; Krishnan-Sarin et al., 2007; MacKillop & Kahler, 2009; Mueller et al., 2009; Sheffer et al., 2012; Waters et al., 2003; Yoon et al., 2007) and two among primary marijuana users (Peters, Petry, Lapaglia, Reynolds, & Carroll, 2013; Stanger et al., 2012). One study examined the relationship between impulsivity and treatment outcomes within a heterogeneous sample of drug users, consisting of cocaine, heroin and marijuana dependent subjects (Carpenter, Schreiber, Church, &

McDowell, 2006). Similarly, another study evaluated the relationship between impulsivity and treatment outcomes within a sample consisting of either cocaine or methamphetamine dependent subjects (Winhusen et al., 2013). In both studies however, the effects of impulsivity on treatment outcomes were examined for each group of drug users separately and the results of these studies will be reported accordingly. Finally, one study was conducted within a highly heterogeneous group of drug users (although most participants (i.e., 59%) reported cocaine as their primary substance of abuse) and did not look at the relationship between impulsivity and treatment outcomes for each substance separately (Carroll et al., 2011).

*3.1.2. Impulsivity constructs measured*

When examining correlates of addiction treatment outcomes, researchers increasingly emphasize the need to assess multiple dimensions of impulsivity within the same sample (Potenza et al., 2011). Indeed, a comprehensive assessment including neurocognitive tasks indexing different aspects of impulsivity within the same sample may help to clarify which dimensions are more important to certain outcomes than others. However, the majority of studies selected for this review (n=16) measured only one neurocognitive dimension of impulsivity (Black & Rosen, 2011; Bowden-Jones et al., 2005; Brewer et al., 2008; Carpenter et al., 2006; Cox et al., 2002; Dallery & Raiff, 2007; Janes et al., 2010; MacKillop & Kahler, 2009; Marissen et al., 2006; Peters et al., 2013; Stanger et al., 2012; Streeter et al., 2008; Washio et al., 2011; Waters et al., 2003; Winhusen et al., 2013; Yoon et al., 2007). In contrast, only six studies assessed two neurocognitive dimensions of impulsivity (Carroll et al., 2011; De Wilde et al., 2013; Krishnan-Sarin et al., 2007; Mueller et al., 2009; Schmitz et al., 2009; Verdejo-Garcia et al., 2012) and even a smaller number of studies (n=3) used a test battery indexing three different impulsivity domains (Passetti et al., 2008, 2011; Sheffer et al., 2012) (see Table 1).

Looking at the different neurocognitive dimensions of impulsivity measured, 16 out of the 25 selected studies included a measure of **impulsive action**. Six of these studies used an index of motor inhibition (Carroll et al., 2011; Krishnan-Sarin et al., 2007; Passetti et al., 2008, 2011; Schmitz et al., 2009; Sheffer et al., 2012), whereas ten studies employed a task indexing cognitive inhibition, either of neutral words (Brewer et al., 2008; Mueller et al., 2009; Streeter et al., 2008; Verdejo-Garcia et al., 2012; Winhusen et al., 2013) or drug-related words (Carpenter et al., 2006; Cox et al., 2002; Janes et al., 2010; Marissen et al., 2006; Waters et al., 2003).

Twenty-one studies included a measure of **impulsive choice**, of which 13 employed a task indexing delay discounting. Most studies tested only discounting for money (Black & Rosen, 2011; Dallery & Raiff, 2007; De Wilde et al., 2013; Krishnan-Sarin et al., 2007; MacKillop & Kahler, 2009; Passetti et al., 2008, 2011; Peters et al., 2013; Sheffer et al., 2012; Washio et al., 2011; Yoon et al., 2007), but two studies additionally examined discounting of the drug of choice (Mueller et al., 2009; Stanger et al., 2012). The majority of studies assessed discounting of hypothetical rewards (Black & Rosen, 2011; Dallery & Raiff, 2007; De Wilde et al., 2013; Krishnan-Sarin et al., 2007; MacKillop & Kahler, 2009; Mueller et al., 2009; Passetti et al., 2008, 2011; Sheffer et al., 2012; Stanger et al., 2012; Washio et al., 2011; Yoon et al., 2007), but three studies (additionally) used a real-time task in which participants experienced chosen rewards at specified times throughout the assessment (Krishnan-Sarin et al., 2007; Peters et al., 2013; Sheffer et al., 2012).

Finally, eight studies employed a task indexing impulsive or risky decision-making (Bowden-Jones et al., 2005; Carroll et al., 2011; De Wilde et al., 2013; Passetti et al., 2008, 2011; Schmitz et al., 2009; Sheffer et al., 2012; Verdejo-Garcia et al., 2012).

*3.1.3. Outcome measures*

Twenty of the 25 selected studies examined only one outcome indicator (Black & Rosen, 2011; Bowden-Jones et al., 2005; Cox et al., 2002; Dallery & Raiff, 2007; De Wilde et al., 2013; Janes et al., 2010; Krishnan-Sarin et al., 2007; MacKillop & Kahler, 2009; Marissen et al., 2006; Mueller et al., 2009; Passetti et al., 2008, 2011; Sheffer et al., 2012; Stanger et al., 2012; Streeter et al., 2008; Verdejo-Garcia et al., 2012; Washio et al., 2011; Waters et al., 2003; Winhusen et al., 2013; Yoon et al., 2007), whereas five looked at the effects of impulsivity on both of the selected outcome indicators (Brewer et al., 2008; Carpenter et al., 2006; Carroll et al., 2011; Peters et al., 2013; Schmitz et al., 2009).

