The role of personality and neurocognitive dimensions of impulsivity in predicting addiction treatment outcomes

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Preface

As one of the top behavioral conditions causing high levels of global disease burden, drug addiction profoundly affects our society. Dramatic advances over the last two decades in neurobiology and cognitive neuroscience have revolutionized our understanding of drug addiction. The perspective emerging from several lines of research is that addiction involves significant neuroadaptation to brain structure and function, including signaling pathways, neurotransmitters, and cell mechanisms that overlap with those that mediate normal learning, memory and cognitive control processes. These neural adaptations have been proposed to contribute to the transition from initial drug use (a stage during which the drug is voluntarily consumed due to its reinforcing effects) to the loss of control over drug-seeking and taking behavior, the hallmark characteristic of drug addiction. To the extent that some of these changes are long-lasting and, in some instances perhaps even irreversible, they support the conceptualization of drug addiction as a chronic brain disease.

Options available for treatment are growing along with our understanding of the neurobiological mechanisms underlying the development and maintenance of addiction and have progressed from purely corrective, social and behavioral approaches to encompass cognitive and pharmacological interventions that attempt to disrupt the neural mechanisms underlying compulsive drug use. Despite these advances, current addiction treatment options are helpful to some, but far from satisfactory, as is true for many chronic brain diseases. In fact, effect sizes remain modest for most available therapies and drug users show considerable variability in treatment success: whereas some individuals successfully complete treatment and are able to initiate/maintain abstinence following treatment, others drop out of treatment prematurely and/or relapse soon afterwards. Accordingly, a major focus in optimizing treatment involves the identification of individual factors that contribute to the variability in addiction treatment outcomes in general, and to premature treatment drop-out and relapse propensity specifically.

One factor that may be particularly valuable in the search for key predictors of poor addiction treatment outcomes and that will be the central topic of this doctoral dissertation is impulsivity, a multi-factorial construct comprised of several components. The choice to focus on impulsivity is prompted by theoretical as well as clinical considerations. From a theoretical perspective, growing evidence suggests that impulsivity is critically implicated in the maintenance of drug addiction. Moreover, the neurobiological processes that subserve impulsivity show remarkable overlap with precisely those neurobiological mechanisms that contribute to the persistence of drug abuse and dependence. In fact, impulsivity has been suggested to reflect the behavioral marker of the neurobiological factors underlying compulsive drug use and its maintenance. Because pathophysiological factors maintain the disease state that treatments target and attempt to remediate, it is reasonable to assume that impulsivity will negatively affect treatment outcomes. Additionally, many (empirically-supported) addiction treatment programs rely heavily on functions known to be involved in adequate impulse control, including the ability to plan, postpone immediate gratification and consider the long-term consequences of available options. As a consequence, these treatment programs may be expected to be particularly challenging for drug users with higher levels of impulsivity. From a clinical perspective,

and perhaps most important, impulsivity is amenable to treatment. Accordingly, identification of impulsivity as a factor contributing to poor addiction treatment outcomes may have far-reaching implications for the treatment of individuals with a substance use disorder. Similarly, I sincerely hope that the findings of this doctoral dissertation will open new avenues for the development of better tailored addiction treatment interventions.

Acknowledgements

"The greatest glory in living lies not in never falling, but in rising every time we fall", said Nelson Mandela, referring to the ability to bounce back, to overcome and grow from setbacks, or to show resilience. Looking back at the past four years, resilience has also greatly helped me to accomplish this PhD. Admittedly, it is not just a commodity I was born with, nor something entirely self-manufactured. My resilience has been fuelled by being surrounded by so many people who have challenged me, provided me with trust, confidence, well-reasoned opinions, opportunities, insights, practical support, or who have acted as great examples of resilient persons themselves. Therefore, this dissertation reflects much more than simply the printed words and years of research and writing. It is representative of all the guidance and support that numerous people were willing to share with me along the way. It is sadly impossible to acknowledge here all of them. It is equally impossible to indicate the extent of my dept to those whom I can acknowledge. It is, however, a pleasure to try.

First and foremost, I would like to express my appreciation to all the clients who have been willing to participate in this PhD-study and who gave me their trust, openness and patience while being in an extremely precarious situation. I sincerely thank you for your essential contributions, and I wish you all the best in pursuing your personal goals and dreams.

My desire to undertake research on impulsivity in individuals with a substance use disorder and provide something meaningful for the addiction treatment field mainly developed during my practical training as a master student at ADIC (Antwerp). I was fortunate during this time to be surrounded by many inspiring people, but two clinicians in particular need to be acknowledged: Domien De Decker and Dr. Annemie Vermassen. You have been a great source of inspiration, motivation and confidence, and I cherish each of your contributions to my personal and professional development.

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CHAPTER 1

GENERAL INTRODUCTION

ABSTRACT

This chapter begins with an introduction into the concept of impulsivity. Definitions and assessment approaches of impulsivity adopted in the personality and neurocognitive literature are outlined. Next, attention is given to the concept of drug addiction. We briefly discuss the prevailing conceptualisation of drug addiction as a chronic brain disease and how the construct of impulsivity is firmly embedded within this paradigm. We then provide an intentionally brief overview of addiction treatment options and discuss how poor treatment retention, premature treatment drop-out and relapses represent some of the most prominent challenges pertaining to the treatment of drug addictions. Subsequently, the main topic of the current dissertation, i.e., the role of impulsivity in predicting addiction treatment outcomes, is introduced. After having outlined the main objectives of this doctoral dissertation, an overview of the different chapters is provided.

1.1. Impulsivity: what's in a name?

In our modern world, people often have to pursue long-term goals to achieve high benefits. The ability to restrain impulsive desires or to forego immediate rewards in the service of receiving larger future rewards is crucial for lifetime success; it enables humans to live cooperatively, achieve important goals, and maintain health throughout the life span (Heatherton & Wagner, 2011). Although humans are characterized by an impressive capacity for self-control, failures are common, and are often referred to as impulsive behaviors.

Impulsivity contributes to many societal and behavioral problems, including overeating, suboptimal financial management, crime, risky sexual behaviors and reckless driving, such as driving under influence (Cheng, Ng, & Lee, 2012; Hoyle, Feifar, & Miller, 2000; Ottaviani & Vandone, 2011; Teese & Bradly, 2008). Not surprisingly, impulsive persons also tend to endorse higher levels of psychopathology. Indeed, increased impulsivity is a key component of various clinical conditions (American Psychiatric Association, 1994, 2013), including conduct disorder, attention-deficit/hyperactivity disorder (ADHD), borderline and antisocial personality disorder, bipolar disorder, substance use disorders (SUDs), pathological gambling and trichotillomania (Berlin, Rolls, & Iversen, 2005; Billieux et al., 2012; Bohne, Savage, Deckersbach, Keuthen, & Wilhelm, 2008; Malloy-Diniz, Fuentes, Leite, Correa, & Bechara, 2007; Stevens, Vanderplasschen, Hulstijn, & Dom, 2013; Strakowski et al., 2010; Swann, Lijffijt, Lane, Steinberg, & Moeller, 2009; Tragesser & Robinson, 2009; Verdejo-Garcia, Lawrence, & Clark, 2008). The evidence of elevated impulsivity across these disease-related vulnerabilities and various disorders has moreover led to the prevailing conceptualization of impulsivity as a trans-disease process, accounting for the frequently observed comorbidity between these disorders (Bickel, Jarmolowicz, Mueller, Koffarnus, & Gatchalian, 2012; Bornovalova, Lejeuz, Daughters, Zachary, & Lynch, 2005; Groman, James, & Jentsch, 2009).

Of great concern is that the increased levels of impulsivity associated with these clinical conditions are linked to a variety of adverse events, including an earlier onset and more severe course of illness, worse psychosocial functioning, lower perceived quality of life, increased risk for self-harm or suicide and poorer treatment outcomes (Albein-Urios, Pilatti, Lozano, Martínez-González & Verdejo-Garcia, 2013; Dom, D'haene, Hulstijn, & Sabbe, 2006; Victor, Johnson, & Gotlib, 2011).

In recognition of impulsivity as a key component of many (contemporary) societal, behavioral and psychiatric problems, understanding this construct is potentially of great importance. Accordingly, there has been a resurgence of interest in impulsivity research during the past decade. This renewed focus on impulsivity however, has highlighted the lack of consistency in defining and assessing the construct (Congdon & Canli, 2008). In particular, it appears that the term impulsivity is frequently used to refer to a wide range of apparently unrelated behaviors, including behaving without forethought or consideration of outcomes, an inability to withhold or stop inappropriate responses, a preference for immediate over delayed gratification, a tendency to engage in risky behaviors and heightened novelty-seeking (Mitchell, 2004; Olmstead, 2006; Perry & Carroll, 2008).

The absence of a general agreement regarding the conceptualization of impulsivity that has characterized the impulsivity literature has – at least partially – been fuelled by the fact that impulsivity

has been studied by different research disciplines, each defining and assessing the construct in different ways.

Most notably, personality researchers tend to view facets of impulsivity as *traits* that are fairly stable over time and evident across a range of situations (Cloninger, Svrakic, & Przybeck, 1993; Eysenck & Eysenck, 1985; Tellegen, 1982), whereas neurocognitive researchers tend to approach facets of impulsivity as transitory *states*, sensitive to environmental influences (Dalley, Everitt, & Robbins, 2011). In accordance with these different conceptualizations of impulsivity, different measures have been developed to assess trait or state dimensions of impulsive behavior (Verdejo-Garcia et al., 2008). As a personality trait, impulsivity is typically measured using self-report questionnaires, which assess the subjective views on impulsive behavior. These instruments include questions that cover broad periods of time, making them appropriate for assessing stable or trait aspects of impulsivity. As argued by Gottesman and colleagues (2003), self-report measures can be considered as indicators of the phenotype of a disorder (the disorder as it appears). As transitory states by contrast, aspects of impulsivity are generally measured using computer-based neurocognitive tasks, which capture specific behavioral processes rather than general, trait-like impulsive tendencies. These neurocognitive tasks are often considered to be a more objective method of measuring impulsivity (Chamberlain & Sahakian, 2007). 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 or punishments). 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 self-report and neurocognitive measures may tap into some amount of variance of a similar underlying construct, the small magnitude of the observed effect size suggests that, overall, there is little overlap between self-report and neurocognitive tasks of impulsivity (Cyders & Coskunpinar, 2011). In what follows, the main definitions and measures derived from both personality and neurocognitive research traditions on impulsivity are outlined.

1.1.1. Personality dimensions and self-report measures 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 et al., 1993; Eysenck & Eysenck, 1985; Tellegen, 1982), suggesting that the term encompasses a variety of distinguishable personality traits (Patton, Stanford, & Barratt, 1995; Whiteside & Lynam, 2001). Accordingly, different measures have been developed in order to index trait dimensions of impulsivity, including the Barratt Impulsiveness Scale (BIS-11; Patton et al., 1995), the Eysenck Impulsiveness-Venturesomeness-Empathy Scale (I7; Eysenck, Pearson, Easting, & Allsopp, 1985), the Temperament and Character Inventory (TCI; Cloninger, Przybeck, Svrakic, & Wetzel, 1994) and the Zuckerman's Sensation Seeking Scale (Zuckerman, Eysenck, & Eysenck, 1978). In an attempt to overcome the heterogeneity in how impulsivity is conceptualized and assessed, Whiteside and Lynam (2001) performed a factor-analysis on 17 prominent measures purported to tap aspects of impulsive personality. Results revealed a robust four-factor structure, representing at least four different pathways to impulsive behavior: (1) a

lack of future orientation (i.e., lack of premeditation, motor or non-planning impulsivity), (2) a failure to follow through on goal-related, complex tasks while experiencing boredom (i.e., lack of perseverance/persistence or attentional impulsivity), (3) a need for excitement, novelty and stimulation (i.e., sensation or novelty seeking) and (4) difficulties in resisting strong impulses driven by negative or positive affect (i.e., negative or positive urgency). Whereas the first two pathways to impulsivity can be measured with the BIS-11, the Urgency, Premeditation, Perseverance and Sensation Seeking Impulsive Behavior Scale (UPPS; Whiteside & Lynam, 2001) covers all of these tendencies, with the exception of positive urgency. Motivational pathways to impulsive behavior, most notably sensation and novelty seeking, can additionally be measured with the Eysenck Impulsiveness-Venturesomeness-Empathy Scale, the Novelty Seeking Scale of the TCI and the Zuckerman's Sensation Seeking Scale. A closely related construct, reward sensitivity, refers to an increased reward (behavioral activation) against a reduced punishment (behavioral inhibition) sensitivity. Reward sensitive individuals are thought to have a dominant activation system, rendering them more reactive to positively valenced (incentive) stimuli and predisposing them towards approaching potential sources of reward (Gray, 1973). Over the years, this notion has been translated into several questionnaires, including the BIS/BAS scales (Carver & White, 1994) and the sensitivity to reward scale of the Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ; Torrubia, Ávila, Moltó, & Caseras, 2001). Other scales that mainly revolve around the constructs of reward drive vs. harm avoidance are the reward dependence scale of the TCI (Cloninger et al., 1994) and the three-dimensional constraint factor of the Multidimensional Personality Questionnaire (MPQ; Tellegen, 1982).

With self-report questionnaires, individuals are asked to recognize and report on their own behavior in several contexts and as a consequence, it is assumed that individuals have sufficient insight and cognitive ability to rate their own behavior accurately. Some authors have questioned this assumption and argue that these self-perceptions may not always accurately reflect real-life behavior (Aklin, Lejuez, Zvolensky, Kahler, & Gwadz, 2005; Reynolds et al., 2006). Moreover, having an impulsive personality may directly interfere with the completion of the questionnaires themselves, with impulsive individuals possibly giving less consideration to their answers (Verdejo-Garcia et al., 2008).

1.1.2. Neurocognitive dimensions and tasks of impulsivity

During the past decade, there has been a surge of interest for impulsivity within neuropsychological and neurocognitive research (Verdejo-Garcia et al., 2008). From a neurocognitive perspective, impulsivity is generally perceived as a transitory *state*, sensitive to environmental and personal influences. Often, a distinction is made between two neurocognitive expressions of impulsivity; 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 et al., 2011; Winstanley, Eagle, & Robbins, 2006). An overview illustrating these distinct neurocognitive aspects of impulsivity and some of the neurocognitive tasks that can be used to measure these is provided in Figure 1.

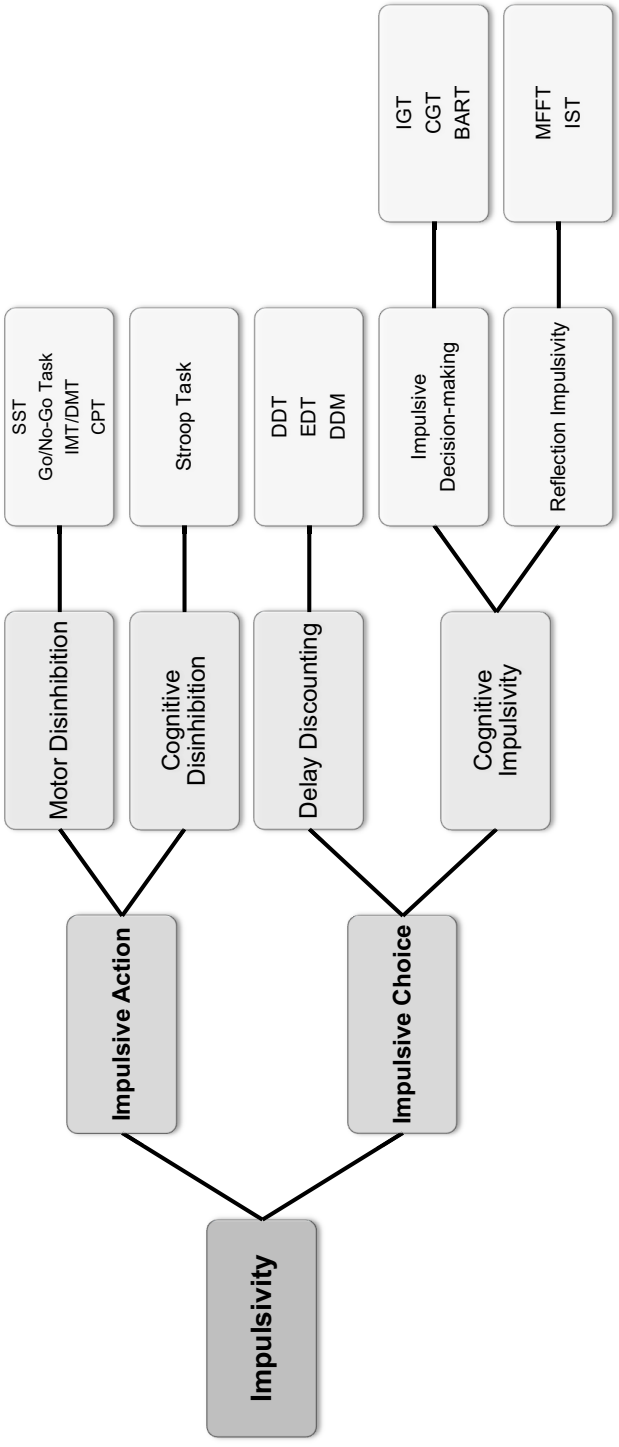

Figure 1: Conceptual overview of neurocognitive dimensions and tasks of impulsivity

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 "emotional versions" of the Stroop test, color words are replaced with words that are emotionally relevant to a certain disorder (e.g., "needle" for heroin-dependent individuals or threat-related words for individuals with an anxiety disorder). Longer interference scores on this test are induced by the motivational significance of the words, which capture attention more automatically. Longer interference scores are therefore believed to reflect a form of attentional bias. *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 et al., 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 et al., 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). Neuroimaging studies for instance, point 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 cognitive impulsivity. *Delay discounting* refers to a decrease in the subjective value of a reinforcer with time and 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). *Cognitive impulsivity* on the other hand, consists out of two subcomponents, which are labeled reflection impulsivity and impulsive decision-making. *Reflection impulsivity* refers to the tendency (not) to collect and evaluate enough information before making complex decisions. In tasks measuring this construct, individuals are required to slow down the decision-making process in order to gather sufficient information to make an accurate decision; these tasks include the Matching Familiar Figures Test (MFFT; Kagan, 1966) and the Information Sampling Test (IST; Clark, Robbins, Ersche, & Sahakian, 2006). *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).

Conclusion

These and other findings suggest that impulsivity is a multifaceted construct, comprised of several distinct, though closely related components (Evenden, 1999). The conceptual distinction between different impulsivity dimensions has been justified by studies showing that different impulsivity dimensions have dissociable concurrent and prospective external correlates (e.g., Billieux, Van der Linden, & Ceschi, 2007; Verdejo-Garcia, Bechara, Recknor, & Pérez-Garcia, 2007) and by neurobiological evidence supporting distinct cortico-striatal substrates and neurobiological processes underlying these various impulsivity constructs (Broos, Schoffelmeer, Pattij, & De Vries, 2012; Diergaarde et al., 2008; Whiteside, Lynam, Miller, & Reynolds, 2005). On the one hand, novelty seeking, sensation seeking and reward drive seem to form an appetitive motivational pathway to impulsive behavior, likely associated with altered functioning of the mesolimbic dopamine system (Gjedde, Kumakura, Cumming, Linnet, & Moller, 2010). On the other hand, lack of perseverance and premeditation pertain to a cognitive control pathway, reflecting inadequate forethought (inability to self-regulate behavior towards distant goals) and disregard of future outcomes. These alterations are related to orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) functioning and implicate multiple monoamine systems dysfunctions, including prefrontal dopamine, serotonin (5-hydroxytryptamine) and noradrenaline (Robbins & Arnsten, 2009). Similar suggestions have been made with respect to neurocognitive aspects of impulsivity. In contrast to response inhibition, which has been considered to represent a "cold" cognitive system largely dependent on the dorsolateral

prefrontal cortex (DLPFC) and ventrolateral prefrontal cortex, delay discounting and cognitive impulsivity can be viewed as feedback-sensitive “hot” affective systems, largely subsumed by ventromedial pathways connecting mesolimbic reward circuitry, including the amygdala and striatum, to the ventromedial prefrontal cortex (VMPFC) (Aron et al., 2007; Hare, O’Doherty, Camerer, Schultz, & Rangel, 2008; Kelly, Scheres, Sonuga-Barke, Castellanos, & 2007; Rubia, 2010).

1.2. Drug addiction

1.2.1. Definition, prevalence and consequences

Illicit drug use is highly prevalent: worldwide, 230 million individuals have been estimated to use illegal drugs at least once a year (UN World Drug Report, 2012). In Europe, at least 85 million adults have used an illicit drug at some point in their lives, representing around a quarter of Europe's adult population (EMCDDA, 2013). Most of these report having used cannabis, with much lower estimates for lifetime use of other drugs, such as cocaine, amphetamines and ecstasy (EMCDDA, 2013).

The occasional use of an addictive substance, often driven by its rewarding or reinforcing effects, is not in itself a pathological behavior (Piazza & Deroche-Gamonet, 2013). It is critically distinct from what to date is believed to fundamentally characterize drug addiction, i.e., compulsive drug intake, referring to the persistence of drug use despite serious negative consequences such as medical illness, failure in significant life roles and financial problems (Everitt & Robbins, 2005). Whereas the desire to elevate or alter mood often motivates initial drug use, the pleasure produced by drugs often habituates and can be markedly reduced over time (e.g., by medical complications) (Hyman & Malenka, 2001). Still, addicted individuals often report that they continue to take the drug, even when it is no longer perceived as pleasurable. Commonly, they describe their continued drug use as an (unsuccessful) attempt to re-experience the initial "highs" (Hyman & Malenka, 2001). Consistent with these clinical reports, it has been argued that the dominant emotional response to drugs in addiction, as opposed to initial drug use, is no longer "liking" but intense drug "wanting" (Robinson & Berridge, 1993). The continued pursue and abuse of substances by addicted individuals, despite their often extensive adverse consequences and in the absence of significant drug liking, suggests that drug use may eventually progress into a condition characterized by a loss of control over behavior. Other, related features are an extremely strong motivation to procure the drug, the emergence of a negative emotional state (e.g., dysphoria, irritability) when access to the drug is prevented and the long-lasting risk of relapse, often initiated by exposure to drug-related cues (Koob & Volkow, 2010).

In the fourth version of the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV; American Psychiatric Association, 1994), the terms substance abuse and substance dependence are used to reflect two independent categories representing a different realm of problematic use (Piazza & Deroche-Gamonet, 2013). Although the term *dependence* has traditionally been used to refer to the manifestation of a withdrawal syndrome upon cessation of drug use, criteria for substance dependence in the DSM-IV are much more than a manifestation of a withdrawal syndrome. In fact, the word is rather equivalent to and often used interchangeably with the term addiction[1] and mainly refers

[1] The term substance dependence (as defined by the DSM-IV) and addiction will be held equivalent for this dissertation to refer to chronic drug use, in which voluntary control over drug or alcohol use is compromised and compulsive behavior ensues, irrespective of consequences. In addition, the word 'drug' will be used to encompass all psychoactive substances (including alcohol) that are abused, despite adverse consequences.

to loss of control over drug taking. The consolidation of abuse and dependence as two conceptually independent categories is probably the most apparent evolution from the DSM-IV to the DSM-5 (APA 2013): in the DSM-5, these two categories have been replaced with a single (substance-specific) category: Substance Use Disorders (SUDs).

Epidemiological studies show that fewer than 20% of drug users lose control over their drug intake and develop clinical signs of addiction, suggesting large individual differences in the vulnerability to become addicted (de Wit, 2009; Koob & Le Moal, 2001; Wagner & Anthony, 2002). Such individual differences are believed to result from complex interactions between the drug, a vulnerable genotype and environment factors (Kreek et al., 2005; Piazza & Le Moal, 1996). Numbers from the UN World Drug Report (2012) suggest that, globally, 27 million individuals are addicted, with a fairly heterogeneous situation at a national level; some countries consistently report low and stable prevalence levels, whereas others report high prevalence rates (World Drug Report, 2010). Still, large gaps remain in our knowledge of the precise extent of problematic use. What is clear however, is that the disease burden attributable to drug addiction at a global level is tremendous, larger than any mental disorder and greater than all maternal conditions combined (Degenhardt & Hall, 2012; Degenhardt et al., 2013; Lopez, Mathers, Ezzati, Murray, & Jamison, 2006; WHO, 2008; Murray et al., 2012). Worldwide, 11.8 million people are estimated to suffer a moderate to severe disability attributable to illegal drug use (Mathers, Stevens, & Mascarenhas, 2009) and the numbers on disability related to alcohol are even higher (Brorson, Arnevik, Rand-Hendriksen, & Duckert, 2013; Degenhardt & Hall, 2012). Drug-associated burdens are multifold and include medical, psychological, cognitive, social, legal, and financial problems. Problematic drug use is also one of the major causes of mortality among young people in Europe, either directly through overdose (i.e., drug-induced deaths) or indirectly through drug-related diseases and accidents, violence and suicide (EMCDDA, 2013; UN World Drug Report, 2012). These drug-associated burdens obviously lead to high costs for society; drug addiction has some of the highest overall medical health costs of any medical disorder, taking into account comorbid disorders such as lung cancer, cardiovascular problems, HIV/AIDS or hepatitis C (Degenhardt & Hall, 2012). Drug-related economic costs for society also include those related to crime and the criminal justice system, loss of productivity and unemployment (French, Salome, & Carney, 2002; Palepu et al., 2001). Although costs are often translated in economic terms, their impact is obviously much more insidious, eroding the foundation of human relationships (Volkow, Baler, & Goldstein, 2011).

1.2.2. Contemporary perspectives on drug addiction

1.2.2.1. Addiction as a chronic brain disease

Historically, different models have been proposed to explain drug addiction, which mainly differ in the causes they attribute to drug use and the role of willpower (van den Brink, 2005). Since the seventies, most researchers and clinicians have adopted a bio-psycho-social model, which emphasizes the complex and continuous interaction between biological, psychological and social factors in drug addiction. Substantial progress in neurobiology however, has recently led to a resurgence of interest in biological explanations of addiction (Dackis & O'Brien, 2005). The perspective emerging from several lines of research is one in which addiction is seen as a cycle of compulsive drug-seeking behavior,

fuelled by dysregulated neurocognitive and neurobiological processes. To date, it is widely accepted that addiction involves significant neuroadaptation to brain structure and function, including signaling pathways, neurotransmitters, and cell mechanisms that overlap with those that mediate normal learning, memory and cognitive control processes (Feil et al., 2010; Koob & Volkow, 2010; Noël, Brevers, & Bechara, 2013). These adaptations have been proposed to contribute to the maintenance of the disorder (Feil et al., 2010; Koob & Volkow, 2010). To the extent that some of these changes are long-lasting and, in some instances perhaps even irreversible, they support the conceptualization of addiction as a chronic brain disease (Leshner, 1997).

1.2.2.2. Dual pathway models

One of the major purposes of recent neurobiological research has been to understand the biological and neural mechanisms that mediate the switch from controlled to compulsive drug use and thus, contribute to the maintenance of the disorder. Whereas no single theory has emerged as correct and many questions remain to be answered, there are at least several common features across theories that appear to be well established. In particular, most contemporary theories propose that the loss of control that is central to addiction reflects 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).

- Bottom-up system

The bottom-up system, also referred to as the impulsive or reactive system (Bechara, 2005; Bickel & Yi, 2008), appraises and responds to stimuli immediately and automatically in terms of their affective and motivational significance, without consideration of long-term consequences or accessing higher order cognitive processes (Morgenstein, Naqvi, Debellis, & Breiter, 2013). This process is largely involuntary, automatic, and associative in nature (Bechara, 2005) and is subserved by subcortical brain areas, including the amygdala and reward-sensitive dopamine-rich areas in the midbrain (Heatherton & Wagner, 2011). Through its connections with subcortical regions, the amygdala automatically triggers a pattern of behavioral (e.g., reward seeking), visceral (e.g., increased heart rate) and cognitive reactions (e.g., attention) upon exposure to a motivational significant stimulus, promoting the obtainment of an immediately available reward or the avoidance of an immediately obtainable punishment (Morgenstein et al., 2013).

The process of addiction is initiated in part by the fast and high drug-induced increases in extracellular dopamine levels in a key region of this system: the nucleus accumbens (Nacc), located in the ventral striatum. These drug-induced increases in extracellular dopamine levels appear to be positively related to the intensity of the “high” and positive reinforcement drug users initially experience (Drevets et al., 2001; Kalivas & Volkow, 2005; Koob & Le Moal, 2001; Volkow et al., 1996). Chronic exposure to the physiological effects of drugs however, triggers a series of molecular changes and adaptations in bottom-up circuits, including those involved in saliency/reward, motivation/drive and memory/conditioning (Volkow, Fowler, & Wang, 2004). These neural changes result in an enhanced motivational value for the drug (Volkow et al., 2004). After repeated and prolonged drug exposure, brain reward thresholds become chronically elevated and drug users become substantially less

sensitive to natural reinforcers (Beck et al., 2009; Goldstein et al., 2007; Lubman et al., 2009; Volkow et al., 2004). These increased reward thresholds do not appear to return to baseline levels with abstinence (Lubman et al., 2009) and may result in an escalation of drug use in order to compensate for reward hyposensitivity.

In addition to their primary reinforcing properties, addictive drugs establish strong Pavlovian associations with the stimuli or cues that have repeatedly been associated with them (e.g., needle, bar) (Childress, Ehrman, Rohsenow, Robbins, & O'Brien, 1992; Goddard, Son Hing, & Leri, 2013). Drug-conditioned stimuli become neurochemically framed as particularly salient and acquire the ability to automatically grab attention (i.e., attentional bias) and produce a variety of physiological and psychological responses (e.g., craving) (Field & Cox, 2008; Goddard et al., 2013; Lubman, Peters, Mogg, Bradley, & Deakin, 2000). The newfound ability of drug-associated cues to evoke conditioned motivational and neurobiological reactions explains why exposure to drug-associated stimuli can automatically trigger drug-seeking responses, an effect that has been implicated in the maintenance of ongoing drug use and in the occurrence of relapses following periods of abstinence (Everitt et al., 2001; Ingjaldsson, Thayer, & Laberg, 2003; Shaham & Miczek, 2003; Van De Laar, Licht, Franken, & Hendriks, 2004). After extended training of these associations, behavior becomes substantially less sensitive to outcome devaluation. Indeed, drug-seeking responses induced by drug-associated cues show remarkable resistance to extinction (Ciccocioppo, Sanna, & Weiss, 2001; Robbinson & Berridge, 2001; Weiss et al., 2001) and persist regardless of the drug's current incentive value (i.e., they are fully dissociable from the pleasure and reward elicited by drug use). Eventually, drug-seeking and taking behavior becomes largely automatic and habitual, i.e., under control of stimulus-response associations. Partially illustrating this point, neuroimaging studies show that the effects of drug use on dopamine neurotransmission become attenuated in the ventral striatal-reward pathway and potentiated in the dorsal striatal-habit learning pathway (Ito, Dalley, Robbins, & Everitt, 2002).

- Top-down system

Whereas traditional models of drug addiction predominantly emphasized the importance of the reward system, the past several years have seen an increased focus on the role of a second, cognitively-driven top-down system (Feil et al., 2010). Once motivational or behavioral associations have been developed between drugs and drug-associated cues, cognitive control over these associations and the responses they elicit becomes increasingly important. According to dual-process models, this control over automatic associations and responses is regulated by a top-down system, also referred to as the executive or reflective system (Bechara, 2005; Bickel & Yi, 2008). The top-down system is largely subserved by distributed networks within the prefrontal cortices, including the DLPFC (goal identification and selection), OFC (impulse control and reversal learning) and ACC (assessment of consequences, response inhibition and error detection) (Feil et al., 2010; Volkow et al., 2007; Yücel & Lubman, 2007), 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 or inhibit habitual responses in favor of longer-term goals or benefits (Braver & Bongiolatti, 2002). Top-down control is particularly critical when the pathways leading to a higher order

goal compete for behavioral output with more immediately rewarding or established patterns. For instance, maintaining a successful diet can be notoriously difficult when confronted with tasty, high calorie food. According to dual-process models, the outcome of such conflicts between the impulse to indulge in immediately rewarding/habitual behaviors and long-term goals critically depends on top-down control (Houben, Wiers, & Jansen, 2011). Top-down control in other words refers to the process whereby conscious internal goals take precedence over automatic, impulsive or habitual processes (Hester & Garavan, 2009).

In addiction however, there is a fundamental impairment or break-down in top-down cognitive control, leading to a tendency to engage in automatic/habitual rather than controlled behaviors and a pronounced focus on immediate rather than long-term outcomes, even in the face of threats to survival (Feil et al., 2010). Corroborating this notion, several studies have provided consistent evidence of a relationship between prolonged drug use and neuroadaptations in the different PFC-striatothalamic circuits underlying cognitive control (Bolla et al., 2004; Feil et al., 2010; Goldstein, Volkow, Wang, Fowler, & Rajaram, 2001; Kaufman, Ross, Stein, & Garavan, 2003). On a cognitive level, these brain disruptions are typically reflected by impaired functioning in a number of domains, such as attention, memory, decision-making, inhibitory control and problem-solving (Bolla et al., 2003; Cunha, Nicastri, Gomes, Moino, & Peluso, 2004; Tucker et al., 2004). Impairments in prefrontal and cognitive functioning likely contribute to the difficulties many drug users have in inhibiting uncontrollable urges to consume drugs regardless of the risks involved (i.e., the loss of control) and therefore, to the persistence of drug-seeking and drug-taking behaviors (Feil et al., 2010).

- The insula

More recently, a triadic neurocognitive model of addiction has been proposed, which posits that the maintenance of drug addiction is also fuelled by abnormal functioning in a third, insula-dependent system, involved in the reception of interoceptive signals and their translation into feeling states (such as urge and craving) (Noël, Brevers, & Bechara, 2013). Engagement of the insula has been proposed to exacerbate activity of the impulsive bottom-up system and to hijack activity of the top-down system, creating a severe imbalance between the two (Noël et al., 2013). In particular, insula dysfunction in substance-dependent individuals (SDI) may contribute to heightened experiences of drug-related urges, potentially at the expense of other interoceptive signals that are normally used to guide advantageous decision-making and the ability to learn from errors (Paulus, 2007; Paulus & Stewart, 2014).