When looking at the different outcome measures assessed within the selected studies, it appears that the majority directly examined the relationship between impulsivity and abstinence/relapse (n=22) (Black & Rosen, 2011; Bowden-Jones et al., 2005; Brewer et al., 2008; Carpenter et al., 2006; Carroll et al., 2011; Cox et al., 2002; Dallery & Raiff, 2007; De Wilde et al., 2013; Janes et al., 2010; Krishnan-Sarin et al., 2007; MacKillop & Kahler, 2009; Marissen et al., 2006; Mueller et al., 2009; Passetti et al., 2008, 2011; Peters et al., 2013; Schmitz et al., 2009; Sheffer et al., 2012; Stanger et al., 2012; Washio et al., 2011; Waters et al., 2003; Yoon et al., 2007). In contrast, only eight of the 25 selected studies used treatment retention or drop-out as an outcome measure (Brewer et al., 2008; Carpenter et al., 2006; Carroll et al.,

2011; Peters et al., 2013; Schmitz et al., 2009; Streeter et al., 2008; Verdejo-Garcia et al., 2012; Winhusen et al., 2013).

## 3.2. Findings

### *3.2.1. Impulsive action*

#### *3.2.1.1. Cognitive inhibition: Interference control over neutral words*

Five studies examined the relationship between interference control over neutral words – as indexed by interference scores on a classic or Comalli-Kaplan version of the Stroop Color Word Test – and treatment retention (n=4) or abstinence/relapse (n=2).

Out of these five studies, four were conducted among primary cocaine dependent subjects (Brewer et al., 2008; Streeter et al., 2008; Verdejo-Garcia et al., 2012; Winhusen et al., 2013). Using carefully screened and well-matched groups, two of these studies found a significant relationship between decreased interference control and drop-out from various RCTs (Brewer et al., 2008; Streeter et al., 2008). In addition, Streeter and colleagues (2008) found that their Stroop model (based on Stroop subscale scores, including color naming, word reading and interference) had a high sensitivity (98%), a fair specificity (42%) and a very good negative predictive value (91%). In contrast with these findings, two recent studies failed to find a significant relationship between Stroop interference and treatment retention among cocaine dependent individuals participating in outpatient (Winhusen et al., 2013) or inpatient (Verdejo-Garcia et al., 2012) treatment settings for substance abuse. Similar findings were obtained for methamphetamine dependent subjects (Winhusen et al., 2013). In the only study among cocaine dependent individuals that examined the association between cognitive inhibition and abstinence, no correlation between Stroop interference and abstinence was found (Brewer et al., 2008).

One study examined the relationship between interference control and relapse in a sample of smokers (Mueller et al., 2009). Results of this study showed that Stroop interference effects differentiated participants dichotomized into early and late relapsers. More specifically, higher interference scores correlated with early relapse following laboratory sessions of reinforcing sustained abstinence (Mueller et al., 2009).

#### *3.2.1.2. Cognitive inhibition: Interference control over drug-related words*

Five studies examined the relationship between interference control over drug-related words – as indexed by interference scores on a drug Stroop Test – and treatment retention (n=1) or abstinence/relapse (n=5).

In the only study available in cocaine dependent individuals, interference effects for cocaine-associated words were related to shorter treatment retention and a greater proportion of cocaine positive urine tests during a cognitive–behavioral coping skills intervention (Carpenter et al., 2006).

Mixed findings have been obtained in samples of heroin dependent individuals (Carpenter et al., 2006; Marissen et al., 2006). In the first out of two studies, it was shown that post-treatment relapse could be predicted by reduced interference control over opiate-related words (Marissen et al., 2006). The same study found that greater difficulties in disengaging attention from drug-associated cues (as reflected by Stroop carry-over effects) were associated with an enhanced propensity to relapse following inpatient treatment. Stroop and carry-over effects continued to predict relapse when controlling for self-reported craving during the test session (Marissen et al., 2006). Using a considerable smaller sample size and requiring a motoric rather than a verbal response to the Stroop stimuli, a second study failed to replicate these findings (Carpenter et al., 2006).

We identified only one study that examined the relationship between interference control over drug-related words and treatment outcomes in a sample of alcohol dependent individuals (Cox et al., 2002). Results of this study demonstrated that increases in alcohol attentional bias over the course of inpatient treatment – as indexed by an increase in interference scores for alcohol stimuli from pre-treatment to post-treatment assessment – only occurred among alcoholics who would subsequently relapse (Cox et al., 2002).

In the two available studies on nicotine users, diminished interference control over smoking-related words was identified as a strong predictor of early relapse during treatment (Janes et al., 2010; Waters et al., 2003). Corroborating evidence in opiate dependent individuals (Marissen et al., 2006), this relationship remained significant after controlling for self-reported urges to smoke (Waters et al., 2003). Consistent with the notion that the effect of attentional bias on relapse is subject to top-down control, Janes and colleagues (2010) moreover found that relapsers had decreased synchrony of task-evoked signal fluctuations between an insula-containing network and frontal brain regions implicated in cognitive control while performing a drug Stroop task.

One study examined the association between drug interference effects and treatment outcomes among a sample of marijuana dependent individuals (Carpenter et al., 2006). Interestingly, this study found that poorer interference control over cocaine- and heroin-related words but not over marijuana words were

associated with shorter treatment retention and a higher proportion of marijuana-positive urine samples among these subjects.

**Overall evaluation**

Evidence regarding the relevance of Stroop interference for treatment drop-out is mixed, with only two out of four studies suggesting that interference control over neutral words may help to identify drug dependent individuals who are at risk for premature treatment drop-out. It is worth noting that the available studies differed in many respects, limiting any definite conclusions that can be made from the overall findings. In some studies, treatment retention was dichotomized into program completion versus non-completion (Streeter et al., 2008; Winhusen et al., 2013), whereas other authors used the number of days or weeks in treatment as an indicator of treatment retention (Brewer et al., 2008; Verdejo-Garcia et al., 2012). Further, average Stroop interference scores were substantially higher in the Streeter-study than those in the Verdejo-Garcia and Winhusen-study, suggesting that participants in the former study were more severely impaired. Other differences, including those pertaining to the treatment setting (inpatient vs. outpatient), treatment program (pharmacological vs. psychosocial) or study design (prospective cohort vs. RCT) may also have contributed to inconsistent findings across studies.

Data regarding the relevance of interference control over drug-related words for abstinence/relapse are more consistent. More specifically, the reviewed findings indicate that the degree to which a drug user can exert control over attentional biases using cognitive inhibitory mechanisms may be an important factor in accounting for relapse during and after treatment across different groups of drug users. Indeed, all of the five studies that examined the influence of drug interference control on abstinence/relapse reported an effect on treatment outcomes, although one study found that this effect was only significant for cocaine and marijuana dependent and not among heroin dependent individuals (Carpenter et al., 2006). It is worth noting that the number of heroin users in this study was small (see Table 1) and therefore, the failure to detect an effect on treatment outcomes in this subsample may – in part – reflect insufficient power.

*3.2.1.3. Motor disinhibition*

Six studies used an index of motor disinhibition in order to examine associations with either treatment retention (n=2) or abstinence/relapse (n=6).

In a study among relatively pure cocaine dependent subjects, commission errors on the IMT/DMT were unrelated to treatment retention or the ability to achieve cocaine abstinence during outpatient treatment (Schmitz et al., 2009). Consistent with these findings, data from a well-controlled clinical trial with high rates of retention failed to support a significant effect of CPT commission errors on retention periods or abstinence in a sample predominantly consisting of cocaine dependent individuals (Carroll et al., 2011).

Similar findings have been obtained in studies among opiate users (n=2). In the first of these studies, Passetti and colleagues (2008) found no differences between abstinent and non-abstinent individuals in the probability of false alarms or in terms of the speed of responding to either go or no-go stimuli. These findings – which were obtained in the context of an outpatient treatment setting – were later replicated in a second study by the same authors in an inpatient treatment facility (Passetti et al., 2011).

The relationship between motor disinhibition and abstinence/relapse has been examined in two nicotine studies (Krishnan-Sarin et al., 2007; Sheffer et al., 2012). One study in adolescents found CPT commission errors to be associated with impairments in the ability to achieve abstinence during CBT treatment (Krishnan-Sarin et al., 2007), whereas another study failed to find an effect of Go/No-go performance on abstinence among adult participants enrolled in intensive CBT for tobacco dependence (Sheffer et al., 2012).

**Overall evaluation**

Out of six studies that employed an index of motor disinhibition, five failed to detect an effect of this impulsivity dimension on any of the outcome indicators. As such, there is relatively consistent evidence suggesting that motor disinhibition is unrelated to abstinence and potentially, treatment retention within drug dependent individuals. The only study available that found a significant relationship between motor disinhibition and abstinence was conducted among adolescent smokers (Krishnan-Sarin et al., 2007). Hypothetically, indices of motor disinhibition may offer better predictions of abstinence/relapse in adolescents than in adults (Krishnan-Sarin et al., 2007), which is in line with evidence indicating that brain systems responsible for response inhibition are still under development during adolescence (Tamm, Menon, & Reiss, 2002). Alternatively, the various inhibition measures used in the different studies may not be comparable in their psychometric properties. Therefore, it may be premature to infer from the evidence that inhibitory control is more important to treatment outcomes in certain groups than in others.

*3.2.2. Impulsive choice*

*3.2.2.1. Delay Discounting*

Thirteen studies used a measure of delay discounting in order to predict abstinence/relapse (n=13) and/or treatment retention (n=1).