1.2.2.3. Impulsivity: a hallmark characteristic of drug addiction

It has been appreciated for a while that the neurobiological factors underlying compulsive drug use and its maintenance often interact in the expression of impulsive traits and impulsive states (see section 1.1.), which can be more easily measured. For example, the imbalance between the strength of the top-down and bottom-up system in addiction typically leads to corresponding failures in the ability to suppress inappropriate *action*s or cognitions (impulsive action) or a preference for immediate rewards while disregarding long-term (negative) consequences (impulsive choice) (Winstanley et al., 2006). Measuring brain activations during choices between immediate and delayed rewards, McClure

and colleagues (2004) for instance found greater activation of the bottom-up system when the immediate monetary option was chosen, and greater relative activation of the top-down system when the later reward was chosen, suggesting that delay discounting provides a summary measure of the relative control of the bottom-up and top-down system (Bickel, Yi, Landes, Hill, & Baxter, 2011; McClure, Laibson, Loewenstein, & Cohen, 2004). The blunted motivational response to natural rewards in drug addicts previously described has also been found to correlate with trait impulsivity and may lead to individual differences in present- versus future-oriented tendencies, i.e., in delay discounting (Beck et al., 2009; Goldstein & Volkow, 2002; Wrase et al., 2007).

Consistent with these theories, there is an extensive literature linking trait and neurocognitive aspects of impulsivity to drug addiction and dependence, as has been reviewed previously (e.g., Congdon & Canli, 2008; Verdejo-Garcia et al., 2008). Personality studies consistently point to higher trait impulsivity in SDI, including sensation/novelty seeking, lack of premeditation, lack of perseverance, urgency and reward sensitivity (Bjork, Hommer, Grant, & Danube, 2004; Coffey, Gudleski Saladin,& Brady, 2003; Dolan, Bechara, & Nathan, 2008; Mitchell, Fields, D'Esposito, & Boettiger, 2005; Moeller et al., 2002; Whiteside & Lynam, 2003). More recently, similar findings have been obtained using neurocognitive tasks of impulsivity. In particular, a growing body of evidence suggests that SDI show notable deficits on tasks indexing aspects of impulsive action (motor and cognitive inhibition) and impulsive choice (delay discounting and cognitive impulsivity) (Clark et al., 2006; Madden, Bickel, & Jacobs, 1999; Reynolds et al., 2006; Verdejo-García et al., 2008). Although few studies have directly compared impulsivity profiles between groups of users dependent upon different substances (Verdejo-Garcia, Perales, & Perez-Garcia, 2007), there is little evidence for disproportionate relationships between impulsivity and any specific substance (Verdejo-Garcia et al., 2008).

In addition to a robust body of cross-sectional data, converging evidence indicates that impulsivity mediates the switch from controlled to compulsive drug use, lending additional support for its contribution to the maintenance of drug addiction (Belin, Mar, Dalley, Robbins, & Everitt, 2008; Diergaarde et al., 2008; Koob & Le Moal, 2001). High-impulsive rats for instance, are more likely to progress from initial drug use to compulsive drug-seeking behavior, defined by the persistence of drug intake despite punishing feedback (Belin et al., 2008; Bird & Schenk, 2012; Everitt et al., 2008). Specifically, rats with a consistent tendency to respond prematurely (designated as high impulsive) on a continuous performance test tend to escalate intravenous cocaine self-administration, tolerate foot-shock in order to seek the drug (the latter being a key criterion of compulsive drug-seeking behavior), and show enhanced relapse of cocaine self-administration behavior following abstinence (see Dalley et al., 2011; Economidou, Pelloux, Robbins, Dalley, & Everitt, 2009). Similar findings have been obtained in human studies. Hogarth and colleagues (2011) for instance, showed that high impulsivity in smokers was predictive of a tendency to over-rely on habit learning. Overall, these different lines of evidence seem to indicate that high levels of impulsivity are predisposing for the development of compulsive drug taking, and that personality and neurocognitive dimensions of impulsivity reflect behavioral markers of the neurobiological processes that support the maintenance of compulsive drug use.

1.2.3. Addiction treatment and outcomes

Despite the chronic nature of drug addiction, a substantial percentage of SDI eventually achieves sustained recovery (Dennis, Scott, Funk, & Foss, 2005; McLellan, Lewis, O'Brien, & Kleber, 2000). Most SDI do so after participating in treatment (Cunningham, Lin, Ross, & Walsh, 2000; Dennis et al., 2005). Several decades of research have demonstrated that addiction treatment can significantly decrease substance use, may help to ameliorate overall social and psychological functioning and can improve legal and employment-related problems (Gossop, Marsden, Stewart & Kidd, 2003; Gossop, Trakada, Stewart, & Witton, 2005; Hubbard, Craddock, Flynn, Anderson, & Etheridge, 1997; Longabaugh et al., 2005; Vanderplasschen et al., 2013).

Besides there being some effective pharmacotherapies available for the treatment of nicotine, alcohol, and opioid addictions (Potenza, Sofuoglu, Carroll, & Rounsaville, 2011; Sofuoglu & Kosten, 2004), a number of effective psychosocial and behavioral interventions have been developed (Dutra et al., 2008), with the strongest level of empirical support for contingency management (CM, where abstinence or other desirable behaviors are reinforced with rewards), motivational interviewing (MI, where a client-centered, directive but nonjudgmental interviewing style is used to enhance readiness to change by helping clients explore and resolve ambivalence), and cognitive behavioral therapy (CBT, which teaches specific (cognitive) strategies and skills to reduce drug use) (Carroll et al., 1994; Higgins et al., 1991; Miller, 1985; Sofuoglu, DeVito, Waters, & Carroll, 2013). Different from the specificity of the effects of most pharmacological interventions for drugs of abuse, empirically validated behavioral therapies such as CM, MI and CBT appear to be effective across the range of SUDs (Dutra et al., 2008; Sofuoglu et al., 2013). To date, increasing efforts are also being made to tailor these standardized interventions in accordance with new insights into the neurobiological and cognitive deficits associated with drug addiction. For example, computerized versions of CBT that can be tailored for drug users with mild cognitive impairments have been developed (Carroll et al., 2008). Over the past 10 years, there has also been a surge of clinical interest in developing new ways to intervene in the neurobiological and cognitive processes underlying drug addiction (Sofuoglu et al., 2013). New strategies are being developed that focus on (1) strengthening the influence of prefrontal cortical and executive control processes on behavior, or (2) desensitizing impulsive or habitual reactions to drug-related stimuli (Bates, Buckman, & Nguyen, 2013; Bickel et al., 2011; Fadardi & Cox, 2009; Garland, Gaylord, Boettiger, & Howard, 2010; Schoenmakers et al., 2010; Wiers, Eberl, Rinck, Becker, & Lindenmeyer, 2011).

Despite these encouraging developments and findings, current treatments for addiction are helpful to some, but far from satisfactory, as is true for many chronic brain diseases (Hyman & Malenka, 2001). In fact, effect sizes remain modest for most available therapies (Dutra et al., 2008) and SDI show considerable variability in treatment success (Sofuoglu et al., 2013). Whereas some individuals successfully complete treatment and are able to initiate/maintain abstinence following treatment, others drop out of treatment prematurely and/or relapse soon following treatment discharge (Brorson et al., 2013; Stotts et al., 2007).

1.2.3.1. Treatment retention and drop-out

Whereas the efficacy and effectiveness of addiction treatment is well established, in order for treatment to produce favorable outcomes, a client must be retained in it. Indeed, the effectiveness of many forms of addiction treatment appears to be predicted by treatment retention, i.e., the length of time spent in treatment (Dalsbø et al., 2010). Yet, treatment retention has been found to be poor across the majority of addiction treatment studies and treatment modalities (Brorson et al., 2013; Stotts et al., 2007). In fact, one of the most difficult problems facing the treatment of individuals with a SUD are the large number of subjects who fail to complete treatment, or who drop out of treatment prematurely. In inpatient detoxification programs for example, which can be seen as an important first step within the broader treatment process, treatment drop-out rates higher than 55% have been reported (Brorson et al., 2013; Gilchrist, Langohr, Fonseca, Muga, & Torrens, 2012; Specka, Buchholz, Kuhlmann, Rist, & Scherbaum, 2011). As such, only a minority of the clients who begin an acute treatment episode reach the stage at which they could transition to continuing care (McKay & Hiller-Sturmhoefel, 2011). High drop-out rates have also been found in long-term treatment programs (Deane, Wootton, Hsu, & Kelly, 2012). In residential therapeutic communities (TCs) for instance, which remain a core modality of the treatment system in Europe and the United States, it is common for as many as 50% of residents to drop out within the first month, whereas another 25-40% drops out during subsequent months (Condelli, 1994; Deane et al., 2012; Samuel et al., 2011). Often, this results in as few as 10% of admissions receiving a moderately to maximally effective dose of treatment in TCs (Condelli, 1994).

High drop-out rates are particularly problematic from a clinical perspective, 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 (Brorson et al., 2013; Dalsbo et al., 2013; Laudet, Stanick, & Sands, 2007; Simpson, 1979; Simpson, 2004; Vanderplasschen et al., 2013; Zhang, Friedmann, & Gerstein, 2003). In particular, a sufficient length of time spent in an intervention constitutes one of the strongest and most consistent predictors of positive post-treatment outcomes, including sustained abstinence, improved mental health, employment and less criminal involvement (Ball, Carroll, Canning-Ball, & Rounsaville, 2006; Brecht, Greenwell, von Mayrhauser, & Anglin, 2006; De Leon, 1991; Hser, Evans, Huang, & Anglin, 2004; Moos & Moos, 2003; Simpson, 1997). Conversely, premature treatment drop-out has been found to limit overall treatment effectiveness, to increase the likelihood of relapse and to exacerbate financial, health and legal consequences (Brewer, Catalano, Haggerty, Gainey, & Fleming, 1998; King & Canada, 2004; Stark, 1992). Evidently, treatment drop-out not only impacts clients' treatment outcomes but also comes with a high cost to society and has obvious negative implications for agencies providing services (Mark, Vandivort-Warren, & Montejano, 2006; Simpson, 1997).

1.2.3.2. Relapse

Relapse, or the resumption of drug taking after periods of abstinence, is another major problem pertaining to the treatment of SDI (Sinha, 2011). Even when drugs are unavailable or when individuals have been successful in curbing their drug use for extended periods, drug users remain extremely vulnerable to events that precipitate relapse (Witkiewitz & Marlatt, 2004). Estimates from clinical

treatment studies suggest that more than two thirds of SDI relapse after initiating treatment (Hyman et al., 2008; Sinha, 2011). Of those who resume drug use following treatment, most do so in the first weeks or months after treatment termination (Bonn-Miller & Moos, 2009). Hyman and colleagues (2008) for instance, found that more than 70% of cocaine-dependent individuals had returned to cocaine use during a 90-day follow-up period following discharge from inpatient treatment. Although estimated relapse rates among SDI vary widely in relation to the definition of relapse[2] and follow-up interval, rates are typically similar to those for other well-characterized chronic medical illnesses, such as diabetes, hypertension and asthma (McLellan et al., 2000). This observation has contributed to the growing recognition that drug addiction should be viewed as a chronic condition (Leshner, 1997; McLellan et al., 2000; McLellan, 2002; O'Brien & McLellan, 1996).

[2] The WHO defines relapse as a return to drinking or drug use after a period of abstinence, often accompanied by reinstatement of dependence symptoms. Whereas in most studies, relapse is defined as any use at all after a period of abstinence, some researchers have distinguished relapses from so-called 'lapses' or 'slips', which refer to isolated occasions of alcohol or drug use (McKay, Franklin, Patapis, & Lynch, 2006).

1.3. The current dissertation: the role of impulsivity in predicting addiction treatment outcomes

1.3.1. Rationale and relevance

In order to break the cycle of repeated re-admissions and recurrent episodes of relapse following treatment, one major focus in optimizing treatment involves the identification of pre-treatment individual factors related to poor addiction treatment outcomes (Sinha, 2011). Identifying reliable predictors of poor addiction treatment outcomes may contribute to the early detection of individuals with the highest risk for premature treatment drop-out and relapse, such that these clients may receive additional monitoring. The identification of dynamic predictors may elucidate potential areas to target in treatment. Accordingly, it may help to prevent treatment failures and to avoid the unnecessary provision of restricted treatment resources (Adamson, Sellman, & Frampton, 2009). Although the characterization of drop-out or relapse "determinants" is not new in the field of addiction research, previous studies have been criticized for testing a large number of variables without benefit of theoretical models defined a priori, nor even a rationale for selecting various predictors (Stotts et al., 2007). Such reliance on completely data-driven systems maximizes the likelihood of chance findings (Stotts et al., 2007). Moreover, an overview of the literature indicates that the majority of previous outcome studies have focused primarily on static (mainly demographic) factors (e.g., race, younger age), which cannot be influenced by intervention (Adamson et al., 2009; Brorson et al., 2013). Consequently, there is a need for studies that focus on a selective set of dynamic predictors based on theoretical considerations and potential implications for treatment development.

We believe that the main focus of the present dissertation, i.e., examining the role of impulsivity in predicting addiction treatment outcomes, is consistent with this recommendation. First, impulsivity is critically implicated in the maintenance of drug addiction. Because pathophysiological factors maintain the disease state that treatments target and attempt to remediate, it is reasonable to assume that these factors may negatively affect the recovery process (Morgenstern et al., 2013). Second, impulsivity has been found to be malleable by treatment (Bickel et al., 2011). Given the malleability of impulsivity, a better understanding of the relationship between impulsivity and treatment outcomes could in future lead to the development of more specific and tailored therapies aimed at improving addiction treatment outcomes.

1.3.2. Statement of the problem

Whilst the clinical literature linking impulsivity to poor addiction treatment outcomes is still in its infancy, converging evidence suggests that increased impulsivity in SDI – as measured at treatment entry – is associated with poor treatment retention, premature treatment drop-out and a higher propensity to relapse. In cocaine-dependent individuals for instance, higher impulsivity at treatment onset has been linked to shorter treatment retention and a greater propensity to drop out of treatment prematurely (Moeller et al., 2001; Patkar et al., 2004). In the same line, preliminary evidence suggests that higher levels of sensation seeking in cocaine users negatively correlate with abstinence rates (Patkar et al., 2004). In opiate-dependent individuals, those with higher novelty seeking traits have been found to attend significantly fewer scheduled visits and show shorter treatment retention during their participation in a CM program (Roll, Saules, Chudzynski, & Sodano, 2004). Comparable findings

have been reported in studies on nicotine- and alcohol-dependent individuals, in which subjects with increased impulsivity were found to have higher drop-out rates and greater difficulties maintaining abstinence than those with lower levels of trait-impulsivity (Bowden-Jones, McPhillips, Rogers, Hutton, & Joyce, 2005; Charney, Zikos, & Gill, 2010; Doran, Spring, McChargue, Pergadia, & Richmond, 2004). Preliminary research is thus supportive of the notion that impulsivity may be a promising candidate in the search for key predictors of poor addiction treatment outcomes. However, it should be noted that these previous studies have suffered from several noteworthy shortcomings, which have hampered significant progress in elucidating the precise mechanisms underlying treatment failure as well as the translation of findings into more effective recovery-oriented services.

First and perhaps most importantly, the majority of previous outcome studies have treated impulsivity monolithically (Moeller et al., 2001; Patkar et al., 2004), despite there being a broad agreement that impulsivity is a multifaceted construct comprised of several components (Verdejo-Garcia et al., 2008; Whiteside & Lynam, 2001). In personality studies on the association between impulsivity and addiction treatment outcomes for example, the different BIS-11 subscales (i.e., motor, non-planning and attention scales) are often summed to produce a total score (Moeller et al., 2001; Patkar et al., 2004), which ignores the multidimensional nature of impulsivity in general and of the BIS-11 specifically. This inappropriate use of summary scores may lead to problems in identifying true relationships between impulsive traits and treatment outcomes, as these relationships may differ among motor, attentional and non-planning impulsivity (Coutlee, Politzer, Hoyle, & Huettel, 2014). This unilateral approach of impulsivity has also dominated the neurocognitive literature. For instance, neurocognitive studies examining the impact of either impulsive action or impulsive choice on addiction treatment outcomes have typically been conducted in separate groups, each focusing on one particular aspect of impulsivity independently (Brewer et al., 2008; De Wilde, Verdejo-Garcia, Sabbe, Hulstijn, & Dom, 2013; Streeter et al., 2008). Moreover, personality and neurocognitive research traditions on impulsivity have historically remained largely independent. Accordingly, the different methods that have been used to index impulsivity (i.e., self-report questionnaires vs. neurocognitive tasks) have rarely been integrated (Enticott & Ogloff, 2006; Evenden, 1999), despite evidence suggesting that both methods represent different levels of analyses (Reynolds et al., 2006; Sharma, Markon, & Clark, 2014). As such, it remains largely unknown whether each assessment strategy is tapping unique variance in addiction treatment outcomes and thus, whether their joint use has incremental predictive power over the use of either type of measure alone. Because different components of impulsivity recruit different brain circuitries and may be susceptible to diverse pharmacological influences (Diergaarde et al., 2008), elucidating which impulsivity aspects are more relevant to treatment outcomes than others may have important treatment implications. Overall, a comprehensive assessment including both self-report and neurocognitive tasks of impulsivity within a given sample may be vital to attain the deep phenotyping required for understanding and buffering the mechanisms responsible for poor addiction treatment outcomes (Potenza et al., 2011).

Second, most previous studies on the relationship between impulsivity and addiction treatment outcomes have been part of randomized clinical trials (RCTs) examining the effects of different pharmacotherapies (e.g., Carroll et al., 2011; Dallery & Raiff, 2007; Schmitz et al., 2009). Whilst these

RCTs are often considered the gold standard in treatment studies, generalizability of findings to more multimodal and real-world clinical treatment settings may be limited. As such, it may be difficult for existing treatment programs to deduce if and how research findings pertain to their own setting. Bridging the currently existing gap between science and clinical practice requires smaller scale investigations conducted in real-world treatment settings that treat a broad mix of clients.

Finally, the majority of previous studies have examined direct pathways by which impulsivity may impact on addiction treatment outcomes, without considering other pathways of influence. Still, effects of impulsivity on treatment drop-out or relapse may not necessarily be direct. Rather, impulsivity may impede addiction treatment outcomes by affecting therapeutic change mechanisms, including readiness to change or self-efficacy (Bates, Pawlak, Tonigan, & Buckman, 2006; Blume, Schmaling, & Marlatt, 2005). Consistent with this expectation, recent evidence suggests that increased impulsivity in drug users is associated with lower motivation to change (Peters, Petry, Lapaglia, Reynolds, & Carroll, 2013). Less motivation to change, in turn, has been identified as an important risk factor for premature treatment drop-out and relapse (Simpson, & Joe, 1993). However, to the best of our knowledge, no previous studies have addressed both aspects of mediation: namely, that impulsivity results in poor motivation for treatment, and that this lower treatment motivation results in poorer treatment outcomes. To the extent that this may contribute to a modification of treatment programs to the specific needs of highly impulsive individuals, studies may benefit from considering such indirect pathways.

1.3.3. Research objectives of the doctoral dissertation

The main objective of this dissertation is to further extend our knowledge regarding the relationship between impulsivity and addiction treatment outcomes, including treatment retention, drop-out and the propensity to relapse. This general objective is further subdivided into two specific aims.

First, we wanted to systematically evaluate the available literature regarding the relationship between impulsivity and addiction treatment outcomes and thereby facilitate interpretation of the existing data. In line with the currently dominant paradigms in addiction research, the recent upsurge of interest for the effects of impulsivity on addiction treatment outcomes has been most prominent in the neurocognitive literature. Given the rapid growth of new research in this area, the focus of the review is narrowed down to neurocognitive studies on impulsivity and addiction treatment outcomes. This focus was further prompted by the observation that many contemporary addiction treatment programs place high demands on top-down cognitive control, and therefore, may be particularly challenging for SDI with neurocognitive deficits related to impulse-control. Moreover, 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). A second aim of the current dissertation was to conduct an empirical study on the relationship between impulsivity and addiction treatment outcomes that explicitly addresses some of the gaps and limitations of previous studies.

First, and in an attempt to bridge the currently existing gap between science and clinical practice, we wanted to examine the relationship between impulsivity and addiction treatment outcomes in the context of *real-world addiction treatment programs*, thereby increasing the generalizability of findings

compared to previous research. We reasoned that impulsivity would particularly affect treatment outcomes in addiction programs that rely heavily on functions known to be involved in adequate impulse control, including the ability to plan, postpone immediate gratification and consider the long-term consequences of available options. Within this respect, the main focus of the current dissertation was on highly structured, inpatient detoxification programs. This choice was not only fuelled by theoretical considerations. Although detoxification programs are rarely effective by themselves (i.e., they represent a first step in the broader treatment process), these programs have the potential for steering a large number of SDI towards long-term treatment. Growing evidence suggests that drop-out and relapse rates are particularly high during this initial phase of treatment, so that only a minority of the clients who begin a detoxification program reach the stage at which they could transition to continuing care (Millery, Kleinman, Polissar, Millman, & Scimeca, 2002). Therefore, a better understanding of the factors associated with poor treatment outcomes in these settings is critical. In contrast to the large literature on outcome predictors in long-term treatment however, little research has been conducted on outcome predictors in detoxification programs.

Second, the empirical part of this dissertation explicitly adopts a *multidimensional approach of impulsivity* while examining the association between impulsivity and post-treatment relapse. This multidimensional approach will help to elucidate whether certain dimensions of impulsivity serve as better predictors of relapse than others and thereby, increase the clinical significance of previous findings. Similarly, by including both personality and neurocognitive measures of impulsivity, our study may help to determine whether the joint use of these methods has incremental predictive power over the use of either type of measure alone.

Finally, in the empirical part of this dissertation, we explore indirect pathways by which impulsivity may negatively affect addiction treatment outcomes. Given the well-established relationship between treatment retention and post-treatment relapse (Gossop, Stewart, Browne, & Marsden, 2002), we investigate whether any observed relationship between impulsivity and relapse is mediated by treatment retention. Second, we explore whether the relationship between impulsivity and treatment retention is mediated by treatment motivation. By *examining indirect mechanisms* by which impulsivity affects treatment outcomes, we hope that the current dissertation supports future work to translate findings into effective recovery-oriented services.

The practice-oriented character of this dissertation is a consequence of its orthopedagogical orientation. Orthopedagogics is an integrative, scientific discipline, with a practice-oriented character directed towards action (Broekaert, D'Oosterlinck, Van Hove, & Bayliss, 2004). Similarly, this dissertation is oriented towards action; one of its broader aims is to gain more insights into how treatment for SDI with inflated impulsivity can be adjusted in order to improve treatment outcomes.

OVERVIEW OF THE CHAPTERS

The study discussed in **Chapter 2** of this dissertation can be viewed as an introduction into the topic of impulsivity in drug addiction. In this study, we examined scores and performance on multiple indices of impulsivity in a sample of cocaine-dependent individuals (CDI) (n=59) and compared these to a group of healthy controls (HC) (n=28). Since increased impulsivity is also a core feature of attention-deficit/hyperactivity disorder (ADHD), a developmental disorder that frequently co-occurs with cocaine dependence, a second aim was to evaluate the potential contribution of ADHD to impulsivity scores in this group. Despite the overall descriptive nature of this study, the findings highlight several interesting directions for future research.

In **Chapter 3**, we reviewed the available evidence regarding the relationship between neurocognitive dimensions of impulsivity and addiction treatment outcomes. A literature search was carried out in the databases PubMed, PsycINFO and Web of Knowledge, based on publication title, abstract or keywords. In total, 25 unique empirical papers were identified from the search criteria. The reviewed findings are discussed in terms of their limitations and clinical implications.

Few studies to date have examined the relationship between impulsive decision-making and treatment drop-out in CDI. In the study discussed in **Chapter 4**, we contrasted baseline performance (at treatment onset) on two validated tasks of decision-making, the Iowa Gambling Task (IGT) and the Cambridge Gamble Task (CGT) in CDI who completed treatment in a therapeutic community (TC) (n=66) and those who dropped out of treatment prematurely (n=84). The unique contribution of these decision-making variables to the prediction of drop-out propensity was evaluated.

To date, few outcome studies have looked at whether delay discounting, an indicator of impulsive choice, is linked to treatment retention in general and premature treatment drop-out specifically. Still, many contemporary addiction treatment programs place high demands on the ability to postpone immediate gratification, and thus, may be particularly challenging for SDI who have an intolerance for delay-of-gratification. In **Chapter 5**, we therefore examined whether delay discounting was predictive of shorter treatment retention and premature treatment drop-out among a heterogeneous sample of SDI (n=84) attending an inpatient detoxification program. Given the importance of understanding the proximal mechanisms by which impulsivity affects treatment outcomes, we further explored whether motivation for treatment served as a mediator of this relationship.

In the study discussed in **Chapter 6** finally, we prospectively examined the role of different impulsivity dimensions in predicting post-treatment relapse among a heterogeneous sample of SDI (n=70) participating in an inpatient detoxification program. Both a self-report questionnaire (measuring personality dimensions of impulsivity) and neurocognitive tasks (indexing neurocognitive dimensions of impulsivity) of impulsivity were used. This integration allowed us to determine whether personality dimensions of impulsivity would explain unique variance in relapse over and above neurocognitive indices of impulsivity. A second aim of this study was to explore whether the effects of impulsivity on relapse were mediated by treatment retention.

Finally, **Chapter 7** provides an integrated overview and general discussion of the main findings of this dissertation. In addition, clinical implications, limitations and guidelines for future research are outlined.

This dissertation comprises several papers, which are currently under editorial review, in press or have already been published. Consequently, to make each of the papers self-containing and to meet the editors' requirements, the content of some of the chapters may overlap.

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CHAPTER 2

IMPULSIVITY IN COCAINE-DEPENDENT INDIVIDUALS WITH AND WITHOUT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER[3]

[3] Based on Stevens, L., Roeyers, H., Joos, L., Dom, G., & Vanderplasschen, W. (2014). Impulsivity in cocaine-dependent individuals with and without attention-deficit/hyperactivity disorder. Manuscript accepted for publication in *European Addiction Research*.

ABSTRACT

Despite growing recognition of its multifactorial nature, most previous studies in cocaine-dependent individuals (CDI) have treated impulsivity monolithically. In addition, the effects of attention-deficit/hyperactivity disorder (ADHD), a developmental disorder known to adversely affect impulsivity in a way similar to cocaine addiction, have often not been taken into account. In this chapter, we examined whether CDI with ADHD differed from CDI without ADHD and healthy controls (HC) on several measures of impulsivity. A total of 87 individuals participated in this study, including 59 CDI (divided in 34 CDI and 25 CDI+ADHD) and 28 healthy controls (HC). These groups were compared on the motor, attentional and non-planning subscales of the Barratt Impulsiveness Scale (BIS-11) and on three neurocognitive impulsivity tasks [i.e., the stop signal task (SST); delay discounting task (DDT); information sampling task (IST)]. With the exception of performance on the DDT, CDI scored higher on all indices of impulsivity when compared to HC, regardless of whether or not they had an ADHD diagnosis. CDI with ADHD may represent a distinct subgroup, characterized by a relative insensitivity to future or to delayed consequences/rewards. Treatment outcomes for this group can potentially improve by targeting the cognitive and biological mechanisms underlying non-planning impulsivity and delay discounting respectively.

2.1. Introduction

Impulsivity is among the most common diagnostic criteria in the Diagnostic and Statistical Manual for Mental Disorders (DSM-5; American Psychiatric Association, 2013). Historically, the construct has predominantly been studied by personality researchers (Eysenck, Pearson, Easting, & Allsopp, 1985; Zuckerman, 1993), who tend to approach impulsivity as a trait that is fairly stable over time and evident across a range of situations (Patton, Stanford, & Barratt, 1995). One of the most widely used and influential measures for assessing trait impulsivity is the Barratt Impulsiveness Scale (BIS-11; Patton et al., 1995), a self-report questionnaire that indexes three subcomponents of impulsivity, i.e., motor, non-planning and attentional impulsivity, respectively.

More recently, growing scientific interest has been noted for impulsivity within neurocognitive research (Verdejo-Garcia, Lawrence, & Clark, 2008). From a neurocognitive perspective, impulsivity is generally perceived as a transitory state, which fluctuates in response to environmental influences. Often, a distinction is made between two neurocognitive expressions of impulsivity; impulsive action and impulsive choice (Winstanley, Eagle, & Robbins, 2006). Impulsive action refers to failures to withhold/suppress inappropriate/prepotent actions, thus reflecting poor response inhibition (Logan, Cowan, & Davis, 1984; Winstanley et al., 2006). Impulsive choice on the other hand, refers to impulsive decisions, often resulting from a distorted evaluation of delayed consequences. Delay discounting for instance, occurs when the subjective value of an outcome decreases because its delivery is delayed and is typically indexed by an individual's preference for smaller immediate rewards relative to larger delayed rewards (Richards, Zhang, Mitchell, & de Wit, 1999). Another – often overlooked – aspect of impulsive choice, reflection impulsivity, refers to the tendency not to collect and evaluate enough information before making complex decisions (Clark, Robbins, Ersche, & Sahakian, 2006). Importantly, the distinction between impulsive action and impulsive choice has been justified by neurobiological evidence supporting distinct cortico-striatal substrates underlying both dimensions of impulsivity (Dalley, Everitt, & Robbins, 2011).

Impulsivity is a hallmark characteristic of substance use disorders (SUDs) in general, and of cocaine dependence in particular (Moeller et al., 2002). Over the years, several studies have shown that cocaine-dependent individuals (CDI) report higher trait impulsivity and demonstrate notable deficits on tasks indexing aspects of impulsive action and impulsive choice (Moeller et al., 2002). On laboratory paradigms of motor inhibition for instance, chronic cocaine users typically display a lower probability of inhibiting their responses and require more time to inhibit their responses to stop signals compared to healthy controls (HC) (Colzato, van den Wildenberg, & Hommel, 2007; Fillmore & Rush, 2002). In addition, CDI have been found to discount delayed monetary rewards more steeply than do non-drug-using controls, suggesting higher levels of impulsive choice in this group (Coffey, Gudleski, Saladin, & Brady, 2003; Heil, Johnson, Higgins, & Bickel, 2006; Kirby & Petry, 2004). Notably, recent studies have established the clinical relevance of impulsivity in substance-dependent individuals (SDI). In particular, increased levels of impulsivity at treatment onset have been found to predict poor addiction treatment outcomes (De Wilde, Verdejo-García, Sabbe, Hulstijn, & Dom, 2013; Stevens et al., 2014).

For instance, we recently demonstrated that higher levels of impulsive choice in CDI were a significant predictor of premature treatment drop-out (Stevens et al., 2013). These and other findings suggest that treatment outcomes for CDI can improve by targeting impulsivity.

Whereas the relationship between cocaine addiction and impulsivity is rarely disputed, impulsivity research in SDI in general and in CDI specifically has historically been slowed due to the absence of a uniformly agreed-upon definition of the construct of impulsivity. As noted previously, there is substantial empirical evidence indicating that impulsivity is a multifactorial construct comprised of several related components (Dawe, Gullo, & Loxton, 2004; Dom, De Wilde, Hulstijn, & Sabbe, 2007; Reynolds, Ortengren, Richards, & de Wit, 2006; Whiteside & Lynam, 2001). In addition, these different components of impulsivity appear to recruit different brain circuitries and may be susceptible to diverse pharmacological influences (Diergaarde et al., 2008). Although these findings suggest that elucidating which impulsivity aspects are more relevant to cocaine dependence than others may have important treatment implications, relatively little research has evaluated various aspects of impulsivity in CDI simultaneously. Rather, most studies have been conducted in separate groups, each performing impulsivity paradigms targeting impulsive action or impulsive choice independently. Whereas these studies demonstrate that cocaine dependence is associated with both impulsive action (Coffey et al., 2003) and impulsive choice (Heil et al., 2006), direct comparisons should be interpreted with caution because of major differences in the sample characteristics of these studies (e.g., age, clinical vs. general population, duration of cocaine use, cocaine use severity, etc.).

In addition, most previous studies in cocaine users did not control for other disorders that are known to adversely affect impulsivity in a fashion similar to cocaine addiction. Indeed, increased trait impulsivity or impairments in impulsive action and impulsive choice are not specific to cocaine abuse or dependence but have been considered as risk factors common to all externalizing disorders, including bipolar, antisocial and borderline personality disorders (Najt et al., 2007; Swann, Lijffijt, Lane, Steinberg, & Moeller, 2009). Moreover, higher levels of impulsive action and choice have been considered core features of attention-deficit/hyperactivity disorder (ADHD) (Alderson, Rapport, & Kofler, 2007; Dai, Harrow, Song, Rucklidge, & Grace, 2013; Oosterlaan & Sergeant, 1998; Paloyelis, Asherson, & Kuntsi, 2009; Wilson, Mitchell, Musser, Schmitt, & Nigg, 2011; Sonuga-Barke, Taylor, Sembi, & Smith, 1992; Winstanley et al., 2006), a developmental disorder that frequently co-occurs with cocaine dependence (van Emmerik van Oortmerssen et al., 2012). Indeed, estimates of co-morbidity between cocaine dependence and ADHD in addiction treatment settings typically range from 10% to 35% (Carroll & Rounsaville, 1993; Levin, Evans, & Kleber, 1998; Pérez de los Cobos et al., 2011; Ros, Valoria, & Nieto, 2004). Given the high prevalence of ADHD in chronic cocaine users, ADHD might be a significant confounding factor when examining neurocognition in general and impulsivity in particular among CDI. For instance, it might be questioned whether the higher levels of trait impulsivity, impulsive action and impulsive choice that have been reported among CDI are specifically associated with the presence of a comorbid ADHD diagnosis. Alternatively, ADHD may have an additive effect on impulsivity in CDI. As both impulsivity as well as the presence of ADHD among CDI have been found to predict worse addiction treatment outcomes (Latimer, Ernst, Hennessey, Stinchfield, & Winters, 2004; Levin et al., 2004; Passetti, Clark, Mehta, Joyce, & King,

2008; Stevens et al., 2013, 2014), elucidating the particular impulsivity profile of CDI with ADHD may be of clinical relevance.

With the present study, we sought to investigate multiple indices of impulsivity among CDI. In addition, we wanted to explore whether the presence of ADHD would have an additive effect on impulsivity in CDI. In accordance with the multifactorial nature of impulsivity, three neurocognitive tasks indexing dissociable dimensions of impulsivity and a personality questionnaire measuring three different components of trait impulsivity were administered to a group of CDI, CDI+ADHD and HC. Both clinical groups were expected to show enhanced impulsivity relative to non-drug-using controls. Given that impulsivity is one of the hallmarks of ADHD, our second hypothesis was that CDI with an ADHD diagnosis would present more pronounced deficits on several indices of impulsivity when compared to CDI without ADHD.

2.2. Methods

2.2.1. Setting and Participants

A total of 87 individuals participated in this study. Fifty-nine of these were CDI, who were all recruited from inpatient detoxification programs. Based on a screening questionnaire and diagnostic interview *(cf. section 2.2.2.2.)*, thirty-four were classified as CDI without ADHD, and 25 were classified as CDI with an ADHD diagnosis. None of the participants in the latter group was being treated with psychostimulants at the time of assessment. Residents were approached for participation by the staff members within the first 4 days of their arrival at the detoxification center. In order to participate in the study, individuals had to meet the DSM-IV criteria for cocaine dependence at the time of admission to the treatment program and report cocaine as their primary substance of abuse. Individuals were excluded if they had (1) past or current major DSM diagnosis of psychotic disorders; (2) a history of neurological condition, such as strokes, intracranial hemorrhages and/or head injuries with loss of consciousness for longer than 30 min; (3) an intellectual quotient (IQ) lower than 70 and; (4) insufficient comprehension of the Dutch language to understand test instructions. Eligible participants were interviewed and tested within the first week from starting treatment (range 3-8 days), i.e., as soon as they had been stabilized. All CDI had a minimum of three days of abstinence (range = 3-60 days, mean = 12.62 days, SD = 12.01) at the time of assessment. Trait impulsivity scores and neurocognitive performance of the CDI were compared to a control group of 28 healthy individuals, who were volunteers, recruited by word of mouth from the community. The exclusion criteria for the control group were: (1) meeting DSM-IV criteria for any psychoactive substance dependence other than nicotine; (2) having a positive ADHD screener, and (3) the same exclusion criteria as those for the cocaine group. Ethical approval for the study was granted by the Ethical Review Board of the Faculty of Psychology and Educational Sciences at Ghent University.

2.2.2. Assessments

2.2.2.1. Background and drug use characteristics

A demographic form was used to collect basic demographic information (e.g., age, gender, education). Information regarding drug use, including the presence of poly-drug use (i.e., concomitant or consecutive use of different licit or illicit drugs), was assessed using a Dutch translation of the

European version of the *Addiction Severity Index (ASI)*, a semi-structured clinical assessment interview (McLellan, Luborsky, Woody, & O'Brien, 1980; Raes, Lombaert, & Keymeulen, 2008). The psychometric properties of the ASI are well established, with strong retest reliability and concurrent, predictive, and discriminate validities (McLellan et al., 2006). Additional information about the frequency and duration of drug use was collected using the *Interview for Research on Addictive Behavior* (IRAB; Verdejo-Garcia, López-Torrecillas, Aguilar de Acros, & Pérez-Garcia, 2005). To make a timesaving but accurate estimation of the current intellectual abilities, IQ was estimated using two subtests of the *Wechsler Adult Intelligence Scale*, third edition (WAIS-III; Wechsler, 1997; WAIS-III, Dutch version, Swets Test Publishers, 2000): matrix reasoning and information. This dyadic short form has been found to be appropriate for obtaining a good estimate of full scale IQ in a psychiatric sample: the estimated IQ derived from the administration of this short form has a correlation of .92 with the full scale IQ (Ringe, Saine, Lacritz, Hynan, & Cullum, 2002).

2.2.2.2. ADHD assessment

For the screening of ADHD, the *ADHD Rating Scale* (ARS; Kooij et al., 2005) was used. The ARS is a 46-item self-report rating scale, which includes all the 18 DSM-IV items on inattention, hyperactivity, and impulsivity. The questionnaire screens for the presence of symptoms in both childhood (23 items) and adulthood (23 items). Each item is scored on a 4-point likert scale ranging from 0 (rarely or never) to 3 (very often). A symptom was considered as present if the answer given to the item was 'often' or 'very often' (score of 2 or 3). Whereas a less stringent cut-off score of 4 DSM-IV criteria has been recommended for adults (Murphy & Barkley, 1996; Kooij et al., 2005), we used the more stringent cut-off score of 6 symptoms for both childhood and adulthood symptoms. This cut-off score was applied to avoid over-diagnosing ADHD, as symptoms associated with intoxication or withdrawal may mimic ADHD symptoms. The ARS has been found to have adequate reliability and validity (Kooij et al., 2005).

Positive screening results (i.e., 6 or more symptoms of either inattention or impulsivity/hyperactivity during both childhood and adulthood) were followed by a diagnostic interview using a Dutch version of the *Mini-International Neuropsychiatric Interview* (M.I.N.I.Plus) (Sheehan & Lecrubier, 1998). The M.I.N.I.Plus-derived ADHD diagnosis is established if, prior to the age of seven, a subject meets 6 of 10 criteria for ADHD and, during adult years, a subject meets 9 of 14 criteria. This instrument does not differentiate between inattentive and hyperactive subtypes. Only those subjects with a positive screening and a M.I.N.I.Plus-derived ADHD diagnosis were assigned to the CDI+ADHD group.

2.2.2.3. Impulsivity

- Self-report questionnaire

The *Barratt Impulsiveness Scale*, version 11 (BIS-11; Patton et al., 1995) is a self-report questionnaire consisting of 30 items, with responses on a four-point Likert-type scale ranging from "rarely/never" to "almost always/always". The questionnaire measures three distinct trait dimensions of impulsivity: attentional impulsiveness, motor impulsiveness, and non-planning impulsiveness. These three domains yield three subscores, which can be summed to yield a total score. Cumulative scores range from 30 (low in trait impulsivity) to 120 (high in trait impulsivity). The questionnaire has been shown to

be reliable in both clinical and population-based samples, with Cronbach's alpha coefficients ranging from .79 to .83 (Patton et al., 1995).

- Neurocognitive tasks

Impulsive action: inhibition of a pre-potent response was measured by a *stop signal task* (SST), operated using E-Prime experiment generation software. A total of 240 trials were presented with a go/stop ratio of 80/20, of which the first 60 trials served as practice trials to obtain stable performance (not included in the analyses). Go-trials require the subjects to react as quickly as possible to a series of left- or rightward pointing airplanes appearing on the screen by pressing a corresponding key ("left" or "right"). This speeded reaction time task establishes a prepotency to respond. On a subset of trials, the go-stimulus is followed, after a variable delay, by a visual stop-signal (i.e., a cross) presented on top of the airplane, to which participants are instructed to inhibit their response. Stop-signals were presented using a tracking algorithm (Eagle et al., 2008), a procedure which dynamically adjusts the delay at which the stop-signal appears after the onset of the go-signal (i.e., the presentation of the airplane) to control inhibition probability. This algorithm ensures a 50% rate of successful inhibition for each subject and compensates for differences in choice reaction time between participants. The main dependent variable reflecting inhibitory control, the stop signal reaction time (SSRT), is calculated by subtracting the stop signal delay (the time between the appearance of the airplane and the stop-signal) from the mean reaction time on go-stimuli. The SSRT reflects the time needed to inhibit the pre-potent response once the stop-signal occurs and is based on an estimate of how long the stop-signal can be delayed after the go-signal before the subject can no longer inhibit the response. Longer SSRTs therefore reflect worse inhibitory control.

Impulsive choice: The *delay discounting task* (DDT) was administered in order to measure the preference for small immediate rewards over large delayed rewards. Subjects had to make preference judgments between a future and an immediate hypothetical monetary reward. The task consisted of six blocks with eight preference judgments per block. The future reward was the same for all trials of a given block, with a block-specific delay in days (i.e., 5, 30, 180, 365, 1095, 3650). The immediate reward varied in magnitude from trial to trial, depending on the responses made by the subjects (see Wittmann, Leland, & Paulus, 2007 for the exact adjustments). The indifference points obtained for each delay, indicating which immediately delivered amount of money would be preferred equally to the delayed reward, were plotted and hyperbolic discount functions were derived through curve-fitting analysis. The *k*-value, which indexes the degree of delay reward discounting, was used as the dependent variable; as *k* increases, the person discounts the future reward more steeply and thus higher *k*-values correspond to higher levels of impulsive choice.

The *information sampling task* (IST; Clark et al., 2006) was used to index reflection impulsivity. The IST presents a series of trials with an array of 25 grey boxes, with two larger colored panels (e.g., red and blue) below at the foot of the screen. Upon being selected, boxes open to reveal one of these two colors. On each trial, subjects had to decide which of the two underlying colors was in the majority. Two conditions were presented: in the fixed win (FW) condition, subjects could win 100 points for correct choices or lose 100 points for incorrect choices, regardless of the number of boxes opened.

Subjects did not lose points by opening boxes. In the decreasing win (DW) condition, the possible number of points for a correct answer started at 250, and the number of available points decreased by 10 with every box opened. Thus, subjects could win more points for earlier decisions. The penalty for a wrong choice remained the same at 100 points. The primary outcome measures were the average number of boxes opened and the probability (P) of the subject being correct at the point of decision in each condition (see Clark et al., 2006). This P(correct) is highly correlated with the number of boxes opened but provides a more sensitive measure of the information available at the time of decision (i.e., it is more directly related to the levels of certainty tolerated during decision-making). A higher number of boxes opened and higher P(correct)-values indicate less impulsivity. Secondary measures included discrimination and sampling errors (to examine the effect of reduced information sampling on decision-making accuracy). Discrimination errors occur when a subject chooses a color that is not in the majority at that point in time, thus making a decision not logically based on the evidence available to them. Sampling errors occur when the color in the visible majority is chosen, but by chance is not the color within the majority of the matrix. In a reflection impulsivity task, the long-term probability of sampling errors should be inversely related to the amount of information sampled: these errors are more likely to occur when fewer boxes are opened and thus, when less information is sampled. Finally, we measured the latency of box opening (i.e., the number of boxes opened divided by the time to make a decision), to provide an index of motivation.

2.2.3. Data analysis

Initial data analysis involved assessing differences between the three groups on demographic (e.g., gender, age, education) and clinical variables (i.e., IQ), using parametric or non-parametric statistics as appropriate. For drug-related variables, independent *t*-tests were used to compare the two cocaine groups on continuous variables, and chi-square tests for dichotomous variables (e.g., poly-drug use). Healthy controls were not included in these analyses, because their drug use values were always 0. In order to assess group differences related to impulsivity, univariate (e.g., BIS-11 total scores), multivariate (e.g., BIS-11 subscales) or repeated measures ANOVA's (e.g., IST) were performed, followed by post-hoc Bonferroni testing when the ANOVA revealed a significant group effect. Variables that significantly differed between the HC and groups of cocaine users (e.g., IQ) or between the two cocaine groups (e.g., poly-drug use) were entered as covariates in all analyses. Correlations between impulsivity measures and cocaine use variables in the cocaine groups were assessed using Pearson product-moment correlations. All statistical analyses were conducted using Statistical Package for the Social Science (SPSS) software version 22.

2.3. Results

2.3.1. Demographic and other group characteristics

Socio-demographic and some clinical characteristics of the three groups are described in Table 2.1. Chi-square analysis revealed a (non-statistically significant) trend for differences in the distribution of male and female participants. The three groups did not differ significantly on age. However, we found significant differences among groups in terms of years of education and IQ. Post-hoc analysis revealed that HC had significantly more years of education and higher IQ-scores as compared to CDI

and CDI+ADHD. The two clinical groups did not differ significantly from one another on these variables.

2.3.2. Drug use characteristics of the CDI and CDI+ADHD group

Independent *t*-tests revealed that the cocaine groups did not significantly differ from one another in terms of their age of cocaine onset, past month cocaine use and duration of cocaine use (years) (see Table 2.1.). Moreover, the two groups did not differ in terms of their mean days of abstinence (i.e., reported length of time since the last use of cocaine at the time of the testing). However, poly-drug use was significantly more prevalent in the comorbid group, with 92% of these comorbid subjects reporting using multiple substances simultaneously (as compared to 62% in the non-comorbid group).

2.3.3. Impulsivity

2.3.3.1. Impulsivity across groups

- Self-reported impulsivity

The results of the BIS-11 self-report questionnaire data are presented in Table 2.2. One-way ANOVA of BIS-11 total scores revealed a significant main effect of group, due to increased scores in the two clinical groups relative to the HC (both $p < .001$). This effect remained significant while controlling for differences in IQ (see Table 2.2.). When years of education was entered as a covariate instead of IQ, results were similar ($p < .001$). Post-hoc comparison further revealed significantly higher BIS-11 total scores in the comorbid relative to the non-comorbid group of CDI, which remained significant when taking into account the effects of poly-drug use ($F_{(1,56)} = 13.64$, $p < .001$, ES = .44). Multivariate ANOVA of the subscale ratings showed a significant overall group effect while taking into account differences in IQ (Wilks' Lambda = 10.68, $p < .001$) or years of education (Wilks' Lambda = 8.96, $p < .001$), with significant univariate effects on the motor, attentional, and non-planning subscales (see Table 2.2.). The two clinical groups scored significantly higher on all three subscales relative to HC (all $p < .001$). In addition, post-hoc comparison revealed significant differences between the CDI and CDI+ADHD on the non-planning subscale, on which the comorbid group scored significantly higher than the CDI-only group. Differences between the two clinical groups on the non-planning subscale remained significant when controlling for the effects of poly-drug use ($F_{(1,56)} = 18.25$, $p < .001$, ES = .50).

Table 2.1.: Group characteristics of HC, CDI and CDI with ADHD

Variables	HC (n=28)	CDI (n=34)	CDI+ADHD (n =25)	Test statistic
Gender (M:F)	19/9	29/5	23/2	[$X^2_{(2)}$ = 5.63, p = .06]
Age	30.39 ± 9.77	30.79 ± 5.90	28.04 ± 7.53	[$F_{(2,49)}$ = 1.16, p = .32]
Education (years)	14.36 ± 2.11	12.53 ± 2.27	11.32 ± 2.25	[$F_{(2,84)}$ = 12.74, p < .001]
Estimated intellectual Quotient (IQ)	108.54 ± 12.23	88.71 ± 9.43	86.40 ± 7.57	[$F_{(2,84)}$ = 41.76, p < .001]
Age of first cocaine use	-	20.12 ± 4.98	18.48 ± 3.92	[$t_{(57)}$ = 1.36, p = .18]
Cocaine use/past month (days)	-	16 ± 11.50	13.12 ± 10.93	[$t_{(57)}$ = .97, p = .34]
Duration of cocaine use (years)	-	8.18 ± 7.53	7.44 ± 6.49	[$t_{(57)}$ = .393, p = .70]
Poly-drug use (%)	-	62%	92%	[$X^2_{(1)}$ = 6.95, p < .01]
Abstinence (days)	-	12.15 ± 9.87	13.24 ± 14.56	[$t_{(56)}$ = -.339, p = .74]

Data are presented as means ± SD, unless otherwise indicated. M: male, F: female

Table 2.2.: Differences between HC, CDI and CDI+ADHD on the total (BIS_T), motor (BIS_M), attentional (BIS_A) and non-planning (BIS_Np) scales of the BIS-11

Variables	HC (n=28)	CDI (n=34)	CDI+ADHD (n=25)	Test statistic while controlling for IQ	Post-hoc effects of group
BIS_T	54.29 ± 8.79	68.56 ± 9.42	78.60 ± 8.08	[$F_{(2,83)}$ = 34.41, p < .001]	HC<CDI<CDI+ADHD
BIS_M	19.04 ± 3.50	24.44 ± 4.84	27.16 ± 4.19	[$F_{(2,83)}$ = 19.52, p < .001]	HC<[CDI=CDI+ADHD]
BIS_A	12.89 ± 2.41	17.73 ± 3.88	19.28 ± 3.18	[$F_{(2,83)}$ = 15.43, p <. 001]	HC<[CDI=CDI+ADHD]
BIS_Np	22.36 ± 4.01	26.68 ± 4.32	31.76 ± 4.02	[$F_{(2,83)}$ = 25.91, p < .001]	HC<CDI<CDI+ADHD

Data are presented as means ± SD

- Neurocognitive tasks

Impulsive action

Stop Signal Task: The mean probability of successful inhibition on stop trials was 50% and no participants were identified whose inhibition accuracy deviated 10% or more from the targeted 50%, indicating that the dynamic tracking algorithm worked well for all subjects. Significant group differences were found in SSRTs, which remained significant while controlling for the effects of IQ (see Table 2.3.). Similar results were obtained when years of education was entered as a covariate ($p < .001$). Post-hoc analyses revealed that SSRTs were significantly longer in the two clinical groups compared to the HC (see Figure 1). However, slowed processing of the stop-stimulus is in itself not informative with regard to the primacy of disinhibition, since it could equally well reflect an impairment of attention to the stop-signal. As such, the slowed processing of the stop-stimulus was studied in relation to the processing speed of the go-stimuli (i.e., mean go-signal reaction times, RT). Although we found a trend towards a group effect on mean go-signal RTs, a post-hoc ANCOVA revealed that group effects on SSRTs remained significant after controlling for differences in mean go-signal RTs ($F_{(2,83)} = 10.14$, $p < .001$). The effect of mean go-signal RTs as a covariate on SSRTs was far from significant ($p = .91$). Therefore, we conclude that a specific lack of inhibitory control rather than a deficit in attention underlies the difference between CDI and HC. The two clinical groups did not significantly differ from one another in terms of SSRT ($p = .81$).

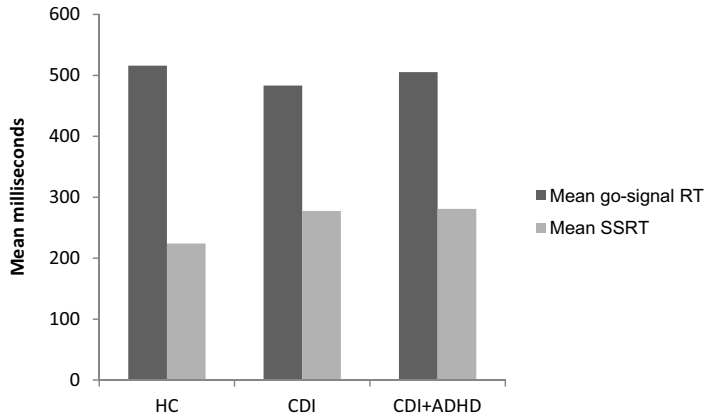


Figure 1. Mean go-stimuli RTs (response latency) and mean SSRT (stopping latency) for HC, CDI and CDI+ADHD

Impulsive choice

Delay Discounting Task: Delay discounting rates (*k-values*) were estimated by nonlinear regression using Mazur's hyperbolic model. Figure 2 represents the fitted hyperbolic discounting curves on the mean indifference points per group. Congruent with previous reports (Heil et al., 2006), the discounting

equation (hyperbolic model) provided a good fit to the data, accounting for 95%, 88%, and 83% of the variance for HC, CDI, and the CDI+ADHD, respectively. Because of positively skewed distributions of discounting coefficients, natural logarithm-transformed *k*-values were estimated = ln(*k*+0.001) and employed in the analyses of discounting (all *k*-based analyses presented hereafter are based on the log-transformed values). Analysis of variance comparing transformed *k*-values for all three groups revealed a significant main group effect, which remained significant while controlling for IQ (see Table 2.3.). Similar results were obtained when years of education was entered as a covariate ($p < .001$). Bonferroni post-hoc tests were used to compare each group to every other. No significant difference in (ln)*k*-values between HC and CDI without ADHD was found ($p = .28$). However, we did find significantly higher (ln)*k*-values in the CDI+ADHD group as compared to the HC ($t_{(83)} = -4.87$, $p < .001$, ES = .47). Moreover, the comorbid group had significantly higher discounting scores relative to the CDI without ADHD. Because the comorbid group was more likely to use multiple substances, a supplementary analysis of covariance was performed to assess the effects of poly-drug use. Group differences in delay discounting remained significant while controlling for poly-drug use ($F_{(1,56)} = 17.40$, $p < .001$, ES = .49).

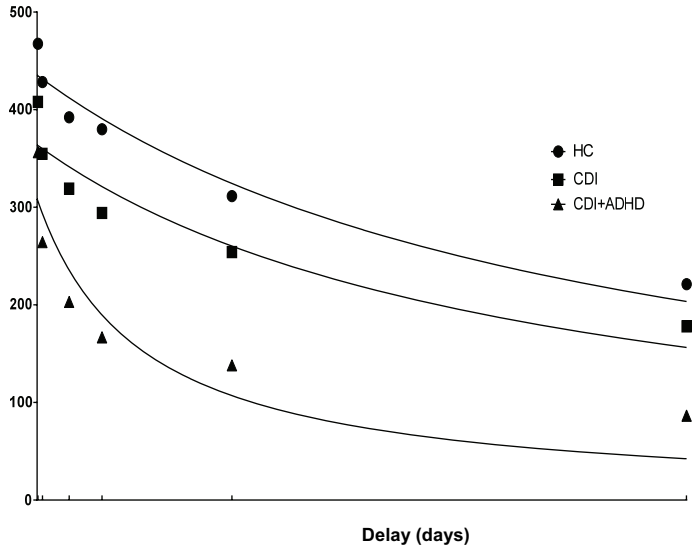


Figure 2. Points represent the median indifference points at the 6 different delay intervals (i.e., 5, 30, 180, 365, 1095, and 3650 days) for HC, CDI and CDI+ADHD. Lines show the best-fitting discounting functions generated by the hyperbolic model. The graphic demonstrates that CDI+ADHD show steeper discounting curves compared to the two other groups.

Information Sampling Task: Figure 3 shows the average number of boxes opened per condition as a function of group. As expected, the number of boxes opened per condition was significantly related to the probability of making a correct choice at the point of decision (r = .98, $p < .001$). Therefore, we focus our main analyses on the P(correct) variable.

P(correct): P(correct)-data were analyzed using a repeated measures ANOVA with condition (FW, DW) as within-subject variable and group as the between-subject variable. There was a significant main effect of condition ($F_{(1,82)} = 98.03$, $p < .001$), due to subjects sampling less information in the DW condition compared to the FW condition. As such, participants tolerated more uncertainty (lower P(correct)) in the DW than in the FW condition and thus, demonstrated sensitivity to the task contingencies. Paired *t*-tests revealed that these significant differences in the degree of information sampling between the FW and DW conditions were present in all three groups (all $p < .01$), meaning that all groups were broadly sensitive to the altered reward characteristics of the two conditions and were motivated to win points. There was also a main effect of group ($F_{(2,82)} = 15.76$, $p < .001$), with post-hoc analysis (collapsed across condition) showing that, compared to controls, both CDI and CDI+ADHD tolerated significantly more uncertainty in their decisions (all $p < .001$). However, this group effect became non-significant while controlling for differences in IQ ($F_{(2,81)} = 2.81$, $p = .07$). Finally, we found a significant condition*group interaction ($F_{(2,82)} = 4.48$, $p = .01$), which remained significant after controlling for IQ ($F_{(2,81)} = 3.97$, $p = .02$) or years of education ($F_{(2,81)} = 4.27$, $p = .02$). The nature of the significant group*condition interaction term was elucidated by calculating a difference score for the number of boxes opened in the FW and DW conditions. Figure 4 displays box adjustment in the three groups, representing the degree to which subjects adjusted their behavior to the reward contingencies. We found a significant group effect on box adjustment, due to greater box adjustment in HC than in the CDI ($p < .001$) and CDI+ADHD ($p = .04$). Although the main effect of group on box adjustment remained significant while controlling for IQ (see Table 2.3.) or years of education ($p < .001$), post-hoc comparison showed that the difference between HC and CDI+ADHD became non-significant ($p = .07$). Contrary to our expectations, we also found a trend towards greater box adjustment in the CDI+ADHD compared to the CDI ($p = .06$). When the two clinical groups were directly compared to one another in terms of their box adjustment, taking into account differences in poly-drug use, we found significantly higher levels of box adjustment in the CDI+ADHD relative to the CDI without ADHD ($F_{(1,56)} = 6.06$, $p = .02$).

Speed of box opening: A significant group effect was found on the mean speed of box opening, an index of task-related arousal, which remained significant while controlling for differences in IQ (see Table 2.3.). Post-hoc comparisons indicated that the two groups of CDI were slower in their box opening compared to HC (both $p < .001$). No significant difference in speed was found between the two clinical groups ($p = .64$).

Error data: Sampling errors committed on the IST were inversely correlated with boxes opened ($r = -.812$ $p < .001$) and P(correct) ($r = -.78$, $p < .001$), confirming a core principle of reflection impulsivity, i.e., the extent of information sampling is predictive of eventual decision accuracy. An analysis of errors revealed a main effect of group on sampling errors, with the two clinical groups having a higher number of sampling errors relative to HC (both $p < .01$). However, this effect became non-significant

when controlling for differences in IQ (see Table 2.3.). The two groups of cocaine users did not significantly differ from one another in terms of the number of sampling errors (p = .96). No group effect on the number of discrimination errors, which are often attributed to carelessness or lack of attention, was found.

Figure 3. Number of boxes opened in the fixed reward (FW) and in the decreasing win (DW) conditions of the IST for HC, CDI and CDI+ADHD

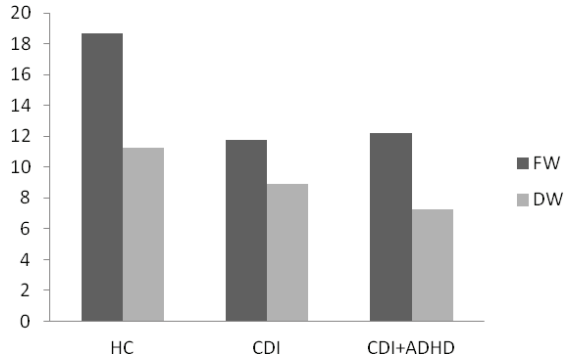
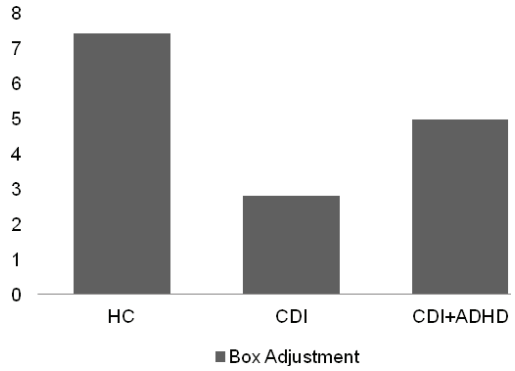


Figure 4. Mean adjustment scores on the IST for HC, CDI and CDI+ADHD



2.3.3.2. Correlations between impulsivity measures

Pearson product-moment correlations were calculated between impulsivity measures and cocaine use variables in the cocaine sample (n=59) and are presented in Table 2.4. We applied a Bonferroni correction to control for multiple comparisons, resulting in corrected alpha level of 0.005 (i.e., 0.05/10). All three BIS-11 subscales significantly correlated (p < .005) with the BIS-11 total scale. We found no significant correlations between trait and neurocognitive measures of impulsivity, with the exception of a trend towards a positive correlation between scores on the BIS-11 non-planning subscale and DDT k-values (p = .049). No correlations were found between scores on the SST, DDT and IST, which is consistent with the idea that response inhibition, delay discounting and reflection impulsivity reflect

separate dimensions of impulsivity. Scores on the motor, non-planning and total BIS-11 scales negatively correlated with the age of onset of cocaine use.

Table 2.3.: Scores of HC, CDI and CDI+ADHD on neurocognitive tasks of impulsivity

Variables	HC (n=28)	CDI (n=34)	CDI+ ADHD (n=25)	Test statistic while controlling for IQ	Post-hoc effects of group
SST					
SSRT	224.06 ± 33	277.61 ± 51.16	280.87 ± 69.32	[$F_{(2,83)}$ = 5.78, p = .004]	HC<[CDI=CDI+ADHD]
Mean go-stimuli RT	516.03 ± 123.75	483.30 ± 84.02	505.37 ± 81.66	[$F_{(2,83)}$ = 2.87, p = .06]	-
DDT					
(Ln)k	-6.50 ± .47	-6.35 ± .58	-5.36 ± 1.36	[$F_{(2,83)}$ = 15.22, p < .001]	CDI+ADHD>[HC=CDI]
IST					
Boxes Opened (/25)	14.95 ± 3.93	10.43 ± 4.54	9.72 ± 3.45	[$F_{(2,81)}$ = 2.18, p = .12]	(NS after controlling for IQ)
P(correct)	.85 ± .08	.75 ± .09	.74 ± .07	[$F_{(2,81)}$ = 2.81, p = .07]	(NS after controlling for IQ)
Box Adjustment	7.42 ± 5.19	2.88 ± 2.54	4.98 ± 4.89	[$F_{(2,83)}$ = 6.39, p = .003]	CDI<[HC=CDI+ADHD]
Speed	1.21 ± .51	2.02 ± .51	2.07 ± .60	[$F_{(2,81)}$ = 14.73, p < .001]	HC<[CDI=CDI+ADHD]
Sampling Errors	0.89 ± .76	1.69 ± .94	1.70 ± .84	[$F_{(2,81)}$ = 1.48, p = .23]	(NS after controlling for IQ)
Discrimination errors	0.19 ± .42	0.52 ± .90	0.40 ± .65	[$F_{(2,81)}$ = .32, p = .73]	-

Data are presented as means ± SD, unless otherwise indicated.
NS = Non Significant

Table 2.4.: Correlations between scores on the motor (BIS_M), attentional (BIS_A), non-planning (BIS_Np) and Total (BIS_T) subscales of the BIS-11, the natural log transformation of the discount rate (DDT_(ln)k) , the stop signal reaction time (SSRT), the probability of being correct at the time of decision on the IST (IST_P(correct)), past month cocaine use, duration of cocaine use (years) and age of cocaine use onset in CDI (n=59).

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
(1) BIS_M	1	,257	,511*	,814*	-,04	-,051	,052	,074	,352	-,371*
(2) BIS_A		1	,382*	,618*	,007	-,082	-,087	,121	,12	-,293
(3) BIS_Np			1	,820*	,257	-,018	-,066	,043	,302	-,419*
(4) BIS_T				1	,101	-,05	-,047	,125	,356	-,485*
(5) DDT_(ln)k					1	-,031	,035	-,281	-,224	-,009
(6) SSRT						1	,029	-,061	,029	,109
(7) IST_P(correct)							1	-,183	,030	-,013
(8) Past month cocaine use								1	,116	,002
(9) Duration cocaine use									1	-,300
(10) Age of cocaine use onset										1

* Correlation is significant at the $p < .005$ level (2-tailed)

2.4. Discussion

2.4.1. Main findings

The aim of the present study was to evaluate the association between different facets of impulsivity and cocaine dependence and to explore the effect of ADHD on this relationship.

CDI proved to be overall more impulsive than HC. First, the two cocaine groups had higher scores on all three subscales and on the total scale of the BIS-11, a well-established questionnaire frequently used to assess trait impulsivity. This finding corroborates previous reports indicating that CDI demonstrate more impulsive personality traits compared to non-drug-using controls (Kjome et al., 2010). Also consistent with prior research, we found significant negative correlations between higher trait impulsivity and an earlier age of onset of cocaine use (Dom, Hulstijn, & Sabbe, 2006; Moeller et al., 2002). Although this finding does not allow us to separate cause from consequence, a growing body of research suggests that high levels of trait impulsivity may predate drug use and predispose subjects to an earlier start of substance use (Kirisci, Vanyukov, & Tarter, 2005; Tarter et al., 2003; Tarter, Kirisci, Habeych, Reynolds, & Vanyukov, 2004; Verdejo-Garcia et al., 2008).

Parallel results of increased impulsivity in the cocaine groups relative to HC were observed on indices of impulsive action and impulsive choice. First, the cocaine users required more time to inhibit their motor responses compared to controls, as estimated by their stop-signal reaction time (i.e. SSRT). By contrast, the cocaine groups did not differ from controls in their ability to execute responses, as suggested by their normal response speed. These findings in other words suggest a specific response inhibition deficit in the CDI, and are consistent with previous findings in cocaine users (Colzato et al., 2007). Although the etiological role of motor disinhibition in cocaine dependence is still a matter of debate, some studies have found the magnitude of the inhibitory impairment in CDI to be proportional to the degree of cocaine consumed (Colzato et al., 2007).

In accordance with previous studies, CDI were also found to discount delayed rewards to a greater extent (i.e., were more impulsive) than non-drug-using controls (Heil et al., 2006). At the same time, our findings suggest that more pronounced levels of delay discounting in CDI may be associated with the presence of ADHD. Indeed, only the comorbid group of CDI showed statistically significant steeper discounting curves compared to HC. Hypothetically, chronic cocaine use may interact with the pathophysiology underlying ADHD to produce more pronounced and clinically significant discounting scores. Partially supporting this notion, a recent study found that, relative to HC, only ADHD patients with and not those without cocaine dependence were characterized by elevated levels of delay discounting (Crunelle, Veltman, van Emmerik-van Oortmerssen, Booij, & van den Brink, 2013). Future studies examining delay discounting in CDI but also in subjects with an ADHD diagnosis therefore need to take into account the effects that either ADHD or cocaine dependence may have on delay reward discounting in these groups.

In addition to the more popular SST and DDT, the present study also used a relatively novel behavioral measure, the IST, to examine an often-overlooked aspect of impulsivity in drug users, i.e. reflection impulsivity. To the best of our knowledge, our study is the first to examine the tendency to evaluate information before decision-making in a sample of CDI and to compare it with that of non-

drug-using controls. Similar to findings in regular cannabis, opiate and amphetamine users (Clark et al., 2006; Clark, Rosier, Robbins, & Sahakian, 2009), CDI demonstrated significantly reduced information sampling relative to HC. Whereas HC sampled information until they had an 85% probability of being correct, the cocaine groups sampled information until they had a 75% (CDI) or 74% (CDI+ADHD) probability of being correct. In contrast to the observed differences on other indices of impulsivity however, differences in reflection impulsivity became non-significant while controlling for the effects of IQ, suggesting that the extent of information sampling is related to intellectual functioning. It is also difficult to fully exclude the possibility that different levels of motivation across groups may have accounted for differences in reflection impulsivity. Whereas the cocaine groups did not specifically differ from HC in terms of discrimination errors (which may be due to inattention or carelessness), the HC were faster in their speed of box-opening, an index of task-related arousal (see Clark et al., 2006). The observation that HC tended to adjust their box opening to a greater degree between the two task conditions compared to CDI without ADHD moreover suggests that the latter group was somewhat less sensitive to the change in reward contingencies. Future studies may help to better understand the nature of the current findings by including more direct measures of motivation when examining group differences in reflection impulsivity. Whereas the clinical implications associated with reduced information sampling in SDI remain to be elucidated, reflection impulsivity might be expected to have a detrimental impact on wider-scale decision-making abilities. Accordingly, it may have potential relevance for treatment retention/engagement and/or the ability to maintain long-term abstinence in drug users (Clark et al., 2006, 2009).