In the first out of two studies in cocaine users, Black and Rosen (2011) found that increases in delay discounting during a money management intervention were associated with decreased abstinence from cocaine. In a more recent study, it was found that steeper delay discounting of hypothetical monetary reinforcers was associated with shorter durations of cocaine abstinence achieved in a voucher-based CM-program (Washio et al., 2011). The same study found that increasing the magnitude of rewards offered as a part of CM treatment appeared to attenuate the negative effect of delay discounting on treatment response (Washio et al., 2011). More specifically, cocaine dependent individuals who exhibited steeper discounting functions achieved shorter periods of abstinence in a low-magnitude voucher condition but not in a high-magnitude voucher condition (Washio et al., 2011).

In the first out of two studies in opiate users, discounting rates at treatment onset failed to predict abstinence levels after outpatient treatment (Passetti et al., 2008). In a subsequent study, the same authors demonstrated that the inclusion of a residential treatment sample strengthened the relationship between DDT performance and abstinence levels (Passetti et al., 2011). When looking at the entire sample (consisting of subjects participating in both inpatient and outpatient settings), it appeared that participants who achieved abstinence had considerably lower discounting rates on the DDT than non-abstinent participants ($d$ =0.525).

One study investigated the relationship between delay discounting and post-treatment relapse in a sample of alcohol dependent poly-substance abusers (De Wilde et al., 2013). Delay discounting scores in this study failed to demonstrate a difference as a function of abstinence status 3 months after discharge from inpatient treatment (De Wilde et al., 2013).

Six studies examined the relevance of delay discounting for smoking cessation outcomes. In the first of these studies, Krishnan-Sarin and colleagues (2007) found that, compared to adolescents who were abstinent at the end of a voucher-based smoking cessation program, those not achieving abstinence discounted monetary rewards more significantly. In a second study among pregnant women who discontinued smoking during pregnancy, greater delay discounting at onset of a voucher-based treatment was a significant predictor of smoking status at 24-weeks postpartum (Yoon et al., 2007). Similarly, a study in treatment-seeking smokers enrolled in a RCT of smoking cessation treatment revealed steeper

delay discounting for individuals who had lapsed by the two-week and eight-week follow-up visits (Mackillop & Kahler, 2009). In addition, delay discounting in this study was a significant predictor of days to first lapse (Mackillop & Kahler, 2009). Similar findings have been obtained in the context of a CBT intervention (Sheffer et al., 2012). In this study, adult smokers who more steeply discounted delayed rewards were less successful in achieving abstinence following treatment (Sheffer et al., 2012). The association between delay discounting and poor smoking cessation treatment response observed in these clinical studies has been substantiated in two laboratory models of smoking lapse (Dallery & Raiff, 2007; Mueller et al., 2009). In the first of these studies, Dallery & Raiff (2007) found that greater delay discounting predicted whether participants would resume smoking in the context of contingent alternative reinforcement. In a more recent study, steeper levels of delay discounting for money and cigarettes were found to be a strong predictor of shorter relapse times following a period of extended abstinence (Mueller et al., 2009).

Finally, two studies examined the relationship between pretreatment levels of delay discounting and treatment outcomes in marijuana users (Peters et al., 2013; Stanger et al., 2012). In the first of these studies, steeper levels of delay discounting at treatment onset predicted shorter periods and lower levels of abstinence among adolescents enrolled in a behavioral treatment for marijuana abuse/dependence (Stanger et al., 2012). Discounting of larger amounts of money showed the strongest relationship with abstinence, whereas discounting of smaller amounts of marijuana showed the weakest association. In a second study, pretreatment discounting levels did not significantly predict treatment retention or abstinence among (primarily court-referred) adult marijuana dependent individuals randomized to treatments involving CM and CBT (Peters et al., 2013).

**Overall evaluation**

Overall, there is replicated and consistent evidence in nicotine dependent individuals (n=6) and preliminary evidence in cocaine dependent subjects (n=2) pointing to the relevance of delay discounting in predicting abstinence/relapse during and following participation in several empirically-supported treatment programs. Notably, evidence in cocaine and opiate dependent individuals suggests that the effect of delay discounting on abstinence may be moderated by the treatment program or setting (Passetti et al., 2011; Washio et al., 2011). If replicated, these findings may have important clinical implications, as they suggest that measures of delay discounting can be used to guide treatment allocation.

From the only available dataset in alcoholics, it would appear that delay discounting at treatment onset is unrelated to post-treatment relapse in this group. Yet, this conclusion is only based on one single study and needs to be replicated. Finally, evidence regarding the relevance of delay discounting for treatment outcomes in marijuana dependent individuals is mixed, with one study reporting a significant effect of delay discounting on abstinence (Stanger et al., 2012) still another study failing to replicate these findings (Peters et al., 2013). Hypothetically, sample differences may partially explain divergent findings. The Stanger-study included adolescents who voluntarily agreed to participate in treatment, whereas the Peters-study recruited adults who were referred by court. Hypothetically, the court-referred status of participants in the latter study may explain why delay discounting levels failed to demonstrate a difference as a function of treatment retention or abstinence levels achieved. First, the "motivational structure" underlying abstinence or treatment retention in subjects in coercive treatment may be different (Peters et al., 2013). Second, individuals with a criminal record have been found to discount delayed rewards substantially more than subjects without a criminal record (Arantes, Berg, Lawlor, & Grace, 2013). Corroborating this notion, rates of discounting in the Peters-study were higher than in other samples (Reynolds et al., 2006). Overall, the court-referred status of these subjects may have introduced a selection bias that ensured little variation in discounting scores among participants. This would (potentially) explain why this study failed to detect a significant effect of delay discounting on treatment outcomes. Also, it should be noted that the Stanger-study and Peters-study used different discounting tasks (see Table 1), varying in the nature (hypothetical monetary rewards/marijuana vs. real monetary rewards) and magnitude (maximum amount of $1000 vs. maximum amount of $0.30) of rewards offered. As Stanger and colleagues found that only discounting of larger amounts of money predicted abstinence, the magnitude of reward offered in the Peters-study may not have been sufficient to evidence a relationship with treatment outcomes.