The current study was the first to directly investigate the effects of ADHD on trait and neurocognitive aspects of impulsivity in a clinical group of CDI. We found that two specific indices of impulsivity, BIS-11 non-planning impulsivity and delay discounting respectively, were able to differentiate CDI from CDI with an ADHD diagnosis. In particular, our results suggest that ADHD may exert synergistic detrimental effects on the ability to plan ahead or orient towards future, rather than to immediate rewards in CDI. The higher scores on non-planning and choice impulsivity in the CDI+ADHD relative to the non-comorbid group of CDI remained significant while controlling for the effects of poly-drug use, which was higher in the comorbid group. Because other drug use characteristics (e.g., days abstinent, duration of cocaine use and past month cocaine use) did not differ between the two clinical groups, our findings suggest that drug use itself may not have accounted for the observed differences in impulsivity. These data are generally consistent with previous reports suggesting that trait impulsivity reflects a disposition that is present prior to the initiation of drug use (de Wit, 2009) and with findings indicating that delay discounting is unaffected by drug use and/or abstinence (Audrain-McGovern et al., 2009; Heil et al., 2006; Perry, Larson, German, Madden, & Carroll, 2005; Robles, Huang, Simpson, & McMillan, 2011). As such, the higher levels of non-planning impulsivity and delay discounting in the comorbid group may have predated drug use, proportionally increasing the risk of developing a SUD. Alternatively, individuals with ADHD may be more vulnerable for cocaine-induced catecholaminergic disruptions as a result of the pathophysiology underlying ADHD, even if amount and duration of cocaine use are similar to non-comorbid CDI (Preller et al., 2013). However, more

research (longitudinally) is clearly needed to evaluate the temporal relationship between non-planning impulsivity, delay discounting, ADHD and cocaine dependence.

In contrast with the disparities in delay discounting, the SST did not reveal any differences between the two cocaine subgroups. This is particularly surprising in light of the generally held view that poor response inhibition represents a core deficit in ADHD (Aron et al., 2003; Bekker et al., 2005; Barkley, 1997; Lijffijt et al., 2005; Nigg et al., 2002; Ossmann & Mulligan, 2003; Wodushek & Neumann, 2003). Several potential explanations can be invoked for this rather unexpected finding. To date, several lines of evidence support the idea that dysregulation of the dopamine system underlies ADHD (Genro, Kieling, Rohde, & Hutz, 2010). Speculatively, cocaine use may have improved the dopaminergic tone of the frontostriatal system in these subjects, thereby enhancing their ability to inhibit behavioral responses (Fillmore, Rush, & Marczinski, 2003; McClernon & Kollins, 2008; Potter & Newhouse, 2004). In support of this suggestion, stimulant drugs have been found to improve performance on the SST in both rodents and humans, but only in subjects with relatively poor baseline inhibitory performance, including those with dopaminergic lesions (de Wit, Crean, & Richards, 2000; Eagle & Robbins, 2003). However, the fact that all subjects in our sample were abstinent for at least three days makes this interpretation less likely. Indeed, abstinence from drugs has been associated with decreased dopaminergic transmission in frontostriatal systems, thereby impairing rather than enhancing response inhibition (Bekker et al., 2005; Powell, Dawkins, & Davis, 2002). Some authors have also proposed the existence of two subtypes of ADHD, which lead to the generation of ADHD symptoms via two distinct pathways: the altered “motivational style” pathway, which generates a strong aversion to delays, and the disordered “thought and action” pathway, which leads to a more fundamental dysregulation of inhibitory control (Sonuga-Barke, 2002). The former subtype is believed to arise through alterations in brain areas involved in reward processing, including the ventral striatum, and innervated by the mesolimbic branch of the dopamine system (Sonuga-Barke, 2002). Hypothetically, subjects with this subtype may be more likely to engage in substance use behavior, explaining why the comorbid group was specifically characterized by greater delay discounting rather than poor response inhibition. This notion would cohere with the growing recognition of excessive delay discounting as a trans-disease process (Bickel, Jarmolowicz, Mueller, Koffarnus, & Gatchalian, 2012). Finally, because both samples consisted of cocaine-dependent individuals, i.e. a population that is by definition characterized by impaired inhibitory control, it remains possible that the absence of significant differences in SSRTs between the two clinical groups reflects a ceiling effect.

In addition to the absence of differences in the area of motor inhibition, the CDI+ADHD did not differ from the CDI without ADHD in terms of their degree of information sampling on the IST, an index of reflection impulsivity. To the best of our knowledge, no studies to date have examined the extent of reflection impulsivity in adults diagnosed with ADHD, making it difficult to interpret the absence of differences on this task. It is possible that adult ADHD is not associated with reflection impulsivity. Alternatively, reflection impulsivity in adult ADHD subjects may partially be normalized by the particular task contingencies of the IST, which involve winning and/losing points. Such a finding would be consistent with suggestions that performance of individuals with ADHD is highly variable depending on whether experimental conditions influence arousal levels (Rosch & Hawk, 2013). For instance,

subjects with ADHD typically take more time to make their decisions when reward is involved, suggesting that reward contingencies may motivate subjects with ADHD to self-impose cognitive strategies (Marx, Höpcke, Berger, Wandschneider, & Herpertz, 2013). Partially supporting this notion, the CDI+ADHD group tended to adjust their box opening to a greater degree between the FW and DW conditions of the IST relative to CDI without an ADHD diagnosis. That is, when an (hypothetical) incentive was introduced for low-certainty responding, CDI+ADHD appeared to be more sensitive to this change in task structure compared to the CDI-only group. However, future studies that examine the extent and nature of reflection impulsivity in adult patients with ADHD are clearly needed before definite conclusions can be drawn from the current findings.

2.4.2. Clinical implications

Despite the overall descriptive nature of the current study, we believe that the findings presented here highlight several interesting directions for future (research) efforts aimed at improving the assessment and treatment of ADHD in CDI. The overall good discriminate ability of the BIS-11 non-planning scale and DDT, combined with their brevity and ease of administration, suggests that these indices can be explored as clinical tools for brief screening in clinical settings. If well constructed and widely available, these screeners could serve to guide professionals in their referrals for assessment and treatment of ADHD in CDI. In contrast to a purely categorical perspective on ADHD (e.g., presence vs. absence of ADHD diagnosis), incorporating a dimensional classification based on impulsivity scores may be of greater clinical utility in terms of predicting treatment outcomes, treatment planning and organizing and selecting treatment interventions. Future studies aimed at developing norms and establishing clinically relevant cut-off points may substantially help the clinical field moving forward in this respect.

During the past decades, several studies have found the presence of ADHD among SDI to be associated with worse addiction treatment outcomes (Carroll & Rounsaville, 1993; Latimer et al., 2004; Levin et al., 2004). Levin and colleagues (2004) for instance, found that CDI with ADHD were less likely to complete treatment in a therapeutic community (TC) compared to those with either no or other Axis I disorders. In the same line, a more recent study by Vergara-Moragues and colleagues (2013) found that CDI who dropped out of TC treatment prematurely were more likely to meet the diagnostic criteria for ADHD than those who completed treatment. To date however, the precise mechanisms mediating the negative effects of ADHD on addiction treatment outcomes remain unexplored. Notably, a growing body of evidence in SDI in general indicates that higher levels of non-planning impulsivity and delay discounting may place drug users at higher risk for relapse or premature treatment drop-out (Moeller et al., 2001; Washio et al., 2011). Since our findings suggest that CDI with ADHD are characterized by higher levels of non-planning impulsivity and delay discounting, a worthwhile prospect for future studies may be to explore whether increased impulsivity in CDI with ADHD accounts for their enhanced risk of treatment failure. If this were true, treatment outcomes for CDI with ADHD could potentially be improved by targeting the cognitive and neurobiological mechanisms underlying lack of future orientation and delay discounting (see Bickel, Yi, Landes, Hill, & Baxter, 2011).

2.4.3. Limitations

Several limitations of this study should be highlighted. First, our group of healthy controls was not matched to the clinical groups in terms of IQ or years of education. However, most of our findings remained significant while controlling for these factors. Second, our samples were relatively small. As such, subtle differences in performance between the two clinical groups may not have been detected, and a larger sample may have had greater statistical power to identify group differences. At the same time, this implies that the observed differences in impulsivity between CDI with and without an ADHD diagnosis represent relatively large effects, with effect sizes of .50 and .49 for non-planning and delay discounting respectively. As a third limitation, it should be noted that our research diagnoses of ADHD were based entirely on self-report from participants, as opposed to diagnoses obtained from a comprehensive diagnostic assessment procedure, which may include collateral reports of ADHD symptoms, academic/school records or medical reports. At the same time, adults have shown the ability to accurately rate childhood ADHD symptomatology and retrospective information provided by adults with ADHD seems to have agreement with parents' reports (Dias et al., 2008). In addition, we used the more stringent cut-off score of 6 symptoms and focused on whether the reported symptoms were associated with impairment and whether impairment occurred in at least two situations. Although we administered a test battery measuring different dimensions of impulsivity in the current study, it must be noted that not all impulsivity aspects were covered. For instance, we did not measure cognitive inhibition, which refers to the ability to suppress competing, distracting information in order to maintain response performance. As preliminary evidence suggests that drug consumption in individuals with ADHD may be associated with poor attentional inhibition in particular (Weafer, Milich, & Fillmore, 2011), future studies may benefit from including a measure of interference control while comparing CDI with and without ADHD. At the same time, it is important to consider that impulsivity is only one aspect of the heterogeneous disorder of ADHD, and future studies may need to focus on a more comprehensive set of measures when examining differences between CDI with and without ADHD. Finally, the present findings may not necessarily generalize to other groups of SDI, as our sample was composed entirely of individuals who reported cocaine as their primary substance of abuse and of individuals with a high problem severity, as exemplified by low IQ and a need for inpatient treatment.

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CHAPTER 3

IMPULSIVITY AS A VULNERABILITY FACTOR FOR POOR ADDICTION TREATMENT OUTCOMES: A REVIEW OF NEUROCOGNITIVE FINDINGS AMONG INDIVIDUALS WITH SUBSTANCE USE DISORDERS[4]

[4] Based on Stevens, L., Verdejo-Garcia, A., Goudriaan, A. E., Roeyers, H., Dom, G., & Vanderplasschen, W. (2014). Impulsivity as a vulnerability factor for poor addiction treatment outcomes: A review of neurocognitive findings among individuals with substance use disorders. *Journal of Substance Abuse Treatment, 47,* 58-72.

ABSTRACT

In this chapter, we explore the hypothesis that individual differences in neurocognitive expressions 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. The relationship between impulsivity and treatment retention needs to be examined more extensively. The reviewed findings are discussed in terms of their clinical implications.

3.1. 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, Eage, & 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.

3.1.1. Neurocognitive aspects of impulsivity

Historically, impulsivity has predominantly been 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). As a personality trait, impulsivity is assessed using personality-based self-report questionnaires which measure individuals' 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). Typically, these measures include questions that cover broad periods of time, making them more appropriate for assessing stable or trait aspects of impulsivity. 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, Ortengren, Richards, & De Wit, 2006). Most current neuropsychological models agree that on a conceptual 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. In contrast to self-report questionnaires, these tasks are often considered to be a more objective method of measuring impulsivity, as they do not require introspection or self-assessment of behavior (Verdejo-Garcia et al., 2008).

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). *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). 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 shown that addicted individuals with impairments in motor inhibition are less able to engage strategic processes to override the attentional bias towards drug-related stimuli (Field & Powell, 2007; Field & Cox, 2008), although their drug-related attentional bias cannot merely be seen as a function of poor inhibitory control. Additional support for this position 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).

3.1.2. 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 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.

3.2. Methods

3.2.1. 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.

3.2.2. 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 3.1.1. 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. Two independent reviewers inspected the remaining 85 articles. 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.

3.2.3. 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 3.1.). 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. 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.

Table 3.1.: Study characteristics, outcome measures and main findings

Studies examining one dimension of Impulsive Action (1)

Study	Sampling - N - Setting - Abstinence	Study Design	Impulsivity Measures	Main Findings	
				Treatment retention	Abstinence
Brewer et al. (2008)	- N=20 CDI - Outpatient - Non-abstinent	RCT1 (n=8) 1. TAU 2. TAU + Computer-assisted CBT RCT2 (n=12) 1. CBT + Placebo 2. CBT + Disulfiram 3. CBT + CM + Placebo 4. CBT + CM + Disulfiram	Comalli-Kaplan version Stroop (interference effects)	+	0
Carpenter et al. (2006)	- N= - 45 CDI - 10 HDI - 25 MDI - Outpatient - Non-abstinent	6 RCTs Combination of coping skills relapse prevention and pharmacotherapy	Drug Stroop (1) cocaine interference scores (2) heroin interference scores (3) marijuana interference scores (4) mixed interference scores	+ (1) CDI 0 HDI + (2) MDI	+ (1)(4) CDI 0 HDI + (1) MDI
Cox et al. (2002)	- N=14 alcohol abusers - Inpatient - Information not provided	Prospective Cohort Study	Drug Stroop (drug interference)	NA	+
Janes et al. (2010)	- N=19 NDI (women) - Outpatient - Non-abstinent	RCT	Drug Stroop (drug interference)	NA	+

Studies examining one dimension of Impulsive Action (1)

Study	Sampling - N - Setting - Abstinence	Study Design	Impulsivity Measures	Main Findings	
				Treatment retention	Abstinence
Streeter et al. (2008)	- N=74 CDI - Outpatient - Non-abstinent	3 RCTs 1. Venlaxine/Pramipexole/Placebo 2. Resperine/Placebo 3. Tiagabine/ Placebo	Stroop (interference effects)	+	NA
Marissen et al. (2006)	- N=110 HDI - Inpatient - Abstinent (≥ 2 weeks)	RCT 1. CET (9 sessions) 2. Placebo Psychotherapy	Drug Stroop (drug interference)	NA	+
Waters et al. (2003)	- N=158 NDI - Outpatient - Abstinent (acute)	RCT 1. NPT 2. Placebo Patch	Drug Stroop (drug interference)	NA	+
Winhusen et al. (2013)	- N= - 125 CDI - 47 MethDI - Outpatient - Non-abstinent	RCT 1. 12-Step 2. TAU	Comalli-Kaplan version Stroop (interference effects)	0	NA

Studies examining one dimension of Impulsive Choice (2)

Study	Sampling - N - Setting - Abstinence	Study Design	Impulsivity Measures	Main Findings	
				Treatment Retention	Abstinence
Black & Rosen (2011)	- N=90 individuals with history of cocaine/ alcohol use - Outpatient - Non-abstinent	RCT 1. TAU 2. Budget Management	MCQ	NA	+
Bowden-Jones et al. (2005)	- N=21 ADI - Inpatient - Abstinent (≥ 21 days)	Prospective Cohort Study	IGT CGT	NA NA	+ +
Dallery & Raiff (2007)	- N=30 smokers - Laboratory - Non-abstinent (no intention to quit)	RCT 1. NPT (n=15) 2. Placebo (n=15)	DDT	NA	+
MacKillop & Kahler (2009)	- N=57 smokers (heavy drinking) - Outpatient - Non-abstinent	RCT 1. NPT + placebo psychotherapy 2. NPT + brief alcohol intervention	MCQ	NA	+
Peters et al. (2013)	- N=93 MDI (93.7% court-referred) - Outpatient - Non-abstinent	RCT 1. CBT alone 2. CBT + CM for Adherence 3. CM for abstinence 4. CM for abstinence + CBT	EDT	0	0

Studies examining one dimension of Impulsive Choice (2)

Study	Sampling - N - Setting - Abstinence	Study Design	Impulsivity Measures	Main Findings	
				Treatment Retention	Abstinence
Stanger et al. (2012)	- N=165 MDI (adolescents) - Outpatient - Non-abstinent	RCT 1. CBT only 2. CBT + CM 3. CBT + CM + Family Management	DDT	NA	+
Washio et al. (2011)	- N=36 CDI - Outpatient - Non-abstinent	RCT 1. CM high-magnitude vouchers (n=18) 2. CM low-magnitude vouchers (n=18)	DDT	NA	+ low-magnitude condition
Yoon et al. (2007)	- N=48 NDI (pregnant women) - Outpatient - Abstinent	RCT 1. Abstinence-contingent vouchers 2. Non-contingent vouchers	DDT	NA	+

Studies examining multiple dimensions of impulsivity (3)

Study	Sampling - N - Setting - Abstinence	Study Design	Impulsivity Measures	Main Findings	
				Treatment Retention	Abstinence
Carroll et al. (2011)	- N=73 DDI - Outpatient - Non-abstinent	RCT 1. TAU 2. TAU + Computer-assisted CBT (CBT4CBT)	BART	0	+ CBT4CBT
			CPT (commission errors)	0	0
De Wilde et al. (2013)	- N=37 poly-substance abusing alcoholics - Inpatient - Abstinent (≥ 6 weeks)	Prospective Cohort Study	DDT	NA	0
			IGT	NA	+
Krishnan-Sarin et al. (2007)	- N=30 smokers (adolescents) - Outpatient (CM + CBT) - Non-abstinent	Prospective Cohort Study	DDM	NA	0
			EDT	NA	+
			CPT (commission errors)	NA	+

Studies examining multiple dimensions of impulsivity (3)

Study	Sampling - N - Setting - Abstinence	Study Design	Impulsivity Measures	Main Findings Treatment Retention	Main Findings Abstinence
Mueller et al. (2009)	- N=19 NDI - Laboratory - Non-abstinent	Prospective Cohort Study	Stroop (interference effects)	NA	+
			DDT	NA	+
Passetti et al. (2008)	- N=37 ODI - Outpatient (Substitute opiate administration) - Non-abstinent	Prospective Cohort Study	Go/No-Go (false alarms)	NA	0
			DDT	NA	0
			IGT	NA	+
			CGT	NA	+
Passetti et al. (2011)	- N=80 ODI - Outpatient (n=48) - Inpatient (n=32) Data were analyzed for the entire sample (1) and for each setting separately (2) - Non-abstinent	Prospective Cohort Study	Go/No-Go (false alarms)	NA	0
			DDT	NA	+ (1)
			IGT	NA	+ (1)
			CGT	NA	+ (1) + (2) outpatient

Studies examining multiple dimensions of impulsivity (3)

Study	Sampling - N - Setting - Abstinence	Study Design	Impulsivity Measures	Main Findings	
				Treatment Retention	Abstinence
Schmitz et al. (2008)	- N=75 CDI - Outpatient - Non-abstinent	RCT 1. CM + CBT + citalopram 2. CM + CBT + placebo	IMT/DMT (commission errors)	0	0
			IGT	0	+
Sheffer et al. (2012)	- N=97 NDI (low SES) - Outpatient (CBT + relapse prevention) - Non-abstinent	Prospective Cohort Study	Go/No-Go (total score)	NA	0
			DDT	NA	+
			BART	NA	0
Verdejo-Garcia et al. (2012)	- N=131 CDI - Inpatient (therapeutic community) - Abstinent (≥ 15 days)	Prospective Cohort Study	Stroop (Interference effects)	0	NA
			IGT	0	NA

Notes: NA : Not Applicable (outcome indicator was not examined); 0 : No relationship was found between impulsivity and this outcome indicator; + : Higher impulsivity was associated with shorter retention or lower abstinence levels; Underlined: Findings pertain to or are restricted to a specified treatment condition, setting or patient group; Abstinent: Abstinence was required to be enrolled in the assessment phase of the study; Non-abstinent: No period of abstinence was required to be enrolled in the assessment phase of the study.
Abbreviations: ADI: Alcohol Dependent Individuals; BART: Balloon Analogue Risk Task; CDI: Cocaine Dependent Individuals; CBT: Cognitive Behavioral Therapy; CET: Cue Exposure Therapy; CGT: Cambridge Gamble Task; CM: Contingency Management; CPT: Continuous Performance Test; DDI: Drug Dependent Individuals; DDT: Delay Discounting Task; DDM: Delay Discounting Measure; EDT: Experiential Discounting Task; HDI: Heroin Dependent Individuals; IGT: Iowa Gambling Task; IMT/DMT: Immediate and Delayed Memory Task; MethDI: Methamphetamine Dependent Individuals; MCQ: Monetary Choice Questionnaire; MDI: Marijuana Dependent Individuals; NDI: Nicotine Dependent Individuals; NPT: Nicotine Patch Therapy; ODI: Opiate Dependent Individuals; RCT: Randomized Clinical Trial; SES: Socio-Economic Status; TAU: Treatment As Usual.

3.3. Results

3.3.1. Description of included studies

3.3.1.1. 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 substance 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 substance users separately and the results of these studies will be reported accordingly. Finally, one study was conducted within a highly heterogeneous group of substance 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).

3.3.1.2. 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). By 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 3.1.).

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).

3.3.1.3. 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). By 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).

3.3.2. Findings

3.3.2.1. Impulsive action

- *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).

- *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 substance-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 substance 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 3.1.) and therefore, the failure to detect an effect on treatment outcomes in this subsample may, in part, reflect insufficient power.

- *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 substance-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.

3.3.2.2. Impulsive choice

- *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 3.1.), 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.

- *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 evidenced 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 substance 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 questions 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.

3.4. Discussion

3.4.1. 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 substance-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 substance-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).

3.4.2. 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.

3.4.2.1. 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.

3.4.2.2. Treatment modification for highly 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.

3.4.2.3. 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).

3.4.3. 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).

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 3.1.). 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.

3.5. 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 substance 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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CHAPTER 4

DISADVANTAGEOUS DECISION-MAKING AS A PREDICTOR OF DROP-OUT AMONG COCAINE-DEPENDENT INDIVIDUALS IN LONG-TERM RESIDENTIAL TREATMENT[5]

[5] Based on Stevens, L., Betanzos-Espinosa, P., Crunelle, C. L., Vergara-Moragues, E., Roeyers, H., Lozano, O., Gonzalez-Saiz, F., Vanderplasschen, W., Verdejo-Garcia, A., & Pérez-Garcia, M. (2013). Disadvantageous decision-making as a predictor of drop-out among cocaine-dependent individuals in long-term residential treatment. *Frontiers in Psychiatry, 15*, 149. doi: 10.3389/fpsyt.2013.00149.

ABSTRACT

The treatment of cocaine-dependent individuals (CDI) is substantially challenged by high drop-out rates, raising questions regarding contributing factors. Recently, a number of studies have highlighted the potential of greater focus on the clinical significance of neurocognitive impairments in treatment-seeking cocaine users. We hypothesized that disadvantageous decision-making, an indicator of impulsive choice, would be one such factor placing CDI at greater risk for treatment drop-out. In order to explore this hypothesis, we contrasted baseline performance (at treatment onset) on two validated tasks of decision-making, the Iowa Gambling Task (IGT) and the Cambridge Gamble Task (CGT) in CDI who completed treatment in a residential therapeutic community (TC) (n=66) and those who dropped out of TC prematurely (n=84). Compared to treatment completers, CDI who dropped out of TC prematurely did not establish a consistent and advantageous response pattern as the IGT progressed and exhibited a poorer ability to choose the most likely outcome on the CGT. There were no group differences in betting behavior. The findings presented in this chapter suggest that neurocognitive rehabilitation of disadvantageous decision-making may have clinical benefits in CDI admitted to long-term residential treatment programs.

4.1. Introduction

The treatment of cocaine-dependent individuals (CDI) is substantially challenged by high drop-out rates. Whereas treatment attrition is high across the majority of substance abuse treatment studies, drop-out rates ranging from 60 to 80% have been reported among CDI (Kampman et al., 2001; Sigueland et al., 2002; Streeter et al., 2008). These high drop-out rates are particularly problematic, given the well-established association between the length of time spent in treatment (i.e., treatment retention) and post-treatment outcomes. More specifically, a sufficient length of time spent in the treatment program constitutes one of the strongest and most consistent predictors of positive post-treatment outcomes, including sustained abstinence (Ball, Carroll, Canning-Ball, & Rousaville, 2006; Hser, Evans, Huang, & Anglin, 2004). Conversely, CDI who drop out of treatment prematurely fare worse than those who stay in treatment for the entire period: high drop-out rates limit overall treatment effectiveness, increase the propensity to relapse and seriously exacerbate health, financial, and legal consequences (King & Canada, 2004; Simpson, Joe, & Brown, 1997). This relationship between treatment drop-out/completion and post-treatment outcomes has been found across all the major addiction treatment modalities (Gossop, Marsden, Stewart, & Rolfe, 1999; Lang & Belenko, 2000; Siegal, Li, & Rapp, 2002), including drug-free inpatient therapeutic communities (TCs), which remain a core modality of the drug treatment system in Europe and the United States (Darke, Campbell, & Popple, 2012; Vanderplasschen et al., 2013).

The high attrition rates observed among CDI and their detrimental consequences raise questions regarding contributing factors that might influence treatment drop-out in this population. Finding a way to predict premature treatment drop-out could help in the early identification of CDI with the highest risk for drop-out, such that these individuals may receive additional monitoring and adequate therapeutic interventions targeting specific risk factors.

A recent generation of research, facilitated by considerable advances in the field of neuroscience, has begun to examine whether neurocognitive impairments in CDI may confer an increased risk of drop-out (Aharonovich et al., 2006; Brewer, Worhunsky, Carroll, Rounsaville, & Potenza, 2008). Indeed, growing evidence indicating that a substantial number of CDI suffer from detectable damage in cortical and sub-cortical brain regions and exhibit deficits across a range of neurocognitive domains (Cunha, Nicastri, Gomes, Moino, & Peluso, 2004; Tucker et al., 2004) has recently encouraged researchers to focus on neurocognitive factors when attempting to predict treatment drop-out. Although preliminary, these studies seem to suggest that CDI who drop out of treatment prematurely demonstrate significantly poorer performance than treatment completers across various cognitive domains, including attention, memory and processing speed (Aharonovich et al., 2006; Brewer et al., 2008; Turner, LaRowe, Horner, Herron, & Malcolm, 2009). As such, intact executive functioning may be a prerequisite to successfully complete treatment or attain treatment objectives.

Surprisingly, very few studies have focused on the prognostic utility of more specific aspects of neurocognitive functioning, such as those related to the domain of (affective) decision-making (Carroll et al., 2011; Verdejo-García et al., 2012). This lack of research is particularly striking given the well-established role of impaired decision-making in the pathogenesis and pathophysiology of addiction (Bechara, 2005; Verdejo-García & Bechara, 2009). A substantial number of substance-dependent

individuals shows behavioral signs of disadvantageous decision-making, characterized by a preference for immediate rewards while disregarding long-term consequences (a pattern coined 'myopia for the future'), despite these choices being less adaptive with regard to overall expected value (Bechara, Damasio, & Damasio, 2000; Bechara, 2004). For example, neurocognitive assessment using the Iowa Gambling Task (IGT) (Bechara, Damasio, Damasio, & Anderson, 1994) has shown that substance-dependent individuals are more likely to make maladaptive decisions, resulting in long-term losses exceeding short-term gains (Grant, Contoreggi, & London, 2000). Similarly, evidence suggests that a number of substance-dependent individuals fail to improve their performance on this task based on trial-by-trial outcomes (Cunha, Bechara, Guerra de Andrade, & Nicastri, 2011). Using alternative probes of decision-making which minimize learning requirements (i.e., decision-making under risk rather than under ambiguous conditions), other studies showed that substance-dependent individuals demonstrated an increased tendency to choose the less likely outcome, despite having processed information regarding outcome probabilities (Rogers et al., 1999).

Over the years, numerous studies have established the ecological and predictive validity of disadvantageous decision-making in drug users (Bechara et al., 2001; Cunha et al., 2011; Verdejo-García et al., 2007). In particular, poor decision-making in substance-dependent individuals has shown significant correlations with real-life everyday functioning, including social impairment, problems with maintaining gainful employment and difficulties with achieving and maintaining substantial periods of abstinence (Bechara et al., 2001; Cunha et al., 2011; Passetti, Clark, Mehta, Joyce, & King, 2008; Passetti et al., 2011; Schmitz et al., 2009). Hypothetically, a decision-making style characterized by impaired integration of affective/cognitive information into future strategies (i.e., poor learning from experience) or an immediate reward preference disregarding long-term future consequences may also put CDI at greater risk for premature treatment drop-out. However, despite the intuitive appeal of such a relationship, the association between poor decision-making and premature treatment drop-out among CDI has remained underexplored.

To the best of our knowledge, only two studies – including one of our own research group – have examined the relationship between disadvantageous decision-making and treatment outcomes in CDI (Schmitz et al., 2009; Verdejo-García et al., 2012). Both studies used the length of stay in treatment as the outcome variable of interest and found that disadvantageous decision-making, as indexed by lower IGT net scores, was unrelated to treatment retention among these individuals (Schmitz et al., 2009; Verdejo-García et al., 2012). However, treatment retention and drop-out have recently been found to be predicted by different variables (Darke et al., 2012) and as such, it remains unknown whether and how disadvantageous decision-making in CDI relates to treatment drop-out. Further, by selectively focusing on overall IGT net scores, previous retention studies did not differentiate between distinct components of decision-making.

With the present study, we aimed to refine our initial findings by introducing a number of relevant novelties compared to previous research: first, we used treatment drop-out (rather than the number of days in treatment) as the outcome variable of interest. Further, to better parse some important components of decision-making that may be relevant to treatment drop-out, the present study utilised two complementary decision-making measures: the Iowa Gambling Task, which factors

reward/punishment-based decision-making learning, and the Cambridge Gamble Task (CGT) (Rogers et al., 1999), which factors risk-based decision-making outside a learning context. We hypothesized that impaired decision-making, as indexed by 1) a failure to develop a preference for the advantageous decks during the course of the IGT and 2) poor decision-making on the CGT, would be associated with treatment drop-out among primarily CDI admitted to residential TCs.

4.2. Methods

4.2.1. Participants

Eligible participants were recruited from six different TCs located in the region of Andalusia (Spain): Cartaya, Almonte, Mijas, Los Palacios, La Línea, and Tarifa. All TCs had a common treatment program that is based on multidisciplinary interventions, including Cognitive Behavioral Therapy (CBT), psycho-education and occupational therapy. More details regarding the recruitment context of this study have been described elsewhere (see Verdejo-Garcia et al., 2012). For inclusion, participants had to 1) meet the DSM-IV-TR for cocaine dependence and report cocaine as their primary substance of abuse 2) be able to understand test instructions and perform the neuropsychological assessment and 3) be abstinent for at least 15 days (in order to avoid potential effects of acute intoxication or withdrawal symptoms on neurocognitive task performance). Individuals meeting the criteria for nicotine or heroin dependence and/or alcohol abuse were also included. Exclusion criteria included dependence on other substances (e.g., other opioids, benzodiazepines, cannabinoids, barbiturates, hallucinogenics) and being abstinent for more than two months. DSM-criteria were determined using the Spanish version of the Psychiatric Research Interview for Substance and Mental Disorders (Torrens, Serrano, Astals, Perez-Dominguez, & Martin-Santos, 2004). Information about the frequency, amount and duration of drug use was collected using the Interview for Research on Addictive Behavior (IRAB) (Verdejo-García, López-Torrecillas, Aguilar de Acros, & Pérez-García, 2005).

4.2.2. Assessments

After the clinical staff had screened potential participants for inclusion criteria, individuals were informed about the aims of the study and provided written informant consent. The study was approved by the Comité de Ética en Investigación Humana (CEIH) of the University of Granada. A baseline neuropsychological assessment was performed between day 20 and 30 following treatment entry. Assessment of decision-making was undertaken by an experienced neuropsychologist in a quiet testing environment in each of the six different TCs.

4.2.2.1. Decision-making assessment

The *Iowa Gambling Task (IGT)* is a computer task that requires individuals to choose from four decks of cards, decks A, B, C and D. Unbeknownst to the participants, two decks (i.e., A and B) are associated with large wins but even larger losses (resulting in net loss), whereas the other two decks (i.e., C and D) are associated with smaller wins but also smaller losses (resulting in overall profit). During the course of the task, healthy participants usually develop a preference for the safe decks (C and D). In contrast, individuals with impaired decision-making often continue to choose cards from the

risky decks (A and B), which in the long run, will take more money than they give. The 100 trials were grouped into five blocks of 20 consecutive cards, with a net score for each block calculated as (C+D) - (A+B) decks. Calculating net scores for each block of 20 trials permits an analysis of learning across the different phases of the IGT. An overall IGT net score was also determined by adding up the individual block scores. Selecting more cards from bad decks results in an overall net loss across the 100 trials of the task, whereas choosing more cards from the good decks results in overall net gains.

The *Cambridge Gamble Test (CGT)* of the *CANTABeclipse* Battery is a computerized task in which participants are presented with a row of 10 boxes at the top of the screen, each of which can be either red or blue. At the bottom of the screen are rectangles containing the words 'Red' and 'Blue'. Participants are instructed to guess whether a yellow token is hidden in a red box or a blue box. After making a choice, participants are asked to place a bet on this choice being correct. Available bets are offered in a sequence, as a proportion of the participant's points total on that trial (ascending condition: 5%, 25%, 50%, 75%, 95%; descending condition: 95%, 75%, 50%, 25%, 5%). After the bet is placed, the hidden token is revealed and the bet is added to or subtracted from the total score. Dependent measures were 1) quality of decision-making (i.e. the percentage of trials subjects bet on the more likely outcome), 2) risk-taking (the mean proportion of current points total that the subject stakes on each gamble test trial for which they had chosen the more likely outcome), 3) deliberation time (average response time to make the probability decision) and 4) risk adjustment (the rate at which participants increase their bets in response to the more favorable ratios blue/red). Healthy controls usually adjust their bet according to the ratio of red and blue boxes; that is, betting fewer points if the odds of winning are lower. Finally, a comparison of the proportion of points bet in the ascending and descending condition enables an assessment of delay-aversion. In particular, delay-aversive individuals will place low bets in the ascending condition, coupled with high bets in the descending condition. In contrast, individuals with a preference for risk will typically delay their response to place high bets in the ascending condition.

4.2.2.2. Operational definition of treatment drop out

Duration of treatment in TCs can range from six months up until two years. Different from our previous study in CDI (Verdejo-García et al., 2012), we coded treatment retention in the present study as a binary variable: treatment completion vs. drop-out. More specifically, we differentiated those participants who completed treatment in the TC and all of the objectives that were laid out at the beginning of treatment (treatment completers) from those that left the program prematurely (drop-outs).

4.2.3. Data analysis

Differences between treatment completers and drop-outs on demographic, drug-use and decision-making variables were tested using independent sample *t*-tests for continuous variables (e.g., years of education) and chi-square analyses for categorical data (e.g., gender). In order to examine whether treatment completers and drop-outs differed in decision-making performance, we performed block*group mixed-design ANOVAs for the IGT (block-by-block) and condition*group designs for the

CGT (ascending vs. descending conditions). When the assumption of sphericity was violated, as assessed using the Mauchly sphericity test, the number of degrees of freedom against which the *F*-ratio was tested was reduced by the value of the Greenhouse–Geisser epsilon (Howell, 1997).

The third set of analyses looked at the degree to which variables that significantly differed between treatment completers and drop-outs predicted treatment drop-out. For these analyses, we used a logistic regression analysis with drop-out as the dependent variable and the main demographic, drug use and decision-making variables as the predictors. Variables significant in the initial (univariate) regression analyses were simultaneously entered into the final logistic regression model (enter method), designed to determine whether these predictors were independently associated with treatment drop-out. Multicollinearity diagnostic statistics for the logistic model (tolerance values and VIF) were examined to exclude multicollinearity due to interdependency between the predictor variables. We calculated the classification accuracy of the final model. All analyses were performed using SPSS, version 22.0.

4.3. Results

4.3.1. Participants

A total of 150 clients were included in the present analyses. Results indicated that more than half of the sample dropped out of treatment prematurely (84/150; 56%), compared to 44% (66/150) who completed treatment. The mean length of stay in TC treatment for the entire sample was 150.15 days (SD = 77.04); there were significant differences between the subjects who completed treatment and those who did not. In particular, treatment completers had a mean stay of 207.61 days (SD = 64.54), whereas drop-outs had a mean stay of 105 days (SD = 52) (t = 10.78, p < 0.01). The demographic and drug-related characteristics/differences between treatment completers and non-completers are presented in Table 4.1. Groups did not differ in terms of gender (χ^2 = 0.28, df = 1, p = 0.60) or years of education (t = -0.33, p = 0.74). However, treatment completers and drop-outs significantly differed in terms of their mean age, with drop-outs being significantly younger (34.87 ± 8.09) compared to treatment completers (37.73 ± 8.34) (t = 2.12, p = 0.04). The only drug-related variable that differed significantly in both groups was the years of regular cocaine use, with drop-outs having a briefer history of regular cocaine use (years) compared to those who completed treatment (15.90 ± 6.95 compared to 18.65 ± 7.82 respectively; t = 2.28, p = 0.02).

Table 4.1.: Descriptive information for demographic variables, patterns of cocaine, heroin and other drug use in treatment completers (N=66) and drop-outs (N=84).

Variables	Treatment completers (N=66)	Drop-outs (N=84)
Gender (% male / female)	94 / 6	92 / 8
Age	37.73 ± 8.34*	34.87 ± 8.09
Years of Education	10.61 ± 2.47	10.74 ± 2.43
Cocaine use		
Age of first use	19.08 ± 4.99	18.96 ± 5.07
Age of onset problem use	22.29 ± 6.18	20.86 ± 5.57
Years of regular use	18.65 ± 7.82*	15.90 ± 6.95
Mean use per week (days)	5.02 ± 1.07	5.06 ± 1.01
Mean amount per use (g)	0.81 ± 0.66	0.82 ± 0.81
Peak amount per use (g)	2.40 ± 2.17	2.56 ± 2.65
Route of administration		
Oral	/	1/84 (1%)
Sniffed	20/66 (30%)	23/84 (27%)
Injected	10/66 (15%)	8/84 (10%)
Smoked	36/66 (55%)	51/84 (61%)
Inhaled	/	1/84 (1%)
Heroin use (71.3%)	45/66 (68%)	62/84 (74%)
Age of first use	21.53 ± 5.89	20.60 ± 4.72
Age of onset problem use	23.04 ± 7.01	21.73 ± 6.25
Years of regular use	12.42 ± 8.35	10.10 ± 7.08
Mean use per week (days)	4.87 ± 1.39	4.53 ± 1.39
Mean amount per use (g)	0.39 ± 0.49	0.28 ± 0.28
Peak amount per use (g)	0.91 ± 0.85	0.70 ± 0.61
Other drug use past 30 days		
Cannabis	26/66 (39.39%)	29/84 (34.52%)
Alcohol	36/66 (54.55%)	44/84 (52.38%)
Stimulants	3/66 (4.55%)	2/84 (2.38%)
Hallucinogens	1/66 (1.52%)	0/84
Benzodiazepines	13/66 (19.70%)	21/84 (25%)

Note. Results shown are mean ± S.D. (range) or %
* $p < .05$

4.3.2. Decision-making tasks

4.3.2.1. Iowa Gambling Task (IGT)

Analyzing the IGT-profile of the entire sample using ANOVA repeated measures, we found a significant effect of block ($F_{(3.62,\ 535.08)} = 8.46$, $p < 0.01$). The pattern of net score change over block was significantly linear ($p < 0.01$). Overall, these results indicate that participants made more advantageous choices as the task progressed**.** However, when the effect of block was examined individually for treatment completers and drop-outs (separate repeated-measures ANOVA's for each group), we found that the main effect of block was only significant among treatment completers

[repeated measures ANOVA, effect of block $F_{(3.09,\ 200.77)} = 6.90$, $p < 0.01$)]. In contrast, the drop-out group did not improve their performance as the task progressed ($F_{(4,80)} = 1.66$, $p = 0.17$) (Fig. 1). Results showed a trend for a block*group interaction ($F_{(3.62,\ 535.08)} = 2.06$, $p = 0.09$). Pairwise block-by-block between-group comparisons showed that performance of treatment completers and drop-outs significantly differed on the last (5^{th}) block of the IGT: drop-outs (mean score = -0.3) selected significantly more often cards from the disadvantageous decks than treatment completers (mean score = 2.9) in this block ($t = 2.24$, $p = 0.03$) (Table 4.2.).

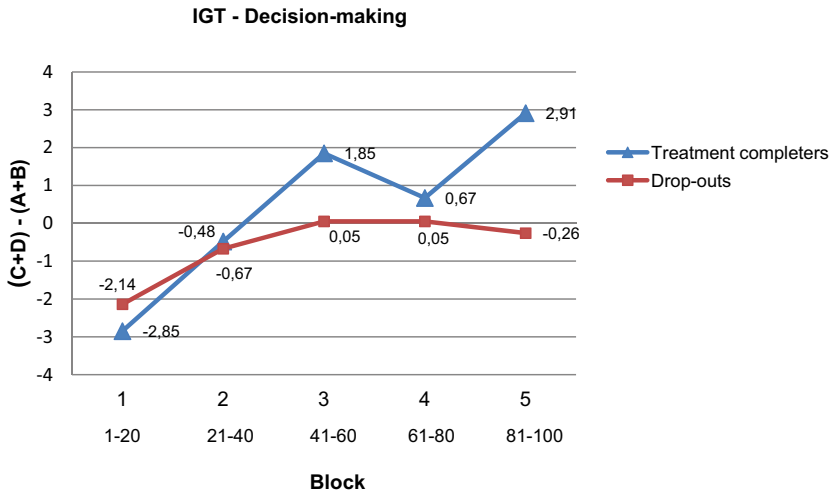

Figure 1. Performance on the Iowa Gambling Task (IGT) as a function of group (drop-outs versus treatment completers) and blocks (1–5). Each block (1–5) represents 20 sequential card selections. Net scores are calculated by subtracting the number of disadvantageous deck selections (A+B) from the number of advantageous card selections (C+D). A negative net score indicates poor decision-making. Compared to treatment completers, individuals in the drop-out group tended to select more cards from the risky decks (A and B) than from the safe decks (C and D), although this difference only reached statistical significance in the fifth block (last 20 trials).

4.3.2.2. Cambridge Gamble Task (CGT)

Quality of decision-making: There was no significant effect of condition ($F_{(1,148)} = 1.70$, $p = 0.19$) on the quality of decision-making. However, we found a statistically significant group effect ($F_{(1,148)} = 5.89$, $p = 0.02$). Whereas a post-hoc analysis showed that, compared to treatment completers, the drop-out group made poorer decisions in the ascending condition ($t = 2.78$, $p < 0.01$) (see Table 4.2.), group by condition interaction was not significant ($F_{(1,148)} = 1.81$, $p = 0.18$).

Deliberation time: Deliberation time was not affected by condition ($F_{(1,148)} < 1$, $p = 0.58$) and between-subject analysis did not reveal a group effect ($F_{(1,148)} < 1$, $p = 0.99$).

Risk-taking: A mixed-model ANOVA of betting data identified a significant main effect of condition ($F_{(1,148)}$ = 227.46, p < 0.01), as subjects placed larger bets in the descending (mean 67%) than in the ascending condition (mean 41%). There was no significant effect of group (treatment completers and drop-outs did not differ in the mean proportion of total points they staked on each gamble test trial for which they had chosen the more likely outcome) ($F_{(1,148)}$ < 1, p = 0.77) and group by condition (ascending vs. descending) interaction terms were not significant ($F_{(1,148)}$ = 1, p = 0.32). This finding suggests that both groups did not differ in their tendency to take an early bet, which provides an index of impulsivity or delay aversion.

Risk-adjustment: A mixed-model ANOVA of risk-adjustment data idefntified a significant main effect of condition ($F_{(1,148)}$ = 20.75, p < 0.01), with subjects showing more adjustment of their bets in the ascending condition. There was no significant effect of group ($F_{(1,148)}$ < 1, p = 0.66) or group*condition interaction ($F_{(1,148)}$ < 1, p = 0.99). As such, there were no differences between treatment completers and drop-outs in the extent to which they adapted their bets according to the ratio of coloured boxes.

Table 4.2.: Decision-making variables

Variables	Treatment Completers (N=66)	Drop-outs (N=84)
IGT		
Net scores	2.1 ± 21.8	-3 ± 23.5
Block 1	-2.9 ± 6.3	-2.1 ± 6.3
Block 2	-0.5 ± 6.1	-0.7 ± 6.4
Block 3	1.9 ± 7.2	0.1 ± 7.5
Block 4	0.7 ± 8.6	0.1 ± 7
Block 5	2.9 ± 9.1*	-0.3 ± 8.2
CGT		
Quality of decision-making (%)	91.4 ± 9.1*	86.6 ± 13.7
Ascending condition	91.4 ± 9.7	85.3 ± 15.5
Descending condition	91.4 ± 10.8	87.9 ± 15.0
Risk-taking	0.5 ± 0.1	0.5 ± 0.1
Ascending condition	0.4 ± 0.2	0.4 ± 0.2
Descending condition	0.9 ± 0.1	0.9 ± 0.2
Deliberation time (ms)	4506.2 ± 4989.9	4512.5 ± 4352.8
Risk adjustment	1.1 ± 0.8	1.07 ± 0.8

Note. Results shown are mean ± S.D.
* p < .05

4.3.3. Prediction of treatment drop-out

Variables that significantly differed between treatment completers and drop-outs were tested for their predictive capacity. For the demographical and drug-related variables, these were age and years of regular cocaine use (see Table 4.1.). For the decision-making variables, we included performance on block 5 of the IGT (as block-by-block comparison showed significant differences between treatment completers and drop-outs on this block, see section 4.3.2.) and mean scores on CGT quality of decision-making (as a repeated measure ANOVA showed a significant group effect on the quality of

decision-making). Initial analyses of the data seemed to support the idea that age ($\chi^2_{(1)}$ = 4.48, p = 0.03), years of regular cocaine use ($\chi^2_{(1)}$ = 5.16, p = 0.02), IGT net scores on block 5 ($\chi^2_{(1)}$ = 4.96, p = 0.03) and CGT quality of decision-making ($\chi^2_{(1)}$ = 6.29, p = 0.01) were all significant predictors of treatment drop-out. Due to the high correlations between age and years of regular cocaine use (r = 0.80, p = 0.01), age was not retained for multivariate regression. A logistic regression analysis was conducted to predict treatment drop-out using years of regular cocaine use, IGT net scores on block 5 and CGT quality of decision-making as predictors. Collinearity statistics for the predictor variables yielded tolerance values between 0.94 and 0.99 and all VIF values were below 10, indicating that the validity of the regression model was not threatened by multicollinearity. A test of the full model against a constant only model was statistically significant, indicating that the predictors as a set reliably distinguished between treatment completers and drop-outs ($X^2_{(3)}$ = 13.51, p < 0.01). Nagelkerke's R^2 of 0.12 indicated that the three predictors explained about 12% of the total (pseudo)variance in treatment drop-out. Prediction success for drop-out was 75%. The Wald criterion demonstrated that only the two decision-making variables made a significant (independent) contribution to prediction (p = 0.05) (Table 4.3.). A stepwise backward regression (likelihood ratio test) showed that the goodness of fit of the model did not change significantly when years of regular cocaine use was removed. Removing this variable from the initial model moreover slightly improved the classification accuracy of drop-outs (from 75 to 77.5%). The standardized beta-coefficients, Wald statistics and significance levels for the predictors included in the two models are displayed in Tables 4.3. and 4.4.

Table 4.3.: Multivariate prediction of treatment drop-out with a logistic regression model

Predictors	B	S.E.	Wald	*P*
Years of regular cocaine use	-0.04	0.02	2.63	0.10
IGT Block 5	-0.04	0.02	3.78	0.05
CGT Quality of Decision-making	-3.28	1.71	3.68	0.05

Table 4.4.: Final prediction model

Predictors	B	S.E.	Wald	*P*
IGT Block 5	-0.04	0.02	4.35	0.04
CGT Quality of Decision-making	-0.04	0.02	5.01	0.02

4.4. Discussion

4.4.1. Main findings

The present study is the first to examine the relationship between two validated tasks of decision-making and treatment drop-out in a relatively large (n=150) and unselected sample of primarily CDI enrolled in long-term residential TCs. Our main finding is that performance on two tasks of decision-making, the IGT and CGT, was significantly related to and predictive of treatment drop-out. Results suggest that after entering long-term residential treatment for cocaine dependence, intact decision-making processes may be crucial to adhere to treatment and complete treatment objectives.

In general, individuals choose increasingly from the advantageous decks as the IGT progresses (Bechara et al., 1994; Bechara, 2005). In corroboration with this normative trend, our sample showed improvements over the course of the tasks as an entire group. However, when split into treatment completers and drop-outs, we found that only treatment completers showed an improvement as the IGT progressed (these individuals ultimately had positive ‘‘money’’ gains). In contrast, the drop-out group did not select more frequently from the advantageous decks, ultimately lost ‘‘money’’ and displayed minimal evidence of learning to select from the advantageous decks across the task, as suggested by their (still) negative net scores on block 5 of the IGT (last 20 trials). Conceptually, the later blocks of the IGT have been suggested to represent post-learning stages (players presumably have developed explicit knowledge of the risk profile across IGT alternatives) and performance on these blocks is believed to reflect decision-making under risk (rather than ambiguity) (Brand, Recknor, Grabenhorst, & Bechara, 2007). This notion has been supported by a number of studies pointing to significant correlations between later stage IGT selections and an individual’s propensity for deliberate risk-taking (Brand et al., 2007; Upton, Bishara, Ahn, & Stout, 2011). However, recent evidence indicates that these correlations may not be present among highly impulsive individuals, potentially suggesting that this group fails to develop explicit knowledge of risky IGT alternatives (Upton et al., 2011).

The finding that drop-outs failed to develop a preference for the advantageous decks and continued to select cards from the bad decks, despite being penalized, may suggest several things. First, this group may be less sensitive to or may fail to generate emotion-related signals (somatic markers) to losing (Bechara & Damasio, 2002). These somatic markers normally facilitate advantageous decisions by steering away from options that, through prior experience, are associated with unpleasant gut feelings (Damasio, 1994). Hypothetically, weaker somatic signals to negative outcomes in CDI may lead them to be less hesitant about terminating treatment prematurely. However, a number of alternative theories have been proposed to explain impaired decision-making in substance-dependent individuals, including poor working memory and cognitive flexibility (Dunn, Dalgleish, & Lawrence, 2006). As the fixed card order on the IGT induces an initial preference for the ultimately risky decks, disadvantageous performance in the drop-out group may reflect a difficulty in reversing behaviors that may once have been rewarding but ultimately bring high costs, such as continued drug use. Corroborating this notion, significant associations between poor decision-making on the IGT and difficulties with achieving and maintaining abstinence have been reported among individuals dependent on cocaine, opiates and alcohol (Bowden-Jones, McPhillips, Rogers, Hutton, & Joyce,

2005; De Wilde, Verdejo-García, Sabbe, Hulstijn, & Dom, 2013; Passetti et al., 2008; Passetti et al., 2011; Schmitz et al., 2009).

Using an alternative task of decision-making (CGT) that is not confounded by information processing demands, we were able to show that drop-outs were less likely to choose the most favorable option (i.e., the box color in the majority) compared to treatment completers. These choices reflect low quality decisions, given that the probabilities associated with each choice are visible at the time of the decision. As both groups equally used the box ratio information about outcome probability to adjust their bets (as shown by the absence of significant differences in adjustment slopes across groups), findings indirectly suggest that the lower-quality decisions in the drop-out group cannot be attributed to poor processing of probability information. A comparison of betting behaviour in the ascending and descending condition between drop-outs and treatment completers further suggests that poor decision-making in the drop-out group was not due to greater delay aversion or impulsivity. In fact, both groups showed evidence of impulsive responding, as indicated by the significantly higher bets placed in the descending condition. Finally, the absence of differences between both groups in terms of deliberation time argues against an explanation in terms of speed-accuracy. Overall, our findings suggest that drop-out vulnerable cocaine users fail to integrate prior experiences into their decisions or neglect probability information, thus ignoring the broader context in which decisions are made. These deficits may be associated with alterations in the orbitofrontal and the ventromedial prefrontal cortex (regions implicated in the use of feedback to improve decision-making) or the dorsolateral prefrontal loop, which has a critical role in overseeing subordinate processes through the exercise of executive control (Brand et al., 2007; Brevers et al., 2012).

4.4.2. Clinical implications

Our findings have important clinical implications. If replicated, the present results suggest that 1) tasks indexing decision-making may be added to the range of clinical information that is collected at treatment intake in order to identify CDI who are at risk for premature treatment drop-out and that 2) treatment drop-out among CDI admitted to TCs may be reduced by targeting cognitive and affective processes involved in decision-making.

In line with the multiple processes implicated in the regulation of decision-making, the integrity of prefrontal cortical and executive functioning in general and aspects involved in risk-reward decision-making (executive functioning, reversal learning and interoceptive awareness) in particular represent interesting targets for consideration (Dunn et al., 2010). Whereas more research is needed in order to examine the feasibility of incorporating these interventions into real-world clinical settings, preliminary evidence suggests that a combination of executive functioning training (e.g., Goal Management Training) and mindfulness-based meditation (Alfonso, Caracuel, Delgado-Pastor, & Verdejo-García, 2011) and/or emotion regulation techniques (Fernandez-Serrano et al., 2011; Gullo & Stieger, 2011) may have the potential to improve adaptive decision-making in substance users. Importantly, these strategies should be modified and employed in a manner that specifically appeals to or targets cognitively-impaired subgroups of substance users. Indeed, some of these interventions assume a certain level of cognitive ability needed to acquire skills, such that clients who are substantially cognitively impaired may be less likely to benefit from them. Similarly, neurocognitive dysfunctions,

including disadvantageous decision-making, have been linked to both structural and functional brain alterations, which are likely to compromise learning and successful behavioral modification during treatment (Martinez et al., 2011). Therefore, pharmacological interventions or neuromodulation-based approaches (e.g., transcranial magnetic stimulation) aimed at upregulating brain functioning (Fecteau et al., 2007; Knoch et al., 2006; Martinez et al., 2011) may provide neurocognitively impaired drug users with a stronger ability to benefit from cognitively-oriented treatment programs. Modafinil for example, could act as a successful adjunct for increasing the effectiveness of executive training programs in cognitively-impaired substance users by boosting neural functioning in regions implicated in learning and cognitive control (i.e., insula, ventromedial prefrontal and anterior cingulate cortices). However, the effectiveness of combining these approaches has yet to be systematically explored and reported on and might be a promising area for future research.

4.4.3. Limitations

Although we believe that the current study has important clinical implications, several limitations should also be noted. First, several factors should be considered before generalizing from our findings. Specifically, our findings are based on a predominantly male sample of poly-drug-using CDI, the majority of whom were crack users, enrolled in long-term, residential TCs. Drug users admitted to TCs often have relatively severe problems, prior drug abuse treatment experience and a criminal justice status. As such, the present findings may not extrapolate to other treatment samples (e.g., women, individuals enrolled in outpatient treatment settings). Still, it should be noted that our sample represents a group of CDI encountered in real clinical contexts, which increases the ecological validity of the study results. Despite our finding that two indices of decision-making predicted treatment drop-out, there was a significant amount of variance that was not accounted for by the variables examined in this study. Importantly, we did not take into account the effects of other potentially relevant person-related factors, such as psychiatric comorbidity, personality (e.g., impulsivity, perseverance) or intellectual functioning (Amodeo, Chassler, Oettinger, Labiosa, & Lundgren, 2008; Curran, Kirchner, Worley, Rookey, & Booth, 2002; Moeller et al., 2001; Patkar et al., 2004). Further, drop-out from treatment is not driven purely by person-related factors (actually, person-related variables typically predict only a small proportion of the variance in drop-out), but also varies as a function of treatment-related variables and interactions between the individual and the treatment environment (McKellar, Kelly, Harris, & Moos, 2006; Passetti et al., 2008; Passetti et al., 2011).

We did not examine potential mediators of both cognitive performance and treatment retention. Among many other factors, motivation may have functioned as a mediator of both apparent cognitive performance as well as treatment retention: motivation has been shown to be an important factor in treatment retention among substance-dependent individuals (Brocato & Wagner, 2008; Joe, Simpson, & Broome, 1998; Simpson & Joe, 1993) and lower motivation to change has been found to correlate with poorer performance on a task of decision-making (Peters, Petry, Lapaglia, Reynolds, & Carroll, 2013). As such, it is possible that the observed differences in cognitive task performance between treatment completers and drop-outs reflect a difference in motivation for treatment and in the motivation to perform well on the decision-making tasks. Also, our data do not exclude the possibility that motivation for treatment or motivation to change functioned as a mediator of the relationship

between disadvantageous decision-making and treatment drop-out. Indeed, the way in which neurocognitive dysfunctions impact upon treatment outcomes may not necessarily be direct (Bates, Buckman, & Nguyen, 2013). Rather, neurocognitive impairments can impede treatment outcomes through their effects on treatment processes or more intrapersonal factors (Bates et al., 2013). These countervailing effects of neurocognitive dysfunctions on intrapersonal processes may cancel out when analyzing direct effects of impairment on treatment drop-out. Future studies may help to better understand the nature of the current findings by examining a range of potential mediators, including motivation and self-efficacy.

In summary, the present study is the first to show that CDI who drop out of residential treatment prematurely fail at properly integrating the outcomes of their actions over time in order to form a global impression of the trade-offs between risk and reward or neglect knowledge regarding outcome probabilities while making decisions. Further, our findings indirectly suggest that previous studies may have failed to find associations between IGT performance and treatment retention because early and late IGT selections were combined into a single measure and changes in task performance were not taken into account. Whereas the precise underlying processes contributing to disadvantageous decision-making patterns remain to be fully elucidated, our findings have potential implications for the treatment of cocaine dependence.

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CHAPTER 5

DELAY DISCOUNTING, TREATMENT MOTIVATION AND RETENTION AMONG SUBSTANCE-DEPENDENT INDIVIDUALS ATTENDING AN IN INPATIENT DETOXIFICATION PROGRAM[6]

[5] Based on Stevens, L., Verdejo-Garcia, A., Roeyers, H., Goudriaan, A. E., & Vanderplasschen, W. (2014). Delay discounting, treatment motivation and retention among substance-dependent individuals attending an in inpatient detoxification program. *Journal of Substance Abuse Treatment* (in press).

ABSTRACT

Recent studies consistently indicate high rates of delay discounting in chronic drug users, which refers to a strong tendency to devaluate delayed rewards. Many addiction treatment programs, however, place high demands on the ability to postpone immediate gratification. Therefore, these programs may be particularly challenging for drug users who are disproportionally oriented towards the present, potentially leading to a drop in their treatment involvement. Still, few studies to date have looked at whether delay discounting in drug users is associated with poorer treatment motivation or shorter treatment retention. In this chapter, we examined whether delay discounting, as measured shortly following treatment entry, was predictive of poor treatment retention among 84 substance-dependent individuals (SDI) attending an inpatient detoxification program. In addition, we examined whether motivation for treatment would act as a mediator of this relationship. Findings revealed that delay discounting was predictive of shorter treatment retention and higher odds of dropping out of treatment prematurely, even after controlling for other (previously) established predictors of treatment retention and drop-out. The effects of delay discounting on treatment retention were partially mediated by a subcomponent of treatment motivation, i.e., treatment readiness. If replicated, the propensity to more steeply discount delayed rewards in SDI has the potential to become a clinically relevant behavioral marker, alerting clinicians that these clients may exhibit lower treatment readiness and are more likely to drop out of treatment prematurely. Targeting delay discounting or increasing treatment readiness in SDI with a low tolerance for delay-of-gratification has the potential to improve treatment retention.

5.1. Introduction

Delay discounting refers to the devaluation of a reward as a function of the delay until its receipt, often expressed as a preference for smaller immediate rewards relative to larger but delayed rewards (Richards, Zhang, Mitchell, & De Wit, 1999). Such a selection bias may be viewed as one form of impulsivity (Evenden, 1999). Growing evidence suggests that pathological levels of delay discounting may result from an imbalance between two neural systems (McClure, Laibson, Loewenstein, & Cohen, 2004). In particular, delay discounting has been linked to a dominant, amygdala-striatum-dependent bottom-up system that promotes immediately rewarding actions, coupled with a hypoactive, prefrontal-dependent executive top-down system involved in cognitive control and the consideration of future consequences (Bechara, 2005; McClure et al., 2004).

Studies over the last decade consistently point to high rates of delay discounting among nicotine, alcohol, opiate, cocaine, and other types of drug users (Bickel, Yi, Kowal, & Gatchalian, 2008; Bjork, Hommer, Grant, & Danube, 2004; Businelle, McVay, Kendzor, & Copeland, 2010; Coffey, Gudleski, Saladin, & Brady, 2003; Heil, Johnson, Higgins, & Bickel, 2006; Kirby & Petry, 2004; Vassileva, Georgiev, Martin, Gonzalez, & Segala, 2011). Notably, converging evidence suggests that greater discounting of delayed rewards in these groups predicts difficulties with achieving and maintaining abstinence (De Wilde, Verdejo-Garcia, Sabbe, Hulstijn, & Dom, 2013; Passetti, Clark, Mehta, Joyce, & King, 2008; Stevens et al., 2014; Washio et al., 2011). Despite the intuitive nature of such a relationship, far fewer studies have examined whether delay discounting predicts shorter treatment retention (i.e., length of stay in treatment), which is a major problem associated with the treatment of individuals with a substance use disorder (SUD): shorter stays in treatment or premature treatment drop-out limit overall treatment effectiveness, increase the likelihood of relapse and exacerbate financial, health and legal consequences (Brewer, Catalano, Haggerty, Gainey, & Fleming, 1998). Conversely, a sufficient length of time spent in treatment constitutes one of the strongest and most consistent predictors of positive post-treatment outcomes, including sustained abstinence (Ball, Carroll, Canning-Ball, & Rounsaville, 2006; Zhang, Friedmann, & Gerstein, 2003).

Delay discounting might affect drug users' length of stay in treatment in several ways. Given that most addiction treatment programs are highly structured and place great demands on the ability to postpone immediate gratification, it is intuitively conceivable how delay discounting may directly promote premature drop-out from these programs. Alternatively, the effects of delay discounting on treatment retention may be indirect, i.e., mediated by other factors (Bates, Buckman, & Nguyen, 2013). In moving towards the motivation and decision to fully engage in treatment, drug users need to complete a decisional balance evaluating the perceived benefits and costs of quitting drug use and/or engaging in treatment. Given that the benefits associated with treatment engagement (e.g., continued abstinence, improved health) are typically temporarily distant, drug users who have a low tolerance for delay-of-gratification (i.e., high delay discounters) may exhibit poorer treatment motivation, which in turn could result in shorter treatment retention. Partially corroborating this notion, a recent study found significant correlations between higher pre-treatment delay discounting and lower readiness to change marijuana use, suggesting that individuals who discount at high rates may be less ready to alter their drug use when initiating treatment (Peters, Petry, Lapaglia, Reynolds, & Carroll, 2013). In line with

previous reports highlighting the clinical relevance of treatment motivation (Joe, Simpson, & Broome, 1998), the same study found a significant relationship between readiness to change and marijuana outcomes. Specifically, lower readiness to change was related to fewer days of marijuana abstinence in this study (Peters et al., 2013). However, the authors did not address both aspects of mediation: namely, that delay discounting results in poor motivation for treatment, and that this lower treatment motivation results in poorer treatment outcomes. Examining these indirect effects may nevertheless be of great clinical relevance, in that a better understanding of the mechanisms by which delay discounting negatively affects treatment outcomes may help to translate findings into effective recovery-oriented services.

The primary purpose of the current study was to examine whether delay discounting, as measured shortly following treatment entry, would be predictive of shorter treatment retention among substance-dependent individuals (SDI). This relationship was examined in the context of highly structured, inpatient detoxification programs that place high demands on the ability to postpone immediate gratification. Age, number of prior treatment episodes, duration of drug use, treatment readiness and comorbid attention-deficit/hyperactivity disorder (ADHD) were included as additional predictors, since these factors have consistently been related to treatment retention (Brorson, Arnevik, Rand-Hendriksen, & Duckert, 2013; Joe et al., 1998; Levin et al., 2004; Wei et al., 2013). In an attempt to better understand one possible mechanism through which delay discounting may exert an influence on treatment retention, we further explored whether motivation for treatment would act as a mediator of this relationship. Our first hypothesis was that greater delay discounting would be associated with shorter treatment retention and a higher propensity to drop out of the detoxification program prematurely. Second, it was hypothesized that motivation for treatment would (partially) mediate the relationship between delay discounting and treatment retention.

5.2. Methods

5.2.1. Participants and procedure

A total of 84 SDI were included in the present analyses. Participants were aged 16 and above and met criteria for any current substance dependence as outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV, American Psychiatric Association, 1994). Exclusion criteria were (1) having an intellectual quotient (IQ) below 70 or not having sufficient comprehension of the Dutch language to understand test instructions, (2) having a history of neurological condition, strokes, intracranial hemorrhages and/or head injuries with loss of consciousness for longer than 30 minutes, and (3) having a past or current major DSM diagnosis of psychotic disorders. Eligible participants provided written informed consent and were interviewed/tested within the first week from starting inpatient detoxification treatment (range 3–8 days), i.e. as soon as they had been stabilized. Treatment retention data were collected from administrative staff at the detoxification facilities with the consent of the participants.

5.2.2. Treatment program

Participants were recruited from three comprehensive, highly structured inpatient detoxification programs. The detoxification and treatment protocols in the three settings were similar, and typical treatment lasted between 5 or 6 weeks. The detoxification programs provided medical management of withdrawal symptoms, offered crisis support with respect to various life areas (e.g., medical, social, administrative, legal), enhanced abstinence motivation, provided information and advice with regard to further treatment options and supported the referral to these treatment modalities. The centers required complete abstinence from drugs and alcohol, with the exception of caffeine and nicotine. Aside from scheduled activities (e.g., physician visits), residents were not permitted to leave the center grounds during treatment. Regular drug testing was provided and any drug use resulted in dismissal from the detoxification program. In terms of their approach, the detoxification programs were closely embedded in and utilized therapeutic community (TC) concepts; the programs were highly structured and strict/explicit behavioral norms were emphasized (i.e., no drugs or alcohol, no violence and no sexual relationships). Because most rules imply a certain degree of delay (e.g., residents have to submit a written request that needs to be approved before they are allowed to contact their friends or family members), complying with rules places high demands on the ability to postpone immediate gratification. Group counseling was considered as the central therapeutic technique.

5.2.3. Assessments

5.2.3.1. Socio-demographic and clinical information

A demographic form was used to collect basic demographic information (e.g., age, gender, race). Sections of the *Mini-International Neuropsychiatric Interview* (M.I.N.I.-plus) (Sheehan & Lecrubier, 1998) were used to assess substance abuse and dependence. Further information regarding drug use (e.g., prior treatment episodes for SUDs, past month drug use at baseline) was assessed using a Dutch translation of the European version of the *Addiction Severity Index* (Europ-ASI), a semi-structured clinical assessment interview (McLellan, Luborsky, Woody, & O'Brien, 1980; Raes, Lombaert, & Keymeulen, 2004). IQ was estimated using two subtests of the *Wechsler Adult Intelligence Scale*, third edition (WAIS-III; Wechsler, 1997; WAIS-III, Dutch version, Swets Test Publishers, 2000): matrix reasoning and information. The estimated IQ derived from scores on these subtests has been found to correlate .92 with the full scale IQ (Ringe, Saine, Lacritz, Hynan, & Cullum, 2002).

5.2.3.2. Delay discounting

The *delay discounting task* (DDT) was administered in order to evaluate the preference for small immediate rewards over large delayed rewards. Participants completed six session blocks with eight preference judgments between a future and an immediate hypothetical monetary reward per block. The delayed reward was the same for all trials of a given block (i.e., 506, 476, 524, 512, 520, 488), with a block-specific delay in days (i.e., 5, 30, 180, 365, 1095, 3650) for blocks 1-6, respectively. The value of the immediate reward was adjusted from trial to trial (depending on the responses made by the subjects) until it was deemed by the participant to be equivalent to the value of the delayed reward (the exact adjustments can be found in Wittmann, Leland, & Paulus, 2007). The indifference points for

each delay, indicating which immediately delivered amount of money would be preferred equally to the delayed reward, were plotted and hyperbolic discount functions were derived through curve-fitting analysis. The *k*-value was used as dependent variable; as *k* increases, the person discounts the future reward more steeply and thus higher *k*-values correspond to higher levels of impulsivity.

5.2.3.3. Motivation for treatment

Motivation for treatment was measured using a Dutch version of the *Motivation for Treatment (MfT) scale* (De Weert-Van Oene, Schippers, De Jong, & Schrijvers, 2002), a questionnaire based upon Simpson and Joe's Texas Christian University Treatment Motivation Assessment (Simpson & Joe, 1993). This scale consists of 24 items and three scales, each representing progressive levels of change similar to those described by Prochaska and DiClemente. The first scale is called *Problem Recognition* and assesses an individual's attitude toward their drug use (e.g., "Your drug use is causing problems in thinking or doing your work"). The second scale, *Desire for Help*, measures the need for assistance (e.g., "You need help in dealing with your drug use"). The third scale, *Treatment Readiness*, measures the extent to which the person is ready to actively engage in treatment as well as clients' expectations about how helpful treatment will be (e.g., "This treatment program seems too demanding for you" or "This treatment program can really help you"). Subjects are asked to respond to the items based on a five-point Likert-type scale ranging from (1) strongly disagree, (2) disagree, (3) neutral, (4) agree, to (5) strongly agree. Raw scores on negatively worded items (e.g., "Treatment will not be very helpful to you") were reversed to ensure intended relationships among items. The Dutch version of the MfT scale has been found to be a valid instrument for measuring treatment motivation in SDI (De Weert-Van Oene et al., 2002).