*3.2.2.2. Impulsive decision-making*

Eight studies used a measure of impulsive or risky decision-making in order to predict treatment retention (n=3) or abstinence/relapse (n=7).

Out of these eight studies, three were conducted among primary cocaine dependent individuals (Carroll et al., 2011; Schmitz et al., 2009; Verdejo-Garcia et al., 2012). Using a relatively large sample, Verdejo-Garcia and colleagues (2012) did not find IGT performance to be predictive of treatment retention in a residential therapeutic community program. These findings partially confirm those of an earlier study by

Schmitz et al. (2009) who failed to find a significant relationship between impulsive decision-making and the length of stay in an outpatient CBT and CM program. However, better baseline scores on the IGT in this study were associated with higher levels of short-term abstinence (Schmitz et al., 2009). Similarly, a third study failed to detect a significant relationship between the degree of risky decision-making – as indexed by the number of pumps on the BART – and treatment retention among cocaine users enrolled in a RCT consisting of a standard and computerized-version of CBT (Carroll et al., 2011). Instead, risky decision-making was associated with lower levels of abstinence, but only among those assigned to the computer-assisted version of CBT, while no such relationships could be found among participants assigned to a standard treatment condition (Carroll et al., 2011).

Two studies examined the relevance of impulsive decision-making for predicting abstinence among opiate dependent individuals (Passetti et al., 2008, 2011). In an outpatient program, clear differences were found between opiate dependent individuals who were abstinent from illicit drugs at 3 months following treatment onset and those who were not in their quality of decision making (CGT) and net scores on the IGT (Passetti et al., 2008). More specifically, two thirds of the subjects performing normally on the CGT and IGT, but none of those impaired on both, were abstinent from illicit drugs at follow up. Interestingly, a subsequent study by the same authors found that in the community, but not in the residential settings, the probability of achieving and maintaining abstinence was higher in individuals who were unimpaired on the CGT than in subjects impaired on this task (Passetti et al., 2011).

In the first out of two studies in alcohol dependent subjects, alcoholics were more likely to relapse during a 3-month period post-detoxification if they sampled significantly more cards from the bad decks on the IGT and if they staked more points on their decisions being correct on a CGT (index of risk-taking) (Bowden-Jones et al., 2005). The relevance of impulsive decision-making for treatment outcomes in alcoholics has recently been replicated in a study by De Wilde and colleagues (2013), who found that poly-substance dependent alcoholics who relapsed within 3 months following treatment discharge showed poorer decision-making performance – as evidence by lower net scores on the IGT – compared to individuals who succeeded in maintaining abstinence.

Only one study examined the relationship between risky decision-making and abstinence in a sample of smokers (Sheffer et al., 2012). Results of this study showed that risky decision-making – as indexed by the number of pumps on the BART – was unrelated to abstinence following CBT treatment.

**Overall evaluation**

Out of the seven studies that examined the relationship between impulsive/risky decision-making and abstinence/relapse, six found a significant effect. As such, there appears to be replicated evidence indicating that poorer decision-making can substantially hamper the ability to achieve and maintain abstinence among alcoholics and illicit drug users. Conversely, a decision-making style characterized by a tendency to take into account information regarding outcome probabilities and consider long-term prospects of available options may be a necessary prerequisite to benefit from targeted behavioral interventions. At the same time, there is reliable evidence suggesting that the negative effect of impulsive decision-making on abstinence may be buffered during treatment in a residential setting (Passetti et al., 2011) or within a (putatively) less cognitively demanding treatment modality (Carroll et al., 2011). Replication of these findings in larger cohorts may have important clinical implications in terms of treatment allocation. At odds with the majority of the available evidence, the only study in smokers found that risky decision-making, as indexed by performance on the BART, was unrelated to abstinence (Sheffer et al., 2012). Finally, from the available evidence (n=3), it would seem that impulsive and risky decision-making are unrelated to treatment retention.

The identification of both delay discounting and impulsive decision-making as relative consistent predictors of abstinence (although precise effects may depend upon the particular task being used, the treatment program and potentially, the particular group of substance users), raises question regarding potential overlap between both dimensions of impulsive choice. Phrased differently: do both constructs represent independent predictors of treatment outcomes or does substantial overlap exists between them such that when both are placed in one model, only one will account for a significant portion of the variance in abstinence? Future studies may help to address this question by examining the effects of delay discounting and impulsive decision-making on abstinence in a multivariate model and by performing multicollinearity diagnostics when attempting to predict treatment outcomes.