5.2.3.4. Treatment retention

Treatment retention was evaluated in two ways to promote comparison with the published literature. For the main analyses, treatment retention was evaluated as a continuous variable, operationalized as the number of days spent in the detoxification program. Second, treatment retention was evaluated as a dichotomous variable (i.e., drop-out vs. treatment completion), operationalized as the individual leaving the detoxification program against treatment center staff's advice, i.e., before completing the predetermined treatment program. Reasons for drop-out could vary from voluntary drop-out to dismissal by treatment staff due to rule breaking behavior.

5.2.4. Data analysis

Preliminary descriptive analyses of the socio-demographic and clinical characteristics of the sample were conducted. Because of positively skewed distributions of discounting coefficients, natural logarithm-transformed *k*-values were estimated = ln(*k*+0.001) and employed in the analyses of discounting.

To test our main hypothesis, i.e., that delay discounting would significantly contribute to the prediction of (shorter) treatment retention, a multiple hierarchical linear regression analysis was used, including delay discounting and (previously) established predictors of treatment retention (e.g., age, duration of drug use, treatment readiness, number of prior treatment episodes and the presence of ADHD). This multiple regression analysis was organized in four different steps (enter-method) in order to estimate if

the inclusion of each new block significantly increased the predictive capacity of the model (change in R^2) (see section 5.3.2.). Potential collinearity effects were tested using specific collinearity diagnoses: Tolerance and the Variance Inflation Factor (VIF). Tolerance is the proportion of a variable's variance that is not accounted for by the other independent variables in the equation, whereas VIF is the reciprocal of tolerance. To promote comparison with the existing literature, we also performed a binary logistic regression to evaluate whether delay discounting significantly contributed to the prediction of treatment drop-out.

Next, Pearson correlation analyses were conducted to explore correlations between delay discounting, motivation subscales and treatment retention, and to determine if the conditions required to test the mediation model were met. A Bonferroni correction was applied to control for multiple comparisons. Mediation analysis was performed using Hayes' PROCESS macro for SPSS (Hayes, 2012) and following the criteria outlined by MacKinnon (2008). According to MacKinnon, two conditions need to be met in order to test for mediation: there needs to be a significant effect from the predictor to the mediator (referred to as path a) and a significant effect from the mediator to the outcome (referred to as path b). By contrast, a significant direct effect from the predictor to the outcome (referred to as path c') is not required. PROCESS is a regression-based computational tool for path-based mediation analysis. The tool estimates the coefficients of the model using OLS regression for continuous outcomes (i.e., number of days in treatment). The indirect effect (a*b) is determined by computing 95% confidence intervals (CI) using bias-corrected bootstrapping. A mediated effect is supported if the CI does not include a value of zeo. Analyses were conducted using the Statistical Package for the Social Sciences (SPSS), version 22.0.

5.3. Results

5.3.1. Sample description

Sample characteristics are displayed in Table 5.1. As can be retrieved from the table, the mean length of stay in the detoxification program was 33 days, and more than half of the sample dropped out of the detoxification program prematurely.

Table 5.1.: Descriptive information of the sample (n=84)

Variables	Means
Gender (% male)	87%
Age	28.71 ± 6.79
Years of Education	11.71 ± 2.29
Estimated IQ	86.79 ± 8.32
Primary substance	
Cocaine (%)	70%
Opiates (%)	12%
Stimulants (%)	10%
Marihuana (%)	8%
Age of Onset	18.63 ± 4.40
Duration drug use (years)	8.11 ± 6.55
Past Month Use (days)	15.47 ± 11.91
Poly-drug use (%)	82.1%
Abstinence (days)	12.70 ± 13.46
Prior treatment episodes	2.79 ± 4.09
Days in treatment	33.09 ± 15.36
Drop-out (%)	56%

Data are presented as means ± SD, unless otherwise indicated

5.3.2. Regression model

To test our main hypothesis, i.e., that delay discounting would significantly contribute to the prediction of (shorter) treatment retention, a multiple hierarchical linear regression analysis was performed. This multiple regression analysis was organized in four different steps by using the “Enter” method. Step 1 included age as the only predictor. In Step 2, the number of prior treatment episodes, treatment readiness, and duration of drug use (years) were added to this. In Step 3, ADHD (presence or absence) was entered. In Step 4 finally, delay discounting (natural log transformation of the discount rate) was added to the previously entered predictors. Tolerance values of the final model ranged between 0.981 and 0.585, and VIF values ranged between 1.019 and 1.710, indicating that the model was not threatened by multicollinearity.

Results showed that the change in the explained variance was only significant when the second and final block of predictors was included. The model including age (Step 1) explained about 2% of the variance in retention. After inclusion of treatment readiness, duration of drug use and the number of prior treatment episodes (Step 2), the model explained about 12% of the variance, producing a significant change in the *F*-value of the full model, (change in $F = 3.046$, $p = 0.034$). The third model,

after inclusion of ADHD (Step 3), explained around 13% of the variance in treatment retention. Finally, the fourth model, after including delay discounting (Step 4), accounted for approximately 18% of the variance in treatment retention. Adding delay discounting resulted in a significant change in the *F*-value of the full model (change in $F = 4.900$, $p = 0.030$). The only significant predictor variables in the final model were treatment readiness and delay discounting (Table 5.2.). Analyses of the beta values showed that, with every unit increase in treatment readiness, treatment retention increased with 7.52 days. With every unit increase in the DDT_(ln)*k*-value (i.e., steeper discounting), treatment retention decreased with 3.75 days.

Similar results were obtained when binary logistic regression was performed (table not presented). A combination of the different predictors (e.g., age, prior treatment episodes, treatment readiness, duration of drug use, ADHD and delay discounting) against a constant only model was significant ($\chi^2_{(6)} = 18.03$, $p = .006$) and accounted for 27% of the (pseudo)variance in treatment drop-out (Nagelkerke R-square). In the final model, only delay discounting uniquely contributed to the prediction of treatment drop-out, as demonstrated by the Wald-criterion (Wald = 5.456, df = 1, $p = .020$). Results showed that, for every unit increase in the (ln)*k*-value (i.e., greater delay discounting), the odds of dropping out of the detoxification program prematurely became 2.45 times higher than the odds of completing treatment.

Table 5.2.: Final prediction model of time in treatment

Predictors	Beta	S.E.	*t*	*p*	Tolerance	VIF
Constant	-23,454	14,502	-1,617	,110		
Age	,059	,306	,192	,849	,585	1,710
Prior treatment episodes	-,104	,392	-,264	,792	,981	1,019
Treatment readiness	7,523	2,986	2,519	,014	,842	1,188
Duration of drug use *(primary substance)*	-,099	,311	-,319	,750	,609	1,643
ADHD	4,797	3,574	1,342	,184	,859	1,164
DDT_(ln)k	-3,752	1,695	-2,214	,030	,745	1,343

Mediation analysis

In order to establish the necessary conditions for testing the mediation model, correlations between delay discounting, the three MfT subscales (i.e., problem recognition, desire for help, treatment readiness) and treatment retention were calculated. A Bonferroni correction was applied to control for multiple comparisons, resulting in a corrected alpha level of .01 (i.e., 0.05/5). As such, only correlations with a *p*-value < .01 were considered significant. Table 5.3. displays the correlation matrix. We found a statistically significant negative correlation between delay discounting and treatment readiness (TR), reflecting that the greater the levels of delay discounting, the lower the level of treatment readiness (path a). In not correlating with discounting scores, the MfT sub-dimensions of problem recognition (PR) and desire for help (DH) did not meet the first criterion for the mediation

model and were not tested further. A significant positive correlation was found between TR and treatment retention (path b). Although not required to test the mediation model based on the criteria outlined by MacKinnon (2008), delay discounting scores were significantly associated with treatment retention (path c'). In particular, individuals with higher levels of delay discounting tended to have shorter stays in treatment.

Table 5.3.: Correlations between the natural log transformation of the discount rate (DDT_(ln)k), problem recognition, desire for help, treatment readiness and treatment retention

	(1)	(2)	(3)	(4)	(5)
(1) DDT_(ln)k	1	.064	-.106	-.342*	-.319*
(2) MfT Problem recognition		1	.405*	.256	.165
(3) MfT Desire for help			1	.525*	.259
(4) MfT Treatment readiness				1	.343*
(5) Treatment retention					1

* Correlation is significant at the $p < .01$ level (2-tailed)

Given that only treatment readiness significantly correlated with delay discounting and treatment retention, a mediation analysis treating delay discounting as predictor, treatment readiness as mediator, and treatment retention as outcome variable was performed. Figure 1 displays the results of this analysis. Delay discounting was a significant predictor of treatment readiness, and treatment readiness significantly predicted treatment retention (see Table 5.4.). The mediation hypothesis was supported by a significant indirect effect, as indicated by the CI excluding zero. The proportion of the total effect mediated was 30%, indicating support for partial mediation. However, the ratio of the indirect effect to the direct effect was .42, thus less than half the size of the direct effect.

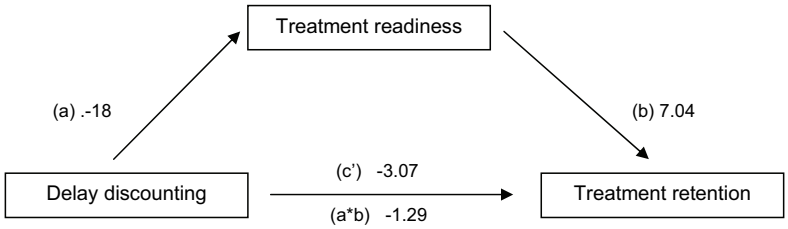

Figure 1. The relationship between delay discounting and treatment retention, as mediated by treatment readiness. Unstandardized regression coefficients (*B*) are presented. For the direct paths from delay discounting to treatment retention, the coefficient is presented inside the diagram, with the coefficient from the mediated model underneath, outside of the triangle.

Table 5.4.: Results of the mediation analysis with delay discounting ((ln)k-values) as predictor, treatment readiness (TR) as the mediator and treatment retention as the outcome (n=84)

Path	Effect	Unstandardized Coefficients (SE)	*P*
c'	Direct effect of delay discounting on treatment retention	-3.07 (1.54)	< .049
a	Effect of delay discounting on TR	-0.18 (0.06)	< .002
b	Effect of TR on treatment retention	7.04 (2.88)	< .016
a*b	Indirect effect	-1.29 (0.73)	CI: -3.20; -0.19

Note: CI excluding zero indicates statistical significance

5.4. Discussion

5.4.1. Main findings

The present study evaluated the relationship between pre-treatment delay discounting and treatment retention in a naturalistic sample of SDI participating in an inpatient detoxification program. In addition, we examined the nature of this relationship by exploring whether motivation for treatment acted as a mediator. The results of our study support two main findings.

First, a significant association between delay discounting and treatment retention was found. More specifically, results revealed that greater discounting of delayed rewards at treatment entry was predictive of shorter treatment retention and higher odds of dropping out of a detoxification program prematurely. In fact, delay discounting was able to account for unique variance in treatment retention, over and above that explained by previously established predictors of retention. This finding is clinically relevant, given the fact that high drop-out rates during the initial phase of treatment (i.e., detoxification) greatly affect the number of subjects who reach the stage at which they could transition to continuing care (McKay & Hiller-Sturmhofel, 2011). Indeed, detoxification programs are rarely effective by themselves, and the future success of many clients is likely to be contingent upon whether they transition to continuing care (Millery, Kleinman, Polissar, Millman, & Scimeca, 2002). Because premature treatment drop-out from detoxification significantly reduces the number of persons who might be transferred to continuing care, a better understanding of the factors predicting treatment attrition from detoxification programs is critical. Our study suggests that higher levels of delay discounting at treatment entry, an indicator of impulsive choice, may be promising in this respect. Highly structured treatment programs may be suboptimal in retaining SDI with high discounting rates in treatment, potentially because of the high demands that are being placed on the ability to postpone immediate gratification. Supporting the notion that the effects of delay discounting on addiction treatment outcomes are moderated by program characteristics, Passetti and colleagues (2011) found that delay discounting in opiate users was associated with relapse during inpatient but not during outpatient treatment. However, future studies may help to determine whether the findings presented here are specific to inpatient settings or rather, generalize to a broader range of treatment programs.

Though not mutually exclusive, the results of the current study point to a second explanation that may account for the link between delay discounting and poorer treatment retention. Specifically, the propensity to more steeply discount delayed rewards in SDI appeared to be associated with poorer treatment readiness, which reflects the degree of commitment to active change through participation in a treatment program (Rapp et al., 2007). Such an association is consistent with preliminary evidence supporting a relationship between neurocognitive impairment and motivation to change substance use (Blume, Marlatt, & Schmaling, 2000; Blume, Schmaling, & Marlatt, 2005; LeBerre et al., 2012; Severtson, von Thomsen, Hedden, & Latimer, 2010). Whereas we did not examine how delay discounting negatively affected treatment readiness, several hypothesis can be proposed. LeBerre and colleagues (2012) recently found evidence to suggest that advantageous decision-making is needed to resolve ambivalence towards drug addiction and treatment engagement. Similarly, an orientation towards the future may be a prerequisite to fully appreciate the (long-term) benefits

associated with treatment participation. Despite being aware that their drug use is causing a problem (i.e., delay discounting was not significantly associated with problem recognition), behavior in delay discounters may be more driven by the immediate prospects of drug reward, rather than by the temporally distant benefits associated with treatment participation and completion. Alternatively, high delay discounters may be less confident in their ability to avoid substance use (i.e., lower self-efficacy) or may conceive treatment as too demanding. This in turn could lead to less optimistic expectations regarding the benefits associated with treatment (Meier, Donmall, McElduff, Barrowclough, & Heller, 2006). Corroborating this notion, Bates and colleagues (2006) found that greater cognitive impairment in alcohol-dependent individuals predicted less treatment compliance and lower self-efficacy, as measured by a client's confidence in their ability to not drink (Bates, Pawlak, Tonigan, & Buckman, 2006). Obviously, it is not certain whether a similar explanation can account for the findings presented in this study. Accordingly, the aforementioned proposals should be subjected to further research in order to gain a more precise understanding of the nature of the relationship between delay discounting and treatment readiness.

Much previous research on impulsivity in SDI has examined direct effects of impulsivity on addiction treatment outcomes, without considering other pathways of influence. Still, evidence in the neurocognitive literature suggests that the effects of neurocognitive impairment are often indirect, i.e., mediated by other factors (Bates et al., 2006). As recently proposed by Bates and colleagues (2013), neurocognitive deficits in SDI may affect treatment outcomes through their ability to change the salience of environmental features as well as the person's emotional and motivational responses. Consistent with this notion, the results of our mediation analysis indicated that delay discounting partially influences treatment retention by affecting treatment readiness, which acts as an important change mechanism in addiction treatment (Joe et al., 1998). At the same time, our data also support the existence of a (more robust) direct relationship between delay discounting and treatment retention. Indeed, the indirect effect (delay discounting → treatment readiness → treatment retention) was about half the size of the direct effect (delay discounting → treatment retention).

5.4.2. Clinical implications

Identification of client characteristics (i.e., delay discounting) and treatment process components (i.e., motivation) that have direct linkages to retention carries important clinical significance: intervention strategies that improve one or more of these elements may be expected to represent enhancements to treatment effectiveness. Accordingly, the findings presented in this study indicate that treatment readiness and retention in SDI can be improved by targeting delay discounting. Consistent with the notion that adaptive decision-making partially depends on the integrity of the dorsolateral prefrontal loop and executive functioning (McClure et al., 2004), neurocognitive training of working memory has been found to be effective at decreasing delay discounting in drug users (Bickel, Yi, Landes, Hill, & Baxter, 2011). A worthwhile prospect for future studies in this regard may be to examine whether training-induced improvements in delay discounting are directly related to changes in treatment readiness and retention. Whereas such a finding would be promising, our data also warn against pinning all hope exclusively on clinical interventions aimed at directly improving delay discounting. In fact, the findings of the current study suggest that impulsive subjects may drop out of treatment before

their lack of orientation towards the future can be adequately addressed. Introducing elements that more directly affect retention rates early during detoxification treatment may therefore be a necessary first step to motivate drug users to stay in treatment, at least in the short term. Making the benefits of early treatment engagement more tangible, for instance by linking treatment retention with monetary rewards, may be one promising strategy in this regard (García-Rodríguez et al., 2009; Higgins, Badger, & Budney, 2000). Longer treatment retention in turn enables the implementation of more specialized interventions later on during treatment.

The findings of this study further suggest that part of the negative effects of delay discounting on treatment retention can be diminished by increasing treatment readiness in high discounters. To date, several relatively brief, focused interventions that target cognitive appraisal processes are available, including motivational interviewing (Miller & Rollnick, 1991). Implementing exercises to shift the decisional balance with clients and making the benefits of change and treatment more apparent may be critical in substance users who are primarily oriented towards the present. Future studies are needed to examine whether implementing these interventions in drug users with inflated impulsivity may help to promote treatment readiness and diminish the negative effects of delay discounting on treatment retention. As a critical note to this, it is important to consider the possibility that poor treatment readiness in high discounters might equally well result from dissatisfaction with treatment components, such as the high demands that are being placed on the ability to postpone immediate gratification. If this is true, the implementation of motivational enhancement interventions alone might not be sufficient to enhance treatment readiness in these individuals. The development of a better understanding of the dynamic interplay between delay discounting and treatment-related factors is therefore critical, and can be used to inform effective treatment development or modifications.

5.4.3. Strengths and limitations

The current findings should be considered in light of the study's strengths and weaknesses. Despite the intuitive nature of such an association, this study was among the first to examine the relationship between delay discounting and treatment retention in SDI, one of the most consistent predictors of post-treatment outcomes (Ball et al., 2006). This relationship was studied in the context of real-world detoxification programs and using a naturalistic sampling approach, which increases the ecological validity of the study results. Despite growing interest in the relationship between impulsivity and treatment retention (Moeller et al., 2001; Streeter et al., 2008), our study was also the first to explore an indirect pathway by which impulsivity may exert its influence on the length of stay in treatment. Our results highlight the need for research designed to study delay discounting within a broader context of treatment-related variables.

Despite some notable strengths, several limitations of the present study are worth noting. First, the cross-sectional nature of this study limits the ability to infer causal relationships regarding the relationship between delay discounting and treatment readiness. A second limitation was our selective focus on one index of impulsivity, i.e., delay discounting, and one particular mediator, i.e., treatment motivation. Although poor treatment retention can partly be explained by delay discounting and treatment motivation, treatment retention relies on many other processes, including clinical, emotional and social factors (Brorson et al., 2013). The variance not accounted for in treatment retention could

be lowered in future studies by the inclusion of other factors, including self-efficacy or therapeutic alliance.

These limitations notwithstanding, our study adds to the available literature by demonstrating that delay discounting is a relevant predictor of shorter treatment retention and higher odds of dropping out of inpatient detoxification programs. The current study further highlights the role of treatment readiness as an explanatory variable in the relationship between delay discounting and treatment retention.

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CHAPTER 6

IMPULSIVE CHOICE PREDICTS POST-TREATMENT RELAPSE IN SUBSTANCE-DEPENDENT INDIVIDUALS ATTENDING AN INPATIENT DETOXIFICATION PROGRAM[7]

[7] Based on Stevens, L., Goudriaan, A. E., Verdejo-Garcia, A., Dom, G., Roeyers, H., & Vanderplasschen, W. (2014). Impulsive choice predicts post-treatment relapse in substance-dependent individuals attending an inpatient detoxification program. Manuscript under review in *Psychological Medicine*.

ABSTRACT

Impulsivity is a hallmark characteristic of substance use disorders (SUDs). Recently, studies have begun to explore whether increased impulsivity in substance-dependent individuals (SDI) is associated with a greater propensity to relapse following treatment. Despite growing recognition of the multidimensional nature of impulsivity however, most relapse studies have treated impulsivity monolithically. As such, it remains unclear whether certain facets of impulsivity are more relevant to relapse than others. In the study discussed in this chapter, we examined the effects of personality and neurocognitive dimensions of impulsivity on post-treatment relapse in a heterogeneous sample of 70 SDI participating in an inpatient detoxification program. Multivariate binary logistic regression analysis was used to investigate the unique contribution of different impulsivity dimensions to the prediction of post-treatment relapse. Mediation analyses were performed to explore whether the effects of impulsivity on relapse were mediated by treatment retention. Findings revealed that two neurocognitive indices of impulsive choice (i.e., delay discounting and impulsive decision-making) were uniquely and significantly associated with relapse and outperformed personality-based trait measures of impulsivity in predicting relapse propensity. Mediation analyses showed that the effects of delay discounting and impulsive decision-making on relapse propensity were mediated by treatment retention. Overall, these findings suggest that neurocognitive indices of impulsivity are more promising in the prediction of relapse than trait-based self-report questionnaires. Further, results indicate that the occurrence of post-treatment relapse can be reduced by targeting the processes involved in impulsive choice and by improving treatment retention in SDI with inflated impulsivity.

6.1. Introduction

Impulsivity plays a critical role in the establishment and maintenance of drug addiction (Belin, Berson, Balado, Piazza, & Deroche-Garmonet, 2011; Belin, Mar, Dalley, Robbins, & Everitt, 2008; Bird & Schenk, 2012; Everitt et al., 2008). Recently, studies have begun to examine whether increased impulsivity among substance-dependent individuals (SDI) is also associated with a greater propensity to relapse following treatment discharge (De Wilde, Verdejo-Garcia, Sabbe, Hulstijn, & Dom, 2013; Stevens et al., 2014). Given that impulsivity is amenable to treatment (Alfonso, Caracuel, Delgado-Pastor, & Verdejo-García, 2011; Bickel, Yi, Landes, Hill, & Baxter, 2011), a better understanding of its involvement in relapse propensity may have important clinical implications.

To date, there is substantial empirical evidence indicating that impulsivity is a multidimensional construct that includes different biologically based and heritable components (Dawe & Loxton, 2004; Evenden, 1999; Reynolds, Ortengren, Richards, & De Wit, 2006; Whiteside & Lynam, 2001). Often, a distinction is made between personality-based dimensions of impulsivity on the one hand and neurocognitive dimensions of impulsivity on the other hand (Goudriaan, Oosterlaan, De Beurs, & Van Den Brink, 2008; Sharma, Markon, & Clark, 2014). From a personality perspective, impulsivity is generally perceived as a *trait* that is fairly stable over time and evident across a range of situations. Dimensions of trait impulsivity are multifold and include (1) a lack of future orientation (i.e., lack of premeditation, motor or non-planning impulsivity), (2) a failure to follow through on goal-related, complex tasks while experiencing boredom (i.e., lack of perseverance/persistence or attentional impulsivity), (3) a need for excitement, novelty and stimulation (i.e., sensation or novelty seeking) and (4) difficulties in resisting strong impulses driven by negative or positive affect (i.e., negative or positive urgency) (Eysenck & Eysenck, 1985; Patton, Stanford, & Barratt, 1995; Whiteside & Lynam, 2001; Zuckerman, Eysenck, & Eysenck, 1978). The distinction between these various personality dimensions of impulsivity has been justified by exploratory factor analysis and by studies indicating that distinct dimensions of impulsivity are predictive of different aspects of addictive behaviors (Billieux, Van der Linden, & Ceschi, 2007; Verdejo-Garcia, Bechara, Recknor, & Pérez-Garcia, 2007; Whiteside & Lynam, 2001). Trait impulsivity is typically measured using self-report questionnaires, which assess subjective views on impulsive behavior and include questions that cover broad periods of time, making them appropriate for assessing stable aspects of impulsivity. From a neurocognitive perspective, impulsivity is generally perceived as a transitory *state*, sensitive to environmental and personal influences. As a transitory state, impulsivity is typically assessed using neurocognitive tasks, which measure specific behavioral processes and are considered to be a more objective method of measuring impulsivity (Verdejo-Garcia, Lawrence, & Clark, 2008). Often, a distinction is made between two neurocognitive expressions of impulsivity; impulsive action and impulsive choice (Winstanley, Eagle, & Robbins, 2006). The former refers to poor inhibitory control or motor disinhibition and the latter refers to impulsive decisions, often due to a distorted evaluation of delayed consequences (Dalley, Everitt, & Robbins, 2011). Impulsive choice can be further subdivided into different components; steep discounting of delayed rewards (delay discounting), a tendency to respond to immediate rewards while disregarding long-term losses (impulsive decision-making) or sampling insufficient information prior to making a decision (reflection impulsivity) (Verdejo-Garcia et al., 2008).

The distinction between impulsive action and impulsive choice has been justified by animal studies showing that both constructs are involved in distinct stages of the addiction cycle. Whereas impulsive action appears to mediate the initial sensitivity to drugs and drug intake, impulsive choice is implicated in the persistence of and relapse into drug abuse (Broos, Diergaarde, Schoffelmeer, Pattij, & De Vries, 2012; Diergaarde et al., 2008). Growing neurobiological evidence moreover indicates that different dimensions of impulsivity recruit different brain circuitries and may be susceptible to distinct pharmacological influences (Broos et al., 2012; Dalley et al., 2011; Diergaarde et al., 2008; Paterson, Wetzler, Hackett, & Hanania, 2011).

Together, these findings suggest that an examination of the relative contribution of separate aspects of impulsivity to the propensity to relapse in drug users could in future lead to the development of more specific and tailored therapies to improve addiction treatment outcomes. Still, the majority of previous outcome studies has treated impulsivity monolithically (see Stevens et al., 2014). Similarly, personality and neurocognitive research traditions on impulsivity have historically remained largely independent (Sharma et al., 2014), despite evidence suggesting that self-report and neurocognitive assessments of impulsivity represent different levels of analyses (Reynolds et al., 2006; Sharma et al., 2014). Whereas preliminary evidence suggests that neurocognitive indices of impulsivity may be more promising in the prediction of relapse than personality-based self-report questionnaires (Goudriaan et al., 2008), it remains largely unknown whether each assessment strategy is tapping unique variance in relapse and thus, whether their joint use has incremental predictive power over the use of either type of measure alone. Previous studies examining the effects of impulsivity on post-treatment relapse have suffered from a number of other limitations. Most notably, few studies have explicitly taken into account potential mediating effects of treatment retention, i.e., the number of days spent in treatment. Given the growing evidence indicating that impulsivity negatively affects treatment retention on the one hand (see Stevens et al., 2014, but also Chapter 4 and 5) and the robust association between treatment retention and post-treatment relapse on the other hand (Zhang, Friedmann, & Gerstein, 2003), apparent effects of impulsivity on relapse propensity may result from shorter stays in treatment and thus, less treatment exposure in the most impulsive patients.

In the current study, we explicitly adopted a multidimensional impulsivity approach while examining the relationship between impulsivity and post-treatment relapse among SDI. We used a test battery comprising measures which are believed to index core aspects of impulsivity, including a self-report questionnaire indexing four trait dimensions of impulsivity (i.e., lack of premeditation, lack of perseverance, sensation seeking and negative urgency) and neurocognitive tasks indexing four dissociable neurocognitive aspects of impulsivity (i.e., response (dis)inhibition, delay discounting, decision-making and reflection impulsivity) (Verdejo-Garcia et al., 2008). As a secondary aim, we wanted to explore whether the relationship between impulsivity and post-treatment relapse would be mediated by treatment retention. Based upon recent findings documented in the animal literature (e.g., Broos et al., 2012), we hypothesized that impulsive choice but not impulsive action would be significantly associated with post-treatment relapse. We further reasoned that neurocognitive measures of impulsivity would outperform trait measures of impulsivity in predicting relapse

(Goudriaan et al., 2008). A third prediction was that any observed effects of impulsivity on relapse would be mediated by treatment retention.

6.2. Methods

6.2.1. Participants

Participants were recruited from three inpatient detoxification programs, spread across Flanders, Belgium. Individuals were included if they met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; American Psychiatric Association, 1994) criteria for any current substance dependence, including cocaine, opioids and marijuana and if they were abstinent for at least 3 days (in order to avoid potential effects of acute intoxication or withdrawal symptoms on neurocognitive task performance). Individuals were excluded if they (1) had an intellectual quotient (IQ) below 70 or did not have sufficient comprehension of the Dutch language to understand test instructions, (2) had a history of neurological condition, such as strokes, intracranial hemorrhages and/or head injuries with loss of consciousness for longer than 30 min, or (3) had a past or current major DSM-IV diagnosis of psychotic disorders.

6.2.2. Treatment program

The detoxification program included (medical) management of withdrawal symptoms, crisis support with respect to various life areas (e.g., medical, social, administrative), enhancement of abstinence motivation, information and advice with regard to further treatment options and support in the referral to these treatment options. All centers required complete abstinence from drugs and alcohol, with the exception of caffeine and nicotine. Aside from scheduled activities (e.g., group activities such as physical exercise, physician visits), residents were not permitted to leave the center grounds during treatment. Regular drug testing was provided and any substance use was grounds for dismissal from the detoxification center. Treatment in these centers typically lasts between 5 or 6 weeks. In terms of their approach, the detoxification centers were strongly based on therapeutic community concepts (De Leon, 2000). Treatment proceeded in a phased format, including different treatment stages, each reflecting increased levels of personal and social responsibility. The programs were highly structured and strict/explicit behavioral norms were emphasized (i.e., no drugs or alcohol, no violence and no sexual relationships).

6.2.3. Instruments

6.2.3.1. Background characteristics

Sections of the *Mini-International Neuropsychiatric Interview* (M.I.N.I.-plus) (Sheehan & Lecrubier, 1998) were used to assess substance dependence and to obtain diagnoses for current or lifetime depression, psychotic disorder, attention-deficit/hyperactivity disorder (ADHD) and antisocial personality disorder (ASPD). Data on education and information regarding drug use were assessed using a Dutch version of the *European Addiction Severity Index* (Europ-ASI), a semi-structured clinical assessment interview (Raes, Lombaert, & Keymeulen, 2004; McLellan, Luborsky, Woody, & O'Brien, 1980). Additional information about the frequency, amount and duration of drug use was collected using the *Interview for Research on Addictive Behavior* (IRAB; Verdejo-Garcia, López-Torrecillas,

Aguilar de Acros, & Pérez-Garcia, 2005). IQ was estimated using two subtests of the *Wechsler Adult Intelligence Scale*, third edition (WAIS-III; Wechsler, 1997; WAIS-III, Dutch version, Swets Test Publishers, 2000): matrix reasoning and information. This dyadic short form is appropriate for obtaining a good estimate of the full scale IQ in a psychiatric sample, as the estimated IQ correlates .92 with the full scale IQ scores (Ringe, Saine, Lacritz, Hynan, & Cullum, 2002).

6.2.3.2. Impulsivity

- Trait impulsivity

The *UPPS* (Whiteside & Lynam, 2001) is a self-report questionnaire containing 45 items that are rated on a four-point Likert scale ranging from 1 (strongly agree) to 4 (strongly disagree). Some items are reversed such that higher scores always indicate a higher level of trait impulsivity. The questionnaire comprises four subscales corresponding to the four distinct personality dimensions of impulsivity as identified through factor-analysis (Whiteside & Lynam, 2001): Urgency (12 items), *lack of* Premeditation (11 items), *lack of* Perseverance (10 items), and Sensation Seeking (12 items).

- Neurocognitive dimensions of impulsivity

Impulsive action

Inhibition of a pre-potent response was measured by a *Stop Signal Task* (SST), operated using E-Prime experiment generation software (for more detailed information, see Chapter 2). Stop-signals were presented using a tracking algorithm (Logan, 1994), a procedure which dynamically adjusts the delay between the onset of the go-signal (i.e., the presentation of the airplane) and the onset of the stop-signal to control inhibition probability. This algorithm ensures 50% successful inhibition for each subject and compensates for differences in choice reaction time between participants. The main dependent variable reflecting inhibitory control, the stop signal reaction time (SSRT), reflects the time needed to inhibit the pre-potent response once the stop-signal occurs. Longer SSRTs reflect worse inhibitory control.

Impulsive choice

The *Delay Discounting Task* (DDT) measures the ability of individuals to tolerate a delay in order to obtain a larger reward instead of a smaller, immediately available reward. The DDT was operated using E-Prime experiment generation software (for more details, see Chapter 5). The *k*-value was used as the dependent variable. As *k* increases, the person discounts future rewards more steeply. Accordingly, higher *k*-values correspond to higher levels of impulsive choice. Because *k*-values (discount rates) had a positively skewed distribution, statistical analyses were performed on the natural logarithmic transformation of these values: $\ln(k + 0.001)$.

The *Iowa Gambling Task* (IGT) was administered in order to measure impulsive decision-making, which refers to a tendency to make choices based on immediate prospects, rather than on the accumulation of long-term outcomes (Goudriaan et al., 2008). Subjects had to choose between four decks of cards; decks A, B, C, and D. Unbeknownst to the participant, two decks (i.e., A and B) gave high rewards, but also resulted in high losses, and were disadvantageous in the long run. The other two decks (i.e., C and D) gave lower rewards, but also lower losses, and resulted in a net gain in the long run. Subjects were instructed to win as much money as possible. They were also informed that

some decks were better than others and that, in order to win, they had to avoid the disadvantageous decks and keep selecting cards from the advantageous decks. A global outcome score (net score) was calculated by subtracting the total number of cards selected from the disadvantageous decks (A + B) from the total number of cards selected from the advantageous decks (C + D). Selecting more cards from the bad decks results in an overall net loss across the 100 trials of the task, whereas choosing more cards from the advantageous decks results in overall net gains. Grouping the 100 trials into five blocks of 20 consecutive cards (e.g., block 1 equals trials 1-20, block 2 equals trials 21-40 and so forth) further allows for an analysis of learning curves. Healthy controls typically learn to avoid the disadvantageous decks over the course of the IGT (Bechara, Damasio, Tranel, & Damasio, 1997). Impulsive subjects on the other hand, may demonstrate difficulties to forgo short-term benefits for long-term benefits, and often display a stubborn preference for disadvantageous deck selection throughout the task.

The *Information Sampling Task* (IST; Clark, Robbins, Ersche, & Sahakian, 2006) was used to index reflection impulsivity (for more detailed information, see Chapter 2). This dimension of impulsive choice refers to the tendency (not) to gather and evaluate sufficient information before making a decision. The primary outcome measures were the average number of boxes opened and the probability (P) of the subject being correct at the point of decision in each condition. A higher number of boxes opened and higher P(correct)-values indicate more information sampling and thus, less impulsivity.

6.2.3.3. Relapse

In order to determine relapse status following treatment, each participant was contacted via telephone 3-months after the baseline assessment, or as close as possible to this target date. Relapse was defined as any use of an illicit substance during the month prior to the follow-up interview, as measured by the IRAB. Abstinence at follow-up was defined as not having used any illicit drug during this period.

6.2.4. Procedure

Residents were approached for participation by the staff members within the first 4 days of their arrival at the detoxification center. Eligible participants provided written informed consent and were interviewed and tested within the first week from starting treatment (range 3–8 days). Baseline assessment had an average duration of 150 minutes and participants were allowed a brief break in between the different tests. After having completed the baseline assessment, participants received a shop voucher of 20 euros. Ethical approval for the study was granted by the Ethical Review Board of the Faculty of Psychology and Educational Sciences at Ghent University.

6.2.5. Data analysis

In order to explore associations between the different impulsivity constructs, Pearson product-moment correlations were calculated. A Bonferroni correction was applied to control for multiple comparisons. The sample was divided into two groups based on their relapse status at the 3-month follow-up interview: those who remained abstinent and those who relapsed during this period. Data for

continuous variables were analyzed using Student's *t*-test or repeated measures analysis of variance (ANOVA) (e.g., IGT, IST), followed by post-hoc Bonferroni testing when the ANOVA revealed a significant group effect. Chi-square tests were used for categorical data (e.g., gender, poly-drug use).

A third set of analyses looked at the degree to which impulsivity predicted relapse. In order to constrain the number of independent variables within the regression analysis, only variables on which abstinent and relapsed subjects differed significantly in the bivariate analyses were entered into a multiple logistic regression model. Predictive accuracy was summarized using standard descriptors, including sensitivity and specificity.

In a final step, mediation analyses were performed to examine whether the effect of impulsivity on relapse was mediated by treatment retention. These analyses were restricted to the impulsivity variables that uniquely contributed to the prediction of relapse. Mediation analyses were performed using Hayes' PROCESS macro for SPSS (Hayes, 2012). PROCESS is a regression-based computational tool for path-based mediation analysis. The tool estimates the coefficients of the model using maximum likelihood logistic regression for dichotomous dependent variables (relapsed vs. abstinent). According to MacKinnon (2008), two conditions need to be met in order to test for mediation: there needs to be a significant effect from the predictor to the mediator (referred to as path a) and a significant effect from the mediator to the outcome (referred to as path b). By contrast, a significant direct effect from the predictor to the outcome (referred to as path c') is not required. All analyses were conducted using Statistical Package for the Social Science (SPSS) 22.0.

6.3. Results

6.3.1. Sample description

A total of 70 SDI were included in the present analyses. Most participants (76%) reported cocaine use as their primary substance use problem, followed by opioids (10%), marijuana (9%) and amphetamines (5%), with multiple types of concurrent substance use being common. Three months following the baseline assessment, 29 subjects (41%) were identified as abstainers, whereas 41 (59%) were classified as relapsers. Characteristics of the 70 SDI, as a function of relapse status, are provided in Table 6.1. The abstinent and non-abstinent group did not differ with respect to any of the demographic, drug use or clinical variables measured at baseline.

6.3.2. Impulsivity

6.3.2.1. Correlations among impulsivity measures

Table 6.2. displays the two-tailed Pearson's correlations between all impulsivity constructs measured. We applied a Bonferroni correction to control for multiple comparisons, resulting in a corrected alpha level of .006 (i.e., 0.05/8). With the exception of a significant correlation between the UPPS premeditation and perseverance scores ($p < .001$), all correlations failed to reach statistical significance. The absence of significant correlations between scores on the SST, DDT, IGT and IST is consistent with the idea that response inhibition, delay discounting, impulsive decision-making and reflection impulsivity represent separate dimensions of impulsivity.

Table 6.1.: Socio-demographic, drug use and clinical characteristics of participants who were abstinent vs. those who relapsed 3 months after starting the detoxification program (n=70)

Variables	Abstainers (n=29)	Relapsers (n=41)	Test statistic
Gender (% Male)	83%	95%	[$X^2_{(1)}$ = 2.89 p = .09]
Age	28.72 ± 7.14	28.15 ± 5.54	[$t_{(68)}$ = .38, p = .70]
Years of education	11.93 ± 2.10	11.85 ± 2.37	[$t_{(68)}$ = .14, p = .89]
Age of onset	19.41 ± 4.56	18.59 ± 4.73	[$t_{(68)}$ = .73, p = .47]
Duration drug use (years)	8.24 ± 7.27	6.80 ± 4.66	[$t_{(68)}$ = 1.01, p = .32]
Past month use (days)	17.52 ± 11.73	15.78 ± 11.65	[$t_{(68)}$ = .61, p = .54]
Poly-drug use (%)	76%	85%	[$X^2_{(1)}$ = 1.02, p = .31]
Abstinence (days)	13.28 ± 10.19	9.93 ± 6.32	[$t_{(43.07)}$ = 1.57, p = .12]
Prior treatment episodes	2.45 ± 4.27	2.95 ± 4.43	[$t_{(68)}$ = -.48, p = .64]
Estimated IQ	86.62 ± 8.34	86.76 ± 8.79	[$t_{(68)}$ = -.07, p = .95]
Current depression (%)	10%	15%	[$X^2_{(1)}$ = .28, p = .60]
ADHD (%)	28%	44%	[$X^2_{(1)}$ = 1.94, p = .16]
ASPD (%)	38%	46%	[$X^2_{(1)}$ = .49, p = .48]

Data are presented as means ± SD, unless otherwise indicated.

6.3.2.2. Impulsivity across groups

- Trait impulsivity

Table 6.3. displays UPPS impulsivity scores as a function of relapse status. Compared to abstainers, relapsers had significantly higher scores on the UPPS sensation seeking subscale (ES = .25) and showed a trend towards higher urgency scores (ES = .22). Abstinent and relapsed participants did not differ significantly in their scores on the UPPS dimensions of *(lack of)* premeditation and *(lack of)* perseverance.

- Neurocognitive dimensions of impulsivity

Impulsive action

SST: Data for this task were available for 26 out of 29 abstinent and 36 out of 41 relapsed participants. The probability of successful inhibition did not differ between the two groups (49% and 50%) and no participants were identified whose inhibition accuracy deviated 10% or more from the targeted 50%, suggesting that the staircase tracking algorithm was successfully applied to equalize response rates between both groups. The two groups did not differ in the time needed to inhibit pre-potent responses, as suggested by the absence of significant group differences in the SSRTs. No group difference was found in terms of the mean reaction time to go-signals and omission errors (Table 6.4.).

Table 6.2.: Correlations between the UPPS dimensions *(lack of)* Premeditation (UPPS_Prem), Urgency, (UPPS_Urg), Sensation seeking (UPPS_SS) and *(lack of)* Perseverance (UPPS_Pers), the Stop Signal Reaction Time (SSRT), the natural log transformation of the discount rate (DDT_(ln)k), IGT net scores (IGT_Net) and the mean probability of being correct at the point of a decision on the IST (IST_P(Correct)).

Variables	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
(1) UPPS_Prem	1	,199	-,012	,452*	,080	,233	-,077	-,115
(2) UPPS_Urg		1	,149	,164	,130	-,087	-,173	-,126
(3) UPPS_SS			1	,018	-,282	,054	-,233	,080
(4) UPPS_Pers				1	,114	,202	-,140	,070
(5) SSRT					1	,023	,125	-,061
(6) DDT_(ln)k						1	,037	,060
(7) IGT_Net							1	,115
(8) IST_P(Correct)								1

* Correlation is significant at the $p < .006$ level (2-tailed)

Table 6.3.: Scores of abstinent and relapsed participants on the UPPS dimensions *(lack of)* Premeditation (UPPS_Prem), Urgency (UPPS_Urg), Sensation seeking (UPPS_SS) and *(lack of)* Perseverance (UPPS_Pers)

Variables	Abstainers (n=29)	Relapsers (n=41)	Test statistic
UPPS_Prem	25.93 ± 5.59	25.76 ± 5.84	[$t_{(68)}$ = 0.13, p = .90]
UPPS_Urg	35.66 ± 5.33	38.27 ± 5.90	[$t_{(68)}$ = -1.90, p = .06]
UPPS_SS	34.69 ± 7.33	38.32 ± 6.57	[$t_{(68)}$ = -2.17, p = .03]
UPPS_Pers	22.55 ± 5.14	23.81 ± 5.13	[$t_{(68)}$ = -1.01, p = .32]

Data are presented as means ± SD

Impulsive choice

DDT: Delay discounting rates (*k*-values) were estimated by nonlinear regression using Mazur's hyperbolic model. Figure 1 represents the fitted hyperbolic discounting curves on the mean indifference points per group. Because of positively skewed distributions of discounting coefficients, natural logarithm-transformed *k*-values were estimated = ln(*k*+0.001) and used in the analyses of discounting. An independent *t*-test of transformed *k*-values revealed that the relapsed group showed significantly greater delay discounting than the individuals who remained abstinent during the follow-up period (ES = .29) (see Table 6.4.).

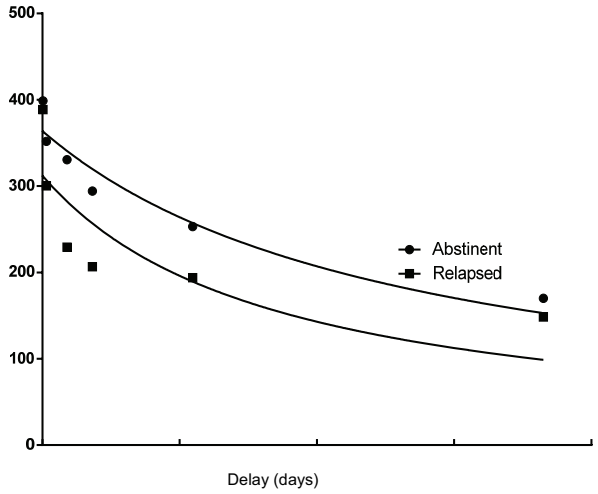


Figure 1. Hyperbolic discounting curve. Points represent the median indifference points at the 6 different delay intervals (i.e., 5, 30, 180, 365, 1095, and 3650 days) for abstinent and relapsed participants. Lines show the best-fitting discounting functions generated by the hyperbolic model. The graphic demonstrates that relapsed participants showed steeper discounting curves compared to the abstinent group.

IGT: There was a significant difference in the mean overall IGT net scores between the two groups, with abstainers achieving an average net score of -0.61 and relapsers achieving an average net score of -16.90 (ES = .32) (see Table 6.4.). The task was then divided into five blocks of 20 card selections

to examine changes in performance over time. These data were analyzed using a repeated measures ANOVA with block (i.e., block 1 to 5) as within-subject variable and group (i.e., abstainers and relapsers) as the between-subject variable. We found a significant block*group interaction ($F_{(4,268)}$ = 2.50, p = .04). The main effect of block was only significant among abstainers ($F_{(4,108)}$ = 3.93, p = .005). In contrast to the abstinent group, relapsers did not improve/change their performance as the task progressed ($F_{(4,160)}$ = 2.04, p = .09). Pairwise post hoc analyses comparing both groups on each of the five blocks showed that abstainers chose more frequently from the advantageous decks on block 2, 4 and block 5 relative to relapsers (see Fig. 2).

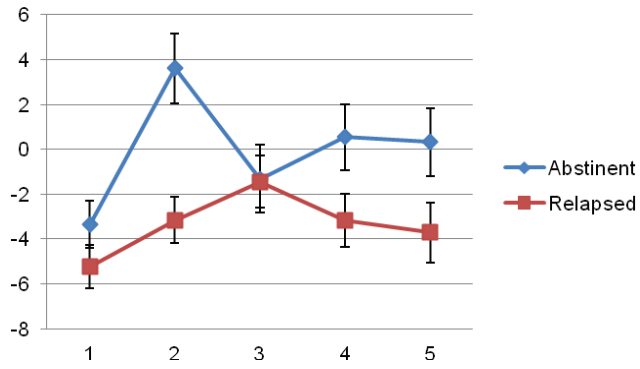


Figure 2. Performance on the Iowa Gambling Task (IGT) across blocks (1-5) as a function of group (abstainers vs. relapsers). Each block (1–5) represents 20 sequential card selections. Significant group differences were found on blocks 2, 4 and 5. Error bars represent standard error of the mean (SEM).

IST: Data for this task were available for 28 out of 29 abstinent and 39 out of 41 relapsed participants. As expected, the number of boxes opened per condition was significantly related to the probability of making a correct choice at the point of decision (r = .97, p < .001).

There was a significant main effect of condition on the number of boxes opened ($F_{(1,65)}$ = 82.18, p < .001) and on the probability of being correct at the point of decision ($F_{(1,65)}$ = 72.22, p < .001), due to subjects sampling less information in the DW condition compared to the FW condition. As such, participants tolerated more uncertainty in the DW than in the FW condition, demonstrating sensitivity to the task contingencies. Paired t-tests revealed that these significant differences in the degree of information sampling between the FW and DW conditions were present in both groups (all p < .001), indicating that both the abstinent and relapsed group were motivated to win points. No group effects were found on the number of boxes opened or on the probability of being correct at the time of a decision (see Table 6.4.): abstinent and relapsed participants opened similar numbers of boxes and were equally likely to be correct at the point of decision. No significant condition*group interaction was found on these two indices.

Table 6.4.: Performance of abstinent and relapsed participants on neurocognitive measures of impulsivity

Variables	Abstainers (n=29)	Relapsers (n=41)	Test statistic
SST			
SSRT	283.97 ± 58.83	268.51 ± 56.72	[$t_{(60)}$ = 1.04, p < .30]
Mean go-stimuli RT	489.26 ± 77.51	505.49 ± 83.10	[$t_{(60)}$ = -.78, p = .44]
Omission errors	1.65 ± 3	2.08 ± 3.17	[$t_{(60)}$ = -.54, p = .60]
DDT			
Ln(k)	-6.29 ± .65	-5.74 ± 1.24	[$t_{(63.20)}$ = -2.40, p < .02]
IGT			
Net Scores	-0.61 ± 22.80	-16.90 ± 24.15	[$t_{(67)}$ = 2.81, p = .006]
IST			
Boxes opened	10.30 ± 4.50	10.42 ± 3.56	[$F_{(1,67)}$ = .02, p = .90]
P_(correct)	.75 ± .09	.75 ± .08	[$F_{(1,67)}$ = .03, p = .87]

Data are presented as means ± SD.

6.3.2.3. Impulsivity and the prediction of post-treatment relapse

Variables on which abstainers and relapsers significantly differed in the primary analyses (i.e., sensation seeking, delay discounting and decision-making) were entered into a multivariate binary logistic regression analysis in order to ascertain the independent contribution of these dimensions to the prediction of relapse. In order to evaluate whether trait impulsivity (i.e., sensation seeking) would still explain unique variance in relapse once neurocognitive dimensions of impulsivity (i.e., delay discounting and decision-making) were taken into account, the analysis was performed in two blocks. In the first block, sensation seeking was entered without delay discounting and IGT decision-making. In the second block, delay discounting and decision-making were entered while keeping sensation seeking in the model. Collinearity statistics for the predictor variables in the combined model yielded tolerance values between 0.94 and 0.99 and all VIF values were below 2, indicating that the validity of the regression model was not threatened by multicollinearity.

A test of the first model against a constant only model was statistically significant, indicating that sensation seeking reliably distinguished between abstainers and relapsers ($\chi^2_{(1)}$ = 5.77, p = .02), with 11% of the (pseudo)variance in relapse explained (Nagelkerke R square = .108). A test of the second model (comprising sensation seeking, delay discounting and decision-making) against a constant only model was also statistically significant, suggesting that the three predictors as a set reliably distinguished between abstainers and relapsers ($\chi^2_{(3)}$ = 17.55, p = .001). A combination of sensation seeking, delay discounting and decision-making as predictors was able to explain about 30% of the variance in relapse status (Nagelkerke R square = .303). A likelihood ratio test on the difference between the first and second model showed that adding delay discounting and decision-making to the sensation seeking block improved the prediction model significantly ($\chi^2_{(2)}$ = 11.79, p < .01). The sensitivity and specificity of the second model in predicting relapse were 78% and 61%, respectively. Overall, the model correctly classified 71% of the sample. Inspection of the Wald criterion demonstrated that only delay discounting and decision-making contributed significantly to the prediction of relapse in the second model (see Table 6.5.). As such, the effects of sensation seeking

on relapse propensity were partialled out once these neurocognitive variables were entered into the regression model, suggesting that sensation seeking did not contribute significant unique variance to the prediction of relapse beyond that accounted for by delay discounting and impulsive decision-making. A likelihood ratio test showed that the goodness of fit of the model did not change significantly when sensation seeking was removed. A combination of delay discounting and impulsive decision-making as predictors was able to account for 25% of the (pseudo)variance in relapse status.

Table 6.5.: Multivariate prediction of relapse using a logistic regression model

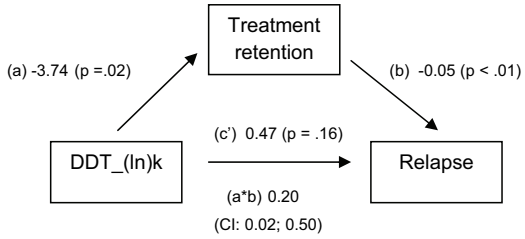
Step 1	**Predictors**	**B**	**S.E.**	**Wald**	**p-value**	**Exp(B)**
	UPPS sensation seeking	0.09	0.04	5.19	.02	1.09
Step 2	**Predictors**	**B**	**S.E.**	**Wald**	**p-value**	**Exp(B)**
	UPPS sensation seeking	0.08	0.04	3.11	.08	1.08
	DDT_(ln)k	0.75	0.36	4.47	.03	2.12
	IGT_NET	-0.03	0.01	5.20	.02	0.97

Mediation model

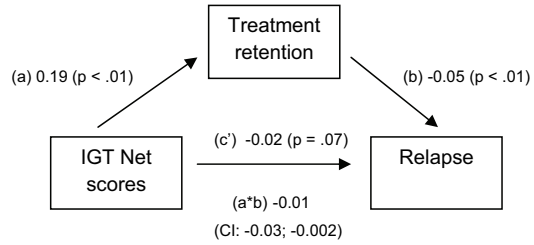
Since both impulsivity and relapse have been associated with shorter treatment retention, a second aim of this study was to explore whether the observed effects of impulsivity on relapse propensity were mediated by treatment retention. Based on zero-order correlations, delay discounting (r = -.271, p = .02) and IGT net scores (r = .315, p < .01) significantly correlated with treatment retention (criterion 1). In addition, treatment retention showed a significant correlation with relapse propensity (r = -.378, p = .001) (criterion 2). As such, the conditions for testing the mediation models were met. Figure 3 displays the results of two mediation analyses with either DDT_(ln)*k*-values or IGT net scores as predictors, treatment retention as mediator and relapse as outcome variable. The 95% CI for the estimates of both indirect effects did not contain zero, providing support for the significance of the mediation effect. In fact, once the effect of treatment retention was taken into account, the direct effects of delay discounting and impulsive decision-making on relapse became non-significant.

Figure 3

(a) The relationship between delay discounting and relapse, as mediated by treatment retention. Unstandardized regression coefficients (*B*) and p-values are presented. For the direct paths from delay discounting to relapse, the coefficient is presented inside the diagram, with the coefficient and CI from the mediated model underneath, outside of the triangle.



(b) The relationship between IGT net scores and relapse, as mediated by treatment retention. Unstandardized regression coefficients (*B*) and p-values are presented. For the direct paths from IGT net scores to relapse, the coefficient is presented inside the diagram, with the coefficient and CI from the mediated model underneath, outside of the triangle.



6.4. Discussion

6.4.1. Main findings

The study described in this chapter is the first to simultaneously examine the influence of multiple facets of impulsivity – covering both trait and neurocognitive dimensions – on post-treatment relapse in a heterogeneous sample of SDI undergoing inpatient detoxification. In addition, we examined whether treatment retention served as a mediator of this relationship. The results of this study support three main findings. First, two indices of impulsive choice, i.e., delay discounting and poor decision-making, as measured shortly following treatment entry, contributed significantly to the prediction of short-term relapse. Second, a multivariate binary logistic regression analysis showed that the DDT and IGT each explained unique variance in relapse and outperformed a trait measure of impulsivity in predicting relapse propensity. Finally, results indicated that the effects of delay discounting and decision-making on relapse propensity were mediated by treatment retention.

Our data revealed that relapsed participants made more impulsive choices, as indicated by (1) a more pronounced devaluation of delayed rewards on the DDT and (2) a tendency to make choices primarily guided by immediate prospects, rather than by the accumulation of long-term positive outcomes on the IGT. These findings are in keeping with a growing body of evidence indicating that delay discounting and impulsive decision-making can substantially hamper the ability to achieve and maintain abstinence among various groups of drug users (Bowden-Jones, McPhillips, Rogers, Hutton & Joyce, 2005; De Wilde, et al., 2013; MacKillop & Kahler, 2009; Passetti, Clark, Mehta, Joyce, & King, 2008; Sheffer et al., 2012; Washio et al., 2011; Yoon et al., 2007). Although often considered as a third dimension of impulsive choice, we found no evidence of differential reflection impulsivity on the IST in abstinent versus relapsed participants. Similarly, in the only other study available that examined the effects of reflection impulsivity on the ability to achieve and maintain abstinence, relapsed and abstinent participants sampled similar amounts of information prior to making a decision (Passetti et al., 2008). Abstinent and relapsed participants in our study further did not differ in their performance on a task measuring impulsive action (i.e., motor inhibition). In line with recent suggestions that the mechanisms mediating addiction treatment outcomes differ from those involved in the etiology of addiction (Garavan & Weierstall, 2012), it is possible that motor (dis)inhibition is implicated in the earlier (i.e., initiation or escalation of drug use) rather than in the latter stages of addiction (i.e., the ability to achieve and maintain abstinence). Consistent with this hypothesis, evidence from animal studies suggests that impulsive action primarily mediates the initial sensitivity to drugs, whereas impulsive choice is implicated in the persistence of drug-taking behavior (Broos et al., 2012; Diergaarde et al., 2008).

Our study was among the first to investigate the unique contribution that different dimensions of impulsivity made in relation to relapse propensity using multiple regression and performing multicollinearity diagnostics. Findings revealed that delay discounting and poor decision-making represent independent predictors of relapse propensity, with the DDT and IGT each tapping some unique variance in relapse. In addition, our data suggest that these neurocognitive tasks of impulsive choice may outperform trait measures of impulsivity in predicting relapse propensity: whereas sensation seeking significantly contributed to the prediction of relapse in a univariate regression

model, these effects were partialled out once the contribution of delay discounting and decision-making was taken into account. From a theoretical perspective, these data suggest that relapse is primarily influenced by transitory behavioral states, which fluctuate in response to environmental influences. Such a finding is consistent with dual process models, which posit that addictive behavior (and potentially relapse) reflects the joint outcome of two qualitatively different types of processes: an impulsive (or associative) bottom-up process and a reflective (or executive) top-down process (Wiers, Ames, Hofmann, Krank, & Stacy, 2010). The relative influence or strength of both types of processes in a given situation depends on a number of personal and situational variables (Wiers et al., 2010). For instance, the influence of executive top-down control on behavior can diminish when exposed to motivationally relevant cues (Bechara, 2005). The dynamic and state-dependent interplay between both processes may be better captured by neurocognitive tasks – in particular those that involve motivational/affective components (see also Wiers et al., 2010). Impulsive decision-making on the IGT for instance, has been attributed to hyperactivity of impulsive processes toward high-uncertain rewards, which can interfere with reflective resources necessary for self-regulation (Brevers, Bechara, Cleeremans, & Noël, 2013). Self-report questionnaires on the other hand, assess general behavioral tendencies, and accordingly, may be less sensitive in predicting specific behaviors in a particular moment or at a particular state. Similarly, neurocognitive tasks that do not include motivationally relevant stimuli (i.e., neutral SST) may be less sensitive in predicting relapse, potentially because they 'decontextualize' the affective nature of inhibitory impairments in SDI. From a clinical perspective, these data indicate that – whilst many drug users may have an impulsive personality – abstinence-oriented interventions might most productively focus on abnormalities in objectively measurable cognitive and motivational processes, such as those found in the current study (Powell, Dawkins, West, Powell, & Pickering, 2010).

Given the well-established relationship between impulsivity and shorter treatment retention on the one hand (Stevens et al., 2013, 2014; Verdejo-Garcia et al., 2012), and shorter treatment retention and relapse propensity on the other hand (Zhang et al., 2003), we examined whether the effects of delay discounting and impulsive decision-making on relapse were mediated by shorter treatment retention. In line with our hypothesis, we found substantial support for such an indirect relationship: once the effects of treatment retention were taken into account, the direct effect of delay discounting and impulsive decision-making on relapse propensity became non-significant. Results of the current study suggest that drug users with elevated levels of impulsive choice tend to have shorter treatment stays, which in turn places them at increased risk for relapse following treatment discharge. Future studies examining the effects of impulsivity on relapse should therefore explicitly take into account this indirect pathway by which impulsivity may influence post-treatment outcomes.

6.4.2. Clinical implications

Our findings have important clinical implications. First, they suggest that neuropsychological assessment of impulsive choice early during treatment may offer a cost-effective way to identify relapse-prone drug users, such that these subjects may subsequently receive additional monitoring. Second, the results of this study indicate that post-treatment relapse in drug users may be reduced by interventions that either (1) target the neural, cognitive and affective processes involved in delay

discounting and impulsive decision-making or (2) improve treatment retention in drug users who tend to make impulsive choices on these indices.

To date, several interventions have proven to be successful in reducing delay discounting and impulsive decision-making in drug users. Consistent with the notion that adaptive decision-making partially depends on the integrity of the dorsolateral prefrontal loop and the executive system (e.g., Brand, Labudda, & Markowitsch, 2006), cognitive working memory training has been found to cause significant reductions in the preference for small immediate rewards over more delayed rewards in drug-dependent individuals (Bickel et al., 2011). Disadvantageous decision-making has also been linked to abnormalities in the processing of emotional signals that normally work to anticipate the prospective outcomes of potential decisions (e.g., Bechara et al., 1997; Weller, Levin, Shiv, & Bechara, 2007). In this regard, interventions aimed at enhancing interoceptive awareness or negative emotions linked to risky decisions may partially normalize decision-making performance (Fernández-Serrano et al., 2011). Hypothetically, a combination of both top-down and bottom-up interventions may be most fruitful in targeting impulsive decision-making. For instance, Alfonso and colleagues (2011) found that a combination of goal-management training – aimed at improving patients' planning and decision-making skills – and mindfulness-based meditation, significantly improved adaptive decision-making in drug users (Alfonso et al., 2011). However, studies examining to what extent training- or emotion-induced improvements in cognitive functioning are directly related to changes in clinically relevant outcomes (e.g., abstinence) are needed.

Whereas the aforementioned interventions may have the potential to improve delay discounting, decision-making and speculatively, abstinence outcomes, our findings also suggest that drug users with high levels of impulsive choice may drop out of treatment before any of these cognitive-motivational impairments can be adequately addressed. Therefore, introducing elements that more directly affect retention rates early during treatment may be a priority in attempts to improve post-treatment outcomes for highly impulsive drug users. One promising strategy to improve treatment retention in drug users may be to offer motivational incentives contingent on consecutive attendance (García-Rodríguez et al., 2009; Higgins, Badger, & Budney, 2000). Longer treatment retention may in turn enable the implementation of more specialized, cognitive-motivational rehabilitation interventions later on during treatment.

6.4.3. Strengths and limitations

The current findings should be considered in light of the study's strengths and weaknesses. The main strength of the current study was its multidimensional assessment of impulsivity, which included both trait and neurocognitive approaches (Potenza, Sofuoglu, Carroll, & Rounsaville, 2011; Sharma et al., 2014). By adopting a multidimensional approach, we were able to elucidate impulsivity dimensions that may be more relevant to short-term relapse than others, thereby extending the clinical relevance of previous research in this area. Second, our study was the first to explicitly explore the mediating role of treatment retention in the relationship between impulsivity and relapse, thereby supporting future work to translate findings into recovery-oriented services. A third strength of this study was that it was conducted in real-world clinical settings which provide treatment to a broad mix of clients, and as a consequence, the ability to extrapolate findings to practicing clinics in the ''real world'' is

increased. Despite some notable strengths, several limitations of the present study are worth noting, including a relatively stringent definition of relapse (i.e., any return to illicit drug use during the month prior to the follow-up interview) and relying solely on self-reported abstinence. Future investigations of relapse may benefit from incorporating more objective, biological measures, e.g., hair analyses, to verify abstinence. Whereas the naturalistic sampling approach of the current study increases the generalizability of our findings, it should be noted that our study was conducted in a relatively severe population of drug users, as indicated by high levels of psychiatric comorbidity, neurocognitive impairment, trait impulsivity and relatively extensive histories of drug use. As such, caution should be taken when transferring the presented findings to less severe (e.g., outpatient) treatment samples. Finally, our samples were relatively small. As such, subtle differences in impulsivity between the abstinent and relapsed groups may not have been detected. In this regard, measures of trait impulsiveness, such as the UPPS, may lack sensitivity to identify differences within small samples. Larger samples may have resulted in greater statistical power to identify group differences, and would have allowed to test a larger number of predictors.

These limitations notwithstanding, the current study extends what is known about the relationship between impulsivity and post-treatment relapse in drug addiction. Our findings suggest that, after deciding to undergo detoxification treatment for drug dependence, a more pronounced preference for immediate smaller rewards (at the expense of larger delayed rewards) and a behavioral strategy that leads to short-term rewards but long-term losses may negatively affect the length of stay in treatment. This in turn may substantially hamper the ability to achieve and maintain abstinence, at least in the short term. Identifying ways to reduce delay discounting and disadvantageous decision-making and to improve treatment retention in drug users with inflated impulsivity should be a clinical research priority.

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CHAPTER 7

GENERAL DISCUSSION

ABSTRACT

The main goal of this doctoral dissertation was to extend our knowledge regarding the relationship between impulsivity and addiction treatment outcomes, including treatment retention, drop-out and relapse propensity. In this final chapter, the main findings of the dissertation and most important conclusions of the five studies are summarised. Next, the implications of these findings for clinical practice are discussed. Finally, we highlight the overall limitations of this dissertation and provide some guidelines for future research.

7.1. Introduction

The main objective of this dissertation was to conduct a more thorough evaluation of the relationship between impulsivity and addiction treatment outcomes, including treatment retention, drop-out and relapse propensity. This dissertation differs in several important ways from previous studies, which provided an impetus to this work: the relationship between impulsivity and addiction treatment outcomes was examined in a variety of addiction treatment facilities (including real-world operating treatment programs), considerable emphasis was placed on the multidimensional nature of impulsivity, and attention was given to potential indirect pathways by which impulsivity may negatively affect addiction treatment outcomes. In this final chapter, we first reprise and discuss the key findings of this doctoral dissertation. Next, implications for clinical practice are noted. The chapter concludes with a discussion of study limitations and proposes an agenda for future research.

7.2. Reprise and discussion of key findings

7.2.1. Impulsivity in substance-dependent individuals (SDI) and the role of ADHD

Numerous studies have shown that impulsivity is a hallmark characteristic of substance dependence (Coffey, Gudleski, Saladin, & Brady, 2003; Heil, Johnson, Higgins, & Bickel, 2006; Moeller et al., 2002; Verdejo-Garcia, Lawrence, & Clark, 2008). Despite having established a clear relationship between substance dependence and impulsivity, these studies bring about limited comprehension of the multiple mechanisms involved, as they have often been conducted without considering the multidimensional nature of impulsivity. In addition, it is not clear whether attention-deficit/hyperactivity disorder (ADHD), a developmental disorder that frequently co-occurs with substance dependence, contributes to the increased impulsivity levels seen in SDI. In the first study of this dissertation *(cf. Chapter 2)*, we therefore adopted a multidimensional approach while comparing scores on multiple indices of impulsivity between cocaine-dependent individuals (CDI) (n=59) with and without comorbid ADHD and healthy controls (HC) (n=28). To the best of our knowledge, this study is the first to show that CDI perform significantly worse and report significantly higher scores on several indices of impulsivity compared to HC, regardless of which impulsivity paradigm or measure is used: CDI reported higher levels of motor, attentional and non-planning impulsivity on the Barratt Impulsiveness Scale (BIS-11), required more time to inhibit their responses to stop signals on the Stop Signal Task (SST), sampled less information prior to making a decision on the Information Sampling Task (IST) and finally, showed steeper discounting of delayed rewards on the Delay Discounting Task (DDT). Most of these findings remained significant while controlling for differences in IQ, with the exception of differences in information sampling. The latter finding suggests that reflection impulsivity is related to intellectual functioning. Importantly, the increased levels of impulsivity in CDI were not exclusively associated with concomitant ADHD: CDI with but also those without an ADHD diagnosis scored significantly higher on the majority of impulsivity measurements relative to HC. There was however one exception to this finding. Specifically, we found that only CDI+ADHD and not those without an ADHD diagnosis showed a more pronounced intolerance to delay-of-gratification compared to HC. This finding in other words indicates that higher levels of delay discounting in CDI are specifically associated with the presence of ADHD or, at minimum, that steeper discounting of delayed rewards is

a hallmark characteristic of the comorbidity between cocaine dependence and ADHD. Consistent with this latter suggestion, a recent study revealed that only ADHD patients with and not those without cocaine dependence were characterized by elevated levels of delay discounting compared to HC (Crunelle, Veltman, van Emmerik-van Oortmerssen, Booij, & van den Brink, 2013). These findings may suggest that chronic cocaine use interacts with the pathophysiology underlying ADHD to produce more pronounced discounting scores.

In order to better understand the impact of ADHD on impulsivity in CDI, the study discussed in *Chapter 2* directly compared impulsivity scores between CDI with and without a comorbid ADHD diagnosis. Compared to CDI without ADHD, the comorbid group reported significantly higher levels of BIS-11 non-planning impulsivity and displayed steeper delay discounting curves. These differences had large effect sizes and remained significant while controlling for poly-drug use, which was higher in the comorbid group. Accordingly, CDI+ADHD may represent a clinically distinct subgroup, characterized by a relative insensitivity to future or delayed consequences/rewards. The absence of significant differences between CDI with and without ADHD in terms of duration of cocaine use (years) or past month cocaine use moreover suggests that increased impulsivity in the comorbid group might have predated drug use, with impulsivity functioning as a trans-disease process (Bickel, Jarmolowicz, Mueller, Koffarnus, & Gatchalian, 2012). Alternatively, individuals with ADHD may be more vulnerable for cocaine-induced catecholaminergic disruptions because of the pathophysiology underlying ADHD, even if amount and duration of cocaine use are similar to non-comorbid CDI (Preller et al., 2013). Clearly, more research (longitudinally) is needed to evaluate the temporal relationships between non-planning impulsivity, delay discounting, ADHD and cocaine dependence.