## 4. Discussion

### 4.1. Main findings

Growing recognition of the centrality of neurocognitive impairments related to impulsivity in addiction should bring with it more attempts to examine the effects of these deficits on treatment outcomes, as this may result in an increased emphasis on top-down and bottom-up rehabilitation in treatment (Bates et al., 2013; Garavan & Weierstall, 2012). Whereas the available evidence is rather scarce and methodological differences made it difficult to make direct comparisons between studies, a conceptual integration of the

reviewed findings suggests that cognitive (dis)inhibition of drug-related words, delay discounting and impulsive/risky decision-making are clinically relevant and may have prognostic utility in the treatment of alcohol and drug dependent individuals.

The relatively consistent evidence regarding the relevance of these impulsivity dimensions for at least one of the selected addiction treatment outcomes (i.e., achieving and maintaining abstinence) raises questions why indices of motor (dis)inhibition failed to demonstrate any difference as a function of treatment outcomes. Whereas several explanations may account for this observation, we believe that the absence of an effect of motor (dis)inhibition on treatment outcomes might in particular be attributed to the poor sensitivity of the tasks used to measure levels of motor disinhibition. All of the selected studies in which the relationship between motor disinhibition and addiction treatment outcomes was examined (n=6) used a simple, neutral reaction time task in which participants either had to respond or inhibit prepotent responses to neutral stimuli. However, it may be that deficiencies in inhibitory control become clinically more relevant when drug dependent individuals are exposed to affectively challenging conditions (e.g., during exposure to drug-related cues or in the face of immediately available rewards). Indeed, in real life or clinical settings, relapses most likely result from a complex interplay between executive top-down control on the one hand and bottom-up inputs (e.g., exposure to drug-related stimuli or contexts) on the other hand, rather than reflecting the outcome of either process alone. In contrast to tasks measuring motor inhibition of affectively neutral stimuli (which primarily measure the robustness of top-down processes), neurocognitive tasks indexing the motivational or affective modulation of this inhibition may capture more accurately the dynamic and state-dependent interplay between both systems (Wiers, Ames, Hofmann, Krank, & Stacy, 2010). Overall, we believe that future studies examining the effects of motor disinhibition on addiction treatment outcomes may benefit from including tasks in which neutral stimuli (e.g., letters) are substituted by motivationally relevant stimuli, which permit analyses of performance in response to cues of affective valences, such as an emotional Go/No-Go task. The aforementioned notion may also explain why the more complex neurocognitive paradigms of cognitive inhibition of drug-related words, delay discounting and impulsive decision-making – which confront participants with motivationally relevant stimuli (e.g., drug-related cues, monetary rewards or punishments) – are better predictors of abstinence/relapse compared to the more simple paradigms used to index motor disinhibition. Indeed, performance on these tasks can be seen as a relatively straightforward index of the balance between top-down and bottom-up processes (Bickel, Jarmolowicz, Mueller, Koffarnus, & Gatchalian, 2012).

## 4.2. Clinical implications and directions for future research

Overall, the current findings suggest that 1) aspects of impulsive action and choice should be considered as critical targets for intervention, 2) existing treatment approaches should be modified and employed in a manner that specifically appeals to substance abusers with higher levels of impulsive action and choice and that 3) neurocognitive measures of impulsive action and choice may assist in ongoing efforts to improve treatment matching for substance abusers (treatment allocation). The potential of translating the current findings into improved addiction treatment outcomes however, will greatly depend upon further progress in this particular research area.

### *4.2.1. Aspects of impulsive action and choice as critical treatment targets for consideration*

The evidence reviewed in this paper indicates that neurocognitive indices of impulsivity, most notably cognitive disinhibition over drug-related words, delay discounting and impulsive decision-making, are reliably associated with a reduced ability to achieve and maintain abstinence across most classes of substances. To the extent that these deficits compromise the recovery process, interventions that improve cognitive inhibitory control and reduce delay discounting or impulsive decision-making may represent valuable therapeutic strategies. In line with the multiple processes implicated in the regulation of impulsive action and impulsive choice, the integrity of prefrontal cortical functioning in general and (executive) functions involved in interference control (inhibition, working memory and attention) and risk-reward decision-making (planning, reversal learning and interoceptive awareness) in particular represent interesting targets for consideration (Dunn et al., 2010; Kane & Engle, 2003). Within this respect, training of attentional biases (Fadardi & Cox, 2009; Schoenmakers et al., 2010) and working memory functions (Bickel et al., 2011; Houben et al., 2011), goal-management training in combination with mindfulness-based meditation (Alfonso et al., 2011) and neuromodulation-based approaches (Sheffer et al., 2013) may help addicted individuals in making less impulsive and more future-oriented decisions and potentially, reduce the propensity to relapse. However, it should be emphasized that evidence linking training-induced improvements in cognitive functioning to changes in clinically relevant outcomes is sparse. Consequently, additional research is needed in order to establish the clinical relevance of these findings.

### *4.2.2. Treatment modification for high-impulsive substance abusers*

Whereas bottom-up and top-down mechanisms have been put forward as potential targets for the treatment of drug addiction in general, these strategies should be modified and employed in a manner that specifically appeals to or targets highly-impulsive populations. Indeed, although impulsivity has been inherently linked to SUDs in general, this systematic review demonstrates that impulsivity also varies considerably among groups of substance abusers. Indeed, the response to available (empirically-supported) addiction treatment programs (e.g., CM, CBT) is modulated by differences in impulsivity; substance abusers with higher levels of impulsive action and choice do not seem to benefit from these programs to the same extent as do their less-impulsive counterparts. Therefore, a more detailed understanding of the (neural) mechanisms underlying the effects of impulsivity on treatment outcomes is needed, as this may lead to novel interventions aimed at minimizing these negative effects and may facilitate treatment responding in these subjects. One neural mechanism potentially linking impulsivity with poor treatment outcomes is a motivational deficit associated with dopamine dysfunction: pronounced disruptions in dopamine functioning associated with impulsivity may produce difficulties in attributing salience to novel reward-indicating stimuli (Beck et al., 2009; Martinez et al., 2011) and affect the ability of the individual to successfully modify behavior in the face of enriched rewarding contingencies (Goto & Grace, 2008). Speculatively, pharmacological interventions aimed at restoring dopamine functioning might facilitate CM-responding in these individuals by targeting neurobiological bottom-up processes associated with reward processing and salience attribution (Schmitz et al., 2008). Similarly, cognitive enhancers may act as a successful adjunct for increasing the effectiveness of CBT programs in these individuals by boosting top-down functions (Kalechstein, De La Garza, & Newton, 2010). However, these possibilities have yet to be systematically explored and reported on and might be a promising area for future research.

As recently outlined in a review by Bates and colleagues (2013), the ways in which neurocognitive problems interfere with addiction treatment outcomes may not be simple or direct. Rather, the effect of neurocognitive dysfunctions on addiction treatment outcomes may be mediated by more intrapersonal or contextual factors, including motivation to change or the ability to form therapeutic alliances (Le Berre et al., 2012). To the extent that this may contribute to a modification of treatment programs to the specific needs of high-impulsive individuals, future studies may need to consider indirect pathways by which impulsivity exerts its influence on treatment outcomes.

*4.2.3. Implications for treatment allocation*

The reviewed data suggest that neurocognitive measures of impulsivity could be added to the range of clinical information that is collected at treatment intake to identify relapse vulnerable and potentially, drop-out vulnerable addicts' prior to treatment and inform clinical decision-making. Depending on their neurocognitive profile, addicted individuals may subsequently be allocated to more appropriate or targeted treatment interventions, rather than following a 'one size fits all' approach (Ersche & Sahakian, 2007; King & Canada, 2004). However, in order to translate the present findings into guidelines for treatment matching, several questions need to be addressed. First, the majority of studies selected for this review did not examine the threshold of neurocognitive impairment associated with relapse or drop-out vulnerability. Whereas differences in neurocognitive task performance between groups with a different likelihood of drop-out or relapse are relevant, the clinical utility of neurocognitive task performance would be greatly enhanced by the availability of clinically significant cut-off scores. Future studies may help the clinical field moving forward by evaluating the sensitivity and specificity of a variety of cut-off scores in predicting participants' relapse or drop-out status. Using the receiver operating characteristic curve (ROC; Metz, 1978) may offer a valuable way to analyze the number of true positives and false-positives based on different cut-off values and to select the optimal cut-off for clinical use.

Second, whereas some tentative suggestions can be made from the reviewed findings, there is currently insufficient evidence to formulate specific guidelines for matching individuals with a particular neurocognitive profile to specific interventions. A worthwhile prospect for future studies may therefore be to elucidate the particular conditions and clinical contexts under which aspects of impulsivity are associated with treatment failure or success. Examining the strength and nature of the relationship between aspects of impulsivity and clinical outcomes in various treatment modalities simultaneously may be a promising avenue in this respect (see Passetti et al., 2011).

### 4.3. Limitations of the review

Whereas this review examined the link between neurocognitive aspects of impulsivity and addiction treatment outcomes, it did so with a number of limitations. First, only published studies were selected for this review. This selective reliance on published research may have introduced a bias, since statistically significant evidence is more likely to be published than studies with null results. As such, our selection method may have led to an overly strong conclusion regarding the role of impulsivity in determining poor addiction treatment outcomes.

A second limitation of this review may be the selective focus on neurocognitive facets of impulsivity at the expense of excluding personality factors related to impulsivity. The literature on the link between impulsivity and addiction treatment outcomes clearly covers many other aspects than those discussed in the present paper, including personality aspects such as novelty and sensation seeking (Helstrom, Hutchison, & Bryan, 2007; Kahler et al., 2009; Patkar et al., 2004), attentional impulsivity (Charney, Zikos, & Gill, 2010) or lack of perseverance (Müller, Weijers, Böning, & Wiesbeck, 2008). These personality traits are typically assessed using self-report questionnaires, which may be less sensitive in identifying differences associated with treatment outcomes compared to neurocognitive tasks detailing specific behavioral processes. As proximate measures of the neurobiology underlying impulsive behavior, neurocognitive instruments moreover serve as indicators of endophenotypes, which may represent particularly attractive therapeutic targets (Gottesman & Gould, 2003).

In accordance with the notion that key nodes within the frontostriatal circuitry regulating impulsivity are also implicated in other cognitive processes, impulsivity does not exist in a vacuum but is often part of a wider set of higher-order executive impairments, including poor working memory and reversal learning deficits (Noël et al., 2011; Winstanley, Olausson, Taylor, & Jentsch, 2010). Consequently, complex behavioral paradigms which rely on multiple cognitive and motivational functions may be argued to have a high ecological validity, although their complexity clearly interferes with the ability to elucidate and distinguish the different processes that may be implicated. Accordingly, when interpreting the reviewed evidence, readers should consider the fact that – whereas impulsivity may manifest itself as impaired IGT or Stroop performance – compromised performance on these tasks is not necessarily due to impulsivity. This notion particularly pertains to disadvantageous performance on the more complex behavioral paradigms of decision-making, for which several alternative interpretations have been proposed (Dunn et al., 2006; Winstanley et al., 2010). Risky decision-making on the CGT for example, may be due to an impairment in accurately estimating outcome probabilities instead of reflecting impulsive reward-seeking per se (Ersche & Sahakian, 2007). Although interference effects on drug-versions of the Stroop task have predominantly been explained as reflecting a selective, rapid, automatic processing bias, alternative explanations should be considered. In a seminal paper, Algom, Chajut, & Lev (2004) argued that the emotional Stroop effect can be interpreted in terms of a general purpose defense mechanism that reacts to threat by temporarily disrupting all ongoing activity (reading as well as color naming). Similarly, for drug dependent individuals undergoing treatment, drug-associated words may potentially represent a threat to

achieving the goal of abstinence (Christiansen & Field, 2013). Exposure to these cues might lead to a general disruption in all ongoing activity and thus, a generalized disengagement from the color-naming task. Exploring a threat-related generic slowdown as an explanation for addiction Stroop effects might be an interesting avenue for further research (Christiansen & Field, 2013).

There are many factors – most of which pertain to the (conceptual/methodological) heterogeneity across the available studies – that substantially hindered comparison between studies and therefore make it difficult to explain inconsistent findings. A substantial number of studies included individuals who abused other substances in addition to their primary substance (e.g., De Wilde et al., 2013; MacKillop & Kahler, 2009) and as such, possible confounding effects of poly-substance abuse cannot be completely ruled out. Further, not all studies required a specific period of abstinence before neurocognitive tasks were administered (see Table 1). Therefore, the potential confounding effects of acute drug or withdrawal symptoms on neurocognitive task performance may have been another source of bias. Also, outcomes were measured at various moments in the treatment process. A number of studies investigated the effect of impulsivity on abstinence/relapse during treatment (Passetti et al., 2008; Schmitz et al., 2009; Stanger et al., 2012), whereas others looked at the relationship between impulsivity and post-treatment abstinence/relapse (De Wilde et al., 2013; Marissen et al., 2006). Because the processes controlling the vulnerability to relapse may be different during and after treatment (MacKillop & Kahler, 2009), variability between studies with respect to the time of assessment may have contributed to inconsistent findings.

Finally, some of the selected studies suffered from important methodological limitations. Many of the studies reviewed had small sample sizes, the consequences of which include low statistical power and therefore, an increased likelihood of type II errors. The majority of studies did not report effect sizes within their reported statistics or failed to provide sufficient data to allow this to be calculated for the purpose of comparison between studies. Also, not all studies controlled for other – potentially important – predictors, including dependence severity or treatment history.

## 5. Conclusion

Although future research is needed to substantiate the findings discussed in this review, the available evidence extends the previously established role of impulsivity in the initiation and escalation of addictive behaviors to a contributing role in treatment failure. In particular, the reviewed studies suggest that higher levels of cognitive disinhibition, delay discounting and impulsive/risky decision-making may substantially hamper the ability to achieve and maintain abstinence during and following addiction treatment. Whereas

the relationship between impulsivity and treatment retention or drop-out needs to be examined more extensively, preliminary evidence suggests that impulsive/risky decision-making is unrelated to premature treatment drop-out among individuals with a SUD.

Although the reviewed findings point to the prognostic utility of neurocognitive tasks indexing aspects of impulsivity for the treatment of alcohol and drug dependence, interpretation of the available evidence is complicated by the methodological and conceptual heterogeneity across studies. Therefore, there is a need for more study replication and equivalence across study designs to allow for more adequate comparison. Worthwhile prospects for future studies may be to develop precise knowledge about the threshold of neurocognitive impairment needed before treatment outcomes are substantially affected and to elucidate the particular conditions under which impulsivity is associated with treatment failure or success. Sampling neurocognitively stratified groups of individuals (e.g., high-discounters and low-discounters) when examining the therapeutic efficacy of pharmacological agents and cognitive training programs may be of great interest within this respect and can provide valuable information for clinical decision-making. Future studies should further explore ways in which existing empirically-supported interventions can be modified to facilitate treatment responding in highly-impulsive addicts. Examining a combination of different approaches (e.g., cognitive enhancers and executive function training) may be one promising avenue in this respect. Ultimately, further research on the construct of impulsivity may have far-reaching implications for guiding treatment matching and for the development of personalized interventions or therapies.

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