7.2.2. The role of impulsivity in predicting poor addiction treatment outcomes

The next chapters *(3-6)* discussed the results of a series of four studies undertaken to evaluate the relationship between impulsivity and treatment retention, drop-out or relapse. This general objective was further subdivided into three specific aims. First, we aimed to investigate the relationship between neurocognitive dimensions of impulsive choice (i.e., delay discounting and impulsive decision-making) and treatment retention in SDI participating in highly structured, inpatient addiction treatment programs *(cf. Chapters 4 & 5)*. Second, we wanted to explore whether certain impulsivity dimensions would be more relevant to the prediction of relapse than others *(cf. Chapters 3 & 6)*. In this regard, we were also interested in whether trait dimensions of impulsivity would explain unique variance in relapse over and above neurocognitive dimensions of impulsivity *(cf. Chapter 6)*. A final aim was to explore two indirect pathways through which impulsivity may negatively affect treatment outcomes in SDI *(cf. Chapters 5 & 6)*. In the following sections, we reprise the key findings of this dissertation with respect to each of these three aims.

7.2.2.1. Impulsivity, treatment retention and drop-out

In *Chapter 3* of this doctoral dissertation, the available evidence regarding the relationship between neurocognitive dimensions of impulsivity and addiction treatment outcomes was reviewed. This review clearly pointed to the lack of studies on the relationship between neurocognitive dimensions of impulsivity and treatment retention or drop-out: only eight of the 25 selected studies focused on one of

these outcome indicators (see Stevens et al., 2014). It is worth noting that these studies differed in many respects, limiting any definite conclusions that can be made from the overall findings.

Perhaps most notable was the absence of studies investigating the effects of delay discounting on treatment retention and drop-out. Many addiction treatment programs, such as drug-free therapeutic communities (TCs), place high demands on the ability to postpone immediate gratification. Accordingly, these programs may be particularly challenging for drug users who are disproportionally oriented towards the present or who have a low tolerance for delay (i.e., high delay discounters), potentially leading to poorer treatment retention or drop-out in these subjects. Starting from this hypothesis, the study discussed in *Chapter 5* examined whether delay discounting, as measured shortly following treatment entry, was predictive of poor treatment retention among SDI (n=84) attending a highly structured, inpatient detoxification program. The average length of stay in the detoxification program was 33 days, and more than 50% of the participants dropped out of the program prematurely. Results of the regression analyses clearly pointed to the contribution of delay discounting, even after controlling for several other (previously) established predictors of treatment retention (i.e., age, duration of drug use, treatment readiness, number of prior treatment episodes and ADHD). In a model including these various predictors, we found that, with every unit increase in delay discounting, treatment retention decreased with 3.75 days. Similarly, for every unit increase in delay discounting, the odds of dropping out of the detoxification program prematurely became 2.45 times higher than the odds of completing treatment. These findings indicate that, after entering inpatient detoxification programs, an orientation towards the future may be crucial to adhere to treatment and complete treatment objectives.

In *Chapter 4*, we examined the relationship between impulsive decision-making and treatment drop-out in a large sample of CDI (n=150) participating in drug-free TCs. Participants performed two validated tasks of decision-making, the Iowa Gambling Task (IGT) and the Cambridge Gamble Task (CGT) within the first weeks following treatment entry. In line with previous reports (Condelli, 1994; Deane, Wootton, Hsu, & Kelly, 2012), more than half of the sample (i.e., 56%) dropped out of the TC prematurely. This finding is particularly problematic from a clinical perspective, since the effectiveness of TC treatment appears to be closely related to the length of stay in the program (Condelli & Hubbard, 1994). In contrast to treatment completers, who learned to avoid the disadvantageous decks as the IGT progressed, the drop-out group did not select more frequently from the advantageous decks, ultimately lost “money” and displayed minimal evidence of learning, as suggested by their (still) negative net scores on block 5 of the IGT. This finding indicates that drop-out prone drug users exhibit more pronounced difficulties to forgo short-term benefits for long-term benefits. Using an alternative task of decision-making (CGT), we were able to show that drop-outs were also less likely to choose the most favorable option (i.e., the box color in the majority) compared to treatment completers. The choices of the drop-out group were indicative of low quality decisions, given that the probabilities associated with each choice were visible at the time of the decision. Our main analysis indicated that low quality decisions on the CGT and negative net scores on the last block of the IGT significantly contributed to the prediction of drop-out. Overall, the results of this study suggest that CDI who fail to

integrate prior experiences into their decisions or neglect probability information (i.e., ignore the broader context in which decisions are made) are at increased risk for dropping out of treatment in TCs.

7.2.2.2. Impulsivity and relapse: are certain impulsivity dimensions more relevant than others?

Despite growing recognition of the multidimensional nature of impulsivity (Dalley, Everitt, & Robbins, 2011; Winstanley, Eagle, & Robbins, 2006), the majority of the studies selected for the review in *Chapter 3* measured only one neurocognitive dimension of impulsivity. As such, detailed research on the relationship between various dimensions of impulsivity and addiction treatment outcomes is still scarce. In order to address this limitation, the study discussed in *Chapter 6* explicitly adopted a multidimensional approach while examining the relationship between impulsivity and post-treatment relapse in a heterogeneous sample of SDI (n=70) participating in an inpatient detoxification program. We used a test battery comprising four behavioral tasks to index four distinct neurocognitive dimensions of impulsivity (i.e., motor inhibition, delay discounting, impulsive decision-making and reflection impulsivity) and a self-report questionnaire measuring four trait dimensions of impulsivity (i.e., lack of premeditation, lack of perseverance, sensation seeking and urgency). An integration of the reviewed findings *(cf. Chapter 3)* and the results obtained by our own empirical study *(cf. Chapter 6)* indirectly supports several conclusions regarding the relative importance of each impulsivity dimension in the prediction of relapse propensity among SDI.

First, the findings presented in this doctoral dissertation yield relatively consistent evidence to support the notion that the role of *motor inhibition* in predicting relapse susceptibility in SDI is limited. In *Chapter 3*, the majority of the selected studies (5/6) failed to detect an effect of motor disinhibition on abstinence/relapse. This pattern of findings was replicated in our own empirical study, in which no significant relationship between baseline motor (dis)inhibition and post-treatment relapse was found. More specifically, abstinent and relapsed participants did not differ in terms of the time needed to inhibit a prepotent response on the SST. In line with recent propositions suggesting that the mechanisms contributing to addiction treatment outcomes differ from those involved in the etiology of addiction (Garavan & Weierstall, 2012), it is possible that motor (dis)inhibition is implicated in the earlier (i.e., initiation or escalation of drug use) rather than in the later stages of addiction (i.e., the ability to achieve and maintain abstinence). Consistent with this hypothesis, evidence from animal studies suggests that impulsive action primarily mediates the initial sensitivity to drugs, whereas impulsive choice is implicated in the persistence of drug-taking behavior (Broos, Diergaarde, Schoffelmeer, Pattij, & De Vries, 2012; Diergaarde et al., 2008). Alternatively, the apparent absence of a relationship between motor inhibition and abstinence/relapse could reflect poor sensitivity of the tasks that have been used to capture this dimension, rather than a lack of relevance of the corresponding processes. Although the lack of an association between motor inhibition and the ability to achieve or maintain abstinence has been replicated in studies using different inhibition paradigms (Carroll et al., 2011; Passetti, Clark, Mehta, Joyce, & King, 2008; Schmitz et al., 2009), no study to date has used motor inhibition tasks in which neutral stimuli (e.g., airplanes) are substituted by motivationally relevant stimuli, such as an emotional Go/No-Go task. Given that relapses most likely result from a complex interplay between executive top-down control and bottom-up inputs (e.g.,

exposure to drug-related stimuli or contexts) (Wiers, Ames, Hofmann, Krank, & Stacy, 2010), we believe that impairments in inhibition could become clinically relevant once SDI are exposed to affectively salient stimuli. Consistent with this expectation, we found that *diminished interference control over drug-related words* (but not over neutral words) served as a reliable predictor of the ability to achieve and maintain abstinence across various groups of SDI *(cf. Chapter 3)*.

In terms of impulsive choice, *delay discounting* and *impulsive decision-making* emerged as relatively consistent predictors of the ability to achieve and maintain abstinence in SDI in our literature review. Again, this pattern of findings was replicated in our own empirical study *(cf. Chapter 6)*. Compared to abstinent participants, SDI who relapsed during the 3-month follow-up period made more impulsive choices at treatment entry, as indicated by (1) a more pronounced devaluation of delayed rewards on the DDT and (2) a greater tendency to make choices that are primarily guided by immediate prospects on the IGT. Analysis of learning curves on the IGT moreover showed that relapsers did not learn to avoid the disadvantageous decks over the course of this task, showing a distinct decision-making pattern from that observed in the abstinent group. These results were found in the absence of any significant differences between both groups with regard to age, estimated IQ, psychopathology or drug use. Both delay discounting and IGT net scores significantly contributed to the prediction of relapse propensity. In fact, a combination of both predictors was able to account for approximately 25% of the (pseudo)variance in relapse status. Importantly, the abstinent and relapsed participants did not differ in their performance on another decision-making task on which SDI tend to perform differently from controls, the IST. This finding corroborates previous evidence in opiate-dependent individuals (Passetti et al., 2008; Passetti et al., 2011) and might reflect insufficient power of the test to detect deficits associated with poor short-term outcomes.

The identification of delay discounting and impulsive decision-making as relative consistent predictors of relapse in the literature in general and in the study described in *Chapter 6* specifically, raises questions regarding potential overlap between these two impulsivity constructs (see Stevens et al., 2014). In this regard, the study in *Chapter 6* was the first to investigate the unique contribution that these two dimensions of impulsive choice made in relation to relapse propensity using multiple regression and performing multicollinearity diagnostics. Extending previous findings, the results of our study demonstrate that delay discounting and impulsive decision-making represent independent predictors of relapse propensity, with the DDT and IGT each tapping some unique variance in relapse.

And what about personality dimensions of impulsivity?

A question often raised in characterizing impulsivity is whether it reflects a trait that is fairly stable over time, or a transient state that fluctuates in response to environmental influences (Sharma, Markon, & Clark, 2014). Self-report questionnaires of impulsivity are purported to measure the former, while the latter is typically assessed using neurocognitive tasks (Verdejo-Garcia et al., 2008). Although self-report and neurocognitive measures of impulsivity may tap into some same amount of variance, the small magnitude of the observed effect sizes in the literature (Cyders & Coskunpinar, 2011; Sharma et al., 2014) and in the present dissertation *(cf. Chapters 2 & 6)* suggests that, overall, there is little overlap between what is being measured using self-report and laboratory tasks of impulsivity. This general lack of overlap has the potential advantage that – precisely because the two approaches do

not share method variance – any consistent relation that these measures show to a third variable of interest (e.g., relapse) is likely due to true, unique variance in each type of measure (Sharma et al., 2014). To date however, there has been no systematic integration of these two research traditions to demonstrate how personality-based self-report questionnaires and neurocognitive tasks of impulsivity may incrementally predict addiction treatment outcomes. Accordingly, there is no consensus regarding which impulsivity dimensions or measures possess the greatest discriminating power for addiction treatment outcomes. In line with previous recommendations (Potenza, Sofuoglu, Carroll, & Rounsaville, 2011; Sharma et al., 2014), the study described in *Chapter 6* explored whether trait dimensions of impulsivity had incremental value over and above neurocognitive indices of impulsivity in predicting relapse propensity. Although initial analyses showed that sensation seeking reliably contributed to the prediction of relapse, this effect was partialled out once the contribution of delay discounting and decision-making was taken into account. As such, sensation seeking did not explain unique variance in relapse over and above that explained by delay discounting and impulsive decision-making. To the best of our knowledge, only two other studies have specifically dealt with this issue (Goudriaan, Oosterlaan, De Beurs, & van den Brink, 2008; Krishnan-sarin et al., 2007). Consistent with our own findings, the results of these studies indicated that neurocognitive measures of impulsivity or the detailed behavioral processes they assess might be more promising in the prediction of relapse propensity than self-report questionnaires or personality-based dimensions of impulsivity (Goudriaan et al., 2008; Krishnan-sarin et al., 2007).

Overall, our findings lend support to dual process models, which posit that the maintenance of compulsive drug use (and potentially relapse) reflects the joint outcome of two qualitatively different types of processes: impulsive/associative and reflective/controlled processes (Wiers et al., 2010). The dynamic and state-dependent interplay between both processes may be better captured by neurocognitive tasks which measure cognitive control over specific motivational/impulsive processes, such as the suppression of drug-related information or the evaluation of reward and punishment (e.g., drug Stroop, IGT, DDT). Making choices between immediate and delayed rewards on the DDT for instance, depends upon a complex interaction between activity in the impulsive bottom-up system (favors the immediate monetary option) and reflective top-down system (considers the later reward), suggesting that delay discounting provides a summary measure of the relative control of the bottom-up and top-down system (Bickel, Yi, Landes, Hill, & Baxter, 2011; McClure, Laibson, Loewenstein, & Cohen, 2004). Neurocognitive tasks which measure cool processes (e.g., neutral versions of the SST, Go/No-Go or Stroop task) on the other hand, may be less relevant to the prediction of relapse propensity, potentially due to the fact that they "decontextualize" the affective nature of inhibitory impairments in SDI, i.e., the presence of motivationally relevant stimuli at a certain moment may overwhelm or diminish the relative strength of the top-down system and shape an individual's behavior in a relapse situation. Similarly, trait measures of impulsivity tend to index the strength of one particular process alone (e.g., lack of premeditation/cognitive processes vs. sensation seeking/impulsive processes), rather than their joint interaction (Wiers et al., 2010). Because they assess general behavioral tendencies over time, self-report questionnaires may be limited in their ability to predict behavior in a particular moment or at a particular state. Moreover, the validity of self-

report questionnaires may be particularly problematic in relation to substance use disorders (SUDs), which have been associated with reduced self-insight and impaired self-awareness (Goldstein et al., 2009; Goldstein & Volkow, 2011). The observation that neurocognitive dimensions of impulsivity are more likely to contribute to relapse propensity than trait aspects is not uninteresting however. Trait dimensions of impulsivity reflect relatively stable personality characteristics and, consequently, may not in themselves be modifiable. Neurocognitive facets of impulsivity by contrast, serve as indicators of the addiction endophenotype, can be influenced by intervention, and may represent particularly attractive therapeutic targets.

7.2.2.3. From impulsivity to addiction treatment outcomes: direct or indirect pathways?

Although recent studies show that neurocognitive impairments (including those related to impulsivity) may hinder treatment effectiveness, translation of this knowledge into the development of more effective treatments has lagged behind. One reason behind the lack of progress in this area might be the absence of research on indirect pathways by which neurocognitive deficits may hinder addiction treatment outcomes. Indeed, a better understanding of the mechanisms by which neurocognition influences treatment outcomes can help to translate findings into recovery-oriented interventions. Therefore, two potential mediators of the relationship between impulsivity and addiction treatment outcomes were explored in the current dissertation.

- *Delay discounting and treatment retention: a mediating role for treatment readiness*

In *Chapter 5*, we showed that higher delay discounting significantly contributed to poorer treatment retention in SDI. In order to isolate one potential mechanism underlying this relationship, attention was given to the role of a more dynamic, process-oriented treatment construct, i.e., treatment motivation. Three dimensions of motivation (i.e., problem recognition, desire for help, and treatment readiness) were measured using the *Motivation for Treatment (MfT) scale* (De Weert-Van Oene, Schippers, De Jong & Schrijvers, 2002). Correlation analyses indicated that delay discounting was not significantly associated with problem recognition or desire for help. However, a significant negative correlation between delay discounting and treatment readiness was found. This subcomponent of treatment motivation reflects the degree of commitment to active change through participation in a treatment program as well as the client's acknowledgement of the importance of treatment for personal recovery goals (Rapp et al., 2007). In fact, this finding corroborates a recent study by LeBerre and colleagues (2013), who found that alcohol-dependent individuals with brain damage in structures known to be involved in decision-making (e.g., ventromedial prefrontal cortex) exhibited lower readiness to change. We hypothesized that high delay discounters – despite being aware that their drug use is causing a problem and despite expressing a desire for help – may conceive treatment as too demanding or be less confident in their ability to avoid substance use (i.e., lower self-efficacy). This in turn could lead to less optimistic expectations regarding the benefits associated with treatment (Meier, Donmall, McElduff, Barrowclough, & Heller, 2006). Such a finding would be consistent with the observation that low hope for change is one of the more common reasons clients endorse for dropping out of treatment (Ball, Carroll, Canning-Ball, & Rounsaville, 2006) and with data indicating that SDI with neurocognitive deficits exhibit poorer self-efficacy (Bates, Pawlak, Tonigan, & Buckman, 2006). Moreover, it is

intuitively easy to imagine how an orientation towards the future might be a necessary prerequisite to fully appreciate the (long-term) benefits associated with treatment participation, which are typically associated with a certain delay (e.g., continued abstinence, improved health). Regardless of the pathways through which delay discounting exerts its effects on treatment readiness, it is clear that treatment readiness has a robust relationship with the length of time spent in treatment (Joe, Simpson, & Broome, 1998). A mediation analysis indicated that part of the negative effects of delay discounting on treatment retention were mediated by lower treatment readiness. More specifically, drug users with higher levels of delay discounting reported poorer treatment readiness, which in turn was associated with shorter stays in treatment. Whereas the ratio of the indirect to the direct effect was modest, the findings of this study help to clarify the proximal role that delay discounting (or impulsivity more generally) plays in modifying a key therapeutic change processes in addiction treatment. In addition, they help to translate findings into effective, recovery-oriented services.

- *Impulsive choice and post-treatment relapse: a mediating role for treatment retention*

Increased impulsivity in SDI may negatively affect treatment retention, as indicated by the findings presented in *Chapters 3*, *4*, and *5* of this dissertation. Shorter treatment retention in turn, has been found to predict post-treatment relapse (Zhang, Friedmann, & Gerstein, 2003). This latter relationship received additional support in the study described in *Chapter 6*: compared to SDI who were abstinent at the time of the follow-up, those who relapsed tended to have spent significantly fewer days in the detoxification program [mean relapsers = 28.23 days vs. mean abstainers = 39.45 days, ($t_{(67)} = 3.35$, $p < .001$)] and were more likely to have dropped out of the treatment program prematurely [drop-out in relapsers = 80% vs. drop-out in abstainers = 31%, ($X^2_{(1)} = 17.31$, $p < .001$)]. Given the associations between impulsivity and treatment retention on the one hand, and treatment retention and relapse on the other hand, any apparent effects of impulsivity on relapse may result from shorter stays in treatment and thus, less treatment exposure in the most impulsive clients. In *Chapter 6* of this dissertation, we therefore performed two mediation analyses treating delay discounting and impulsive decision-making as the predictors, treatment retention as the mediator, and post-treatment relapse as the outcome variable. Results showed that the effects of delay discounting and impulsive decision-making on relapse propensity were mediated by treatment retention. In fact, once the effects of treatment retention were taken into account, the direct relationship between these indicators of impulsive choice and post-treatment relapse became non-significant. These results in other words suggest that SDI with elevated levels of impulsive choice tend to have shorter treatment stays, which in turn places them at increased risk for relapse following treatment discharge. These findings converge with those reported by Bates and colleagues (2006), who found that poorer treatment compliance served as a mediator of the relationship between neurocognitive impairment and abstinence achieved during a 6-month period following treatment for alcohol dependence (Bates et al., 2006).

Future studies examining the effects of impulsivity on post-treatment relapse should therefore explicitly take into account the confounding effects of treatment retention. First, such a finding has important clinical implications, as it suggests that promoting treatment retention in drug users with elevated

impulsivity should be a priority. Second, reporting outcomes on those with less treatment exposure can result in biased estimates of intervention efficacy.

7.3. Clinical implications of the research findings

Previous studies have shown that poor treatment readiness in SDI is a reliable predictor of shorter treatment retention (Joe et al., 1998), and that shorter treatment retention is associated with an increased propensity to relapse (Bell, Richard, & Feltz, 1996; Rapp, Siegal, Li, & Saha, 1998). The findings outlined in this doctoral dissertation extend these lines of evidence by demonstrating that these negative recursive paths are exacerbated by the presence of neurocognitive deficits related to impulsivity. Accordingly, highly impulsive drug users need additional and individualized support throughout the treatment process. Furthermore, existing addiction treatment facilities may need to be modified to better meet the needs of this vulnerable group of SDI. In this section, we argue for (1) an integration of impulsivity assessment into routine clinical practice, (2) the development/adaptation of interventions and program change efforts aimed at enhancing treatment retention and engagement in these subjects, and (3) the implementation of clinical interventions that strengthen executive/cognitive control and target or retrain automatic, impulsive processes. Most importantly, we argue for a holistic approach, in which these different recommendations form an integrated entity.

7.3.1. Improving treatment outcomes for highly impulsive SDI: where do we start?

7.3.1.1. Screening for impulsivity at treatment entry: a first priority

The findings presented in this doctoral thesis indicate that SDI with higher levels of impulsivity show poorer treatment retention, are more likely to drop out of treatment prematurely and have a greater propensity to relapse. Accordingly, a first priority should be to identify these at-risk individuals early on during the treatment process. Our findings suggest that this goal can be achieved in a relatively cost-effective way, i.e., by adding neurocognitive tasks of impulsivity to the range of clinical information that is collected at treatment intake and use this information as a prognostic index. Performance on these tasks may provide valuable information for clinical decision-making. For instance, neurocognitive assessment of impulsivity at treatment entry could be used to evaluate the client's rehabilitation needs and guide the selection of treatment interventions accordingly (i.e., treatment matching). Based upon their particular impulsivity profile, subjects may be allocated to qualitatively or quantitatively different treatment programs or settings, rather than following a 'one size fits all' approach (Ersche & Sahakian, 2007; King & Canada, 2004). Although there is currently insufficient evidence to formulate specific guidelines for matching SDI with a particular impulsivity profile to specific interventions, some tentative suggestions can be made based on the findings presented in this dissertation. Preliminary evidence for instance indicates that SDI with more prominent decision-making deficits may particularly benefit from treatment in an inpatient setting (Passetti et al., 2011). Poor decision-making has been associated with an enhanced propensity to context-induced relapse (Broos et al., 2012; Diergaarde et al., 2008). Treatment in residential settings however, reduces exposure to many of the environmental triggers that may lead to relapse and, accordingly, may compensate for impaired cognitive control over more automatic processes (Passetti et al., 2011). Second, preliminary data in CDI suggest that the

negative effects of delay discounting on abstinence may be buffered by contingency management (CM) programs which offer high-magnitude vouchers (Washio et al., 2011). If replicated, poor decision-making or the propensity to more steeply discount delayed rewards may have the potential to become behavioral markers alerting clinicians that such individuals may benefit from specific treatments. Consequently, more expensive treatment modalities can be reserved for individuals who are most likely to benefit from it.

7.3.1.2. Enhancing treatment readiness and retention: a gateway to specialized interventions

In this dissertation, relatively consistent evidence was found to suggest that poor interference control over drug-related words (i.e., attentional bias), delay discounting and impulsive decision-making can substantially hamper the ability to achieve and maintain abstinence in SDI. Accordingly, interventions that improve (the processes underlying) these dimensions may represent valuable therapeutic strategies for reducing relapse propensity. While such an idea has an intuitive appeal, our findings warn against pinning all hope exclusively on clinical interventions aimed at directly improving impulse control. In particular, we found evidence to suggest that SDI with increased impulsivity tend to fall through the cracks of the treatment network early on, as evidenced by their increased drop-out rates during what is generally considered a first stage in the broader treatment process, i.e., detoxification programs. More than 50% of the clients participating in the inpatient detoxification programs did not complete treatment, and impulsivity significantly contributed to the variability in these drop-out rates. Individuals who did not complete the detoxification program stayed, on average, 24 days in treatment, leaving clinicians little to no time to adequately address neurocognitive deficits related to impulsivity. Moreover, it might be unrealistic to expect cognitive or rehabilitation trainings to be effective when introduced as early as in the detoxification process, a phase during which clients are often undergoing profound personal and medical crises and have to deal with severe withdrawal symptoms, which can exacerbate impulsivity or cognitive dysfunctions (Froeliger, Modlin, Wang, Kozink, & McClernon, 2012). Detoxification services do not offer a “cure” for SUDs and are rarely effective by themselves: the majority of SDI requires long-term treatment over several years to achieve and sustain recovery (Dennis, Scott, Funk, & Foss, 2005; Dennis, Foss, & Scott, 2007). Accordingly, the greatest challenge for detoxification programs is to provide effective linkages to continuing care. Poor treatment retention and premature treatment drop-out in impulsive SDI however, greatly reduces their chance to transition to continuing care and makes them more vulnerable to relapse shortly following discharge from detoxification treatment *(cf. Chapter 6)*. These findings clearly indicate that keeping impulsive SDI who enter detoxification programs from “falling through the cracks” should be a first priority[8]. Successful completion of detoxification can be considered as a gateway to more specific, impulsivity- and abstinence-oriented interventions later on during the treatment process. During the past decades, several interventions have proven to be successful at promoting treatment retention and engagement

[8] Although impulsivity was associated with poor treatment retention and higher odds of dropping out of detoxification programs prematurely, this finding was not limited to detoxification programs *(cf. Chapter 4)*. Therefore, improving addiction treatment program's "holding power" in general should be an important starting point for improving outcomes in SDI with inflated impulsivity.

in SDI. In what follows, some of these interventions will be briefly discussed. However, it is important for the reader to bear in mind that the effectiveness of these interventions for improving treatment retention in SDI with inflated impulsivity specifically remains to be determined.

- *Contingency Management (CM)*

Growing evidence suggests that CM programs – which provide (monetary) incentives contingent on abstinence or treatment adherence – may produce significantly better retention rates in SDI compared to standard treatment (García-Rodríguez et al., 2007; Ledgerwood, Alessi, Hanson, Godley, & Petry, 2008; Lussier, Heil, Mongeon, Badger, & Higgins, 2006; Rawson et al., 2006). In addition, CM procedures can increase the rates of successful transitions from detoxification programs to continuing care (Chutuape, Katz, & Stitzer, 2001; Robles, Stitzer, Strain, Bigelow, & Silverman, 2002). Some authors have suggested that the use of concrete incentives as a part of addiction treatment provides an opportunity for SDI to successfully regulate behavior and may generalize to other areas of improved impulse control (Corrigan & Bogner, 2007). However, some of the evidence presented in this dissertation suggests that SDI with higher levels of impulsivity may not benefit from these interventions to the same extent as do their less impulsive counterparts *(cf. Chapter 3)*. This finding is not surprising if one considers that the blunted motivational response to natural rewards often seen in chronic drug users is particularly pronounced among highly impulsive groups of SDI (Beck et al., 2009; Goldstein & Volkow, 2002; Goldstein et al., 2007). At least part of this may result from the pronounced disruptions in dopamine functioning associated with impulsivity, which produces difficulties in attributing salience to reward-indicating stimuli (Beck et al., 2009; Goto & Grace, 2008; Wrase et al., 2007). Accordingly, these neurobiological deficits may affect the ability of impulsive SDI to successfully modify behavior in the face of enriched rewarding contingencies (Beck et al., 2009; Martinez et al., 2007; Martinez et al., 2011). Consistent with this notion, impulsive SDI may need exposure to rewards with a higher magnitude or pharmacological support to enhance dopamine functioning in order to benefit from CM interventions (Martinez et al., 2011; Schmitz et al., 2008; Washio et al., 2011). However, these suggestions are based upon preliminary evidence. More research is therefore needed to elucidate the specific conditions under which the provision of alternative or monetary rewards might enhance treatment retention in SDI with inflated impulsivity.

- *Motivational enhancement*

To the extent that poor treatment retention in highly impulsive SDI is associated with lower treatment readiness *(cf. Chapter 5)*, clinicians may employ motivational interventions to facilitate high discounters' ongoing involvement in treatment. Growing evidence supports the effectiveness of relatively brief, focused motivational interventions (consisting of as little of a single session) at increasing treatment readiness, retention and affiliation to long-term treatment in SDI (Burke, Arkowitz, & Menchola, 2003; Carey, Carey, Maisto, & Pumine, 2002; Carroll et al., 2006; Miller & Rollnick, 2002; Potenza et al., 2011; Steinberg, Ziedonis, Krejci, & Brandon, 2004; Vederhus, Timko, Kristensen, Hjemdahl & Clausen, 2014). Some of these motivational interventions have been designed specifically to fit into standard detoxification programs (Vederhus et al., 2014). Despite promising results, there is a need for studies to investigate whether and to what extent different facets of impulsivity moderate

the effectiveness of motivational interventions. In fact, preliminary evidence suggests that motivational interventions may be less effective in SDI with higher levels of trait impulsivity (Feldstein-Ewing, LaChance, Bryan, & Hutchison, 2009; Helstrom, Hutchison, & Bryan, 2007). If replicated, existing interventions might need to be tailored to the specific profile of SDI with increased impulsivity or be combined with pharmacotherapy to promote behavioral change in these subjects. Speculatively, these subjects might respond better to psycho-educational formats (Helstrom et al., 2007; Weinstein & Shaffer, 1993). These formats may include client-friendly presentations concerning the neurocognitive mechanisms of addiction, with the aim of helping SDI to understand that there are cognitive and biological determinants of their experienced loss of control over drug use (Vederhus et al., 2014). If clients understand the source of their dysfunctions, they may be less likely to attribute their struggles with recovery to personal weakness. According to Potenza and colleagues (2011), the receipt of this and other health-related information may target brain motivational circuitry and brain regions implicated in risk-reward decision-making (e.g., ventromedial prefrontal cortex; VMPFC), cognitive control (e.g., anterior cingulate cortex; ACC), and planning (e.g., dorsolateral prefrontal cortex; DLPFC). Accordingly, it may prompt SDI to alter their decision-making processes to focus on more future-oriented goals (Potenza et al., 2011).

Alternatively, impulsivity might moderate the effect of treatment readiness on treatment outcomes, making it a poor predictor of treatment retention in impulsive clients. Such a finding would be consistent with preliminary evidence indicating that cognitively impaired and unimpaired SDI traverse different pathways to addiction recovery (Bates et al., 2006) and with evidence demonstrating that impulsivity in SDI is associated with a more pronounced intention-behavior gap (Moshier, Ewen, & Otto, 2013). Accordingly, increasing motivation may not be sufficient to promote behavioral change in individuals with inflated impulsivity. Such a suggestion however, should remain tentative, and needs to be subjected to further research.

- *Case management*

Several controlled studies have demonstrated the effectiveness of case management strategies in enhancing treatment engagement and retention among SDI (Siegal, Li, & Rapp, 2002; Rapp, Vandennoortgate, Broekaert, & Vanderplasschen, in press; Vanderplasschen, Wolf, Rapp, & Broekaert, 2007). Case management is also effective at linking drug users to appropriate services and to guarantee coordination and continuity of care. Case managers may be well positioned to keep track of the progress made by (impulsive) clients and signal the need for treatment adaptation or referral.

- *Treatment adaptations*

Although the present dissertation selectively focused on the role played by client characteristics (i.e., impulsivity) in predicting treatment attrition, it has been well-established that aspects of the treatment environment are also involved (McKellar et al., 2006; Meier & Best, 2006). Rather than selectively focusing on the role of impulsivity, recognizing the potential interaction between impulsivity and aspects of the treatment environment/program in promoting drop-out is of great clinical importance. In particular, it can contribute to the implementation of changes in program design, content and service delivery and buffer the negative effects of impulsivity on treatment retention.

Structure, rules and regulations

A seemingly obvious, yet often overlooked aspect of addiction treatment in regards to retention is the client's level of satisfaction with the treatment. Speculatively, SDI with high levels of delay discounting or impulsive decision-making might experience difficulties accepting the rules and regulations of well-controlled treatment environments, in which each day has a relatively formal schedule of therapeutic and educational activities with prescribed formats, fixed times and routine procedures. Moreover, many addiction treatment programs emphasize strict/explicit behavioral norms (i.e., no drugs or alcohol, no violence and no sexual relationships), with most rules implying a certain degree of delay. In drug-free TCs for instance, residents have to submit a written request that needs to be approved before they are allowed to contact their friends or family members. SDI who are disproportionally oriented towards the present may not be comfortable or satisfied with these regulations, leading to lower treatment motivation and early drop-out in these individuals *(cf. Chapters 4, 5, & 6)*. Indirectly supporting this suggestion, Ball and colleagues (2006) found reasons for drop-out among SDI with cluster-B personality disorders and their maladaptive traits (i.e., impulsivity) to be especially related to staff conflicts, boundary concerns, and program expectations.

One replicated finding in the addiction treatment literature is that less intensive treatment programs or treatment environments that clients perceive as less rigid and controlling are associated with a lower odds of drop-out (McKellar et al., 2006; Meier & Best, 2006). Growing evidence moreover suggests that such treatment environments may counteract drop-out in the most vulnerable SDI (Kelly & Moos, 2003; McKellar et al., 2006). Indeed, drop-out vulnerable clients, for instance those with cognitive dysfunctions, are less likely to drop out when treated in less controlling and restrictive treatment environments (Kelly & Moos, 2003; McKellar et al., 2006). This obviously poses a challenge to treatment providers: whereas highly impulsive SDI may need a clear and well-ordered treatment environment, rigid or punitive settings may potentially impel such clients to leave treatment prematurely. Speculatively, modified TCs might offer a balanced solution in this regard. Although most of the key elements and structure of the standard TC are maintained in modified TCs, these environments are typically less confronting in nature, incorporate fewer sanctions, are more flexible, put greater emphasis on orientation and instruction and provide more explicit affirmation for achievements (Sacks, Banks, McKendrick, & Sacks, 2008). Treatment in modified TCs is generally less intense and more individualized, with shorter duration of therapeutic activities (Sacks et al., 2008). Creating such a supportive, less restrictive treatment environment may help to strengthen treatment motivation among impulsive SDI. This is not to argue that SDI with inflated impulsivity should not be considered for referral or treatment in TCs. In fact, there is evidence that – when SDI with inflated impulsivity remain in these programs for a sufficient length of time – they may show remarkable progress in their ability for introspection and self-management as well as substantial decreases in impulsivity over time (Bankston et al., 2009; Goethals, Vanderplasschen, Vandevelde, & Broekaert, 2012). However, TC-based programs might need to be modified so that remaining in these settings becomes a more appealing proposition to SDI with higher levels of impulsivity.

Balancing the cognitive load

A second issue that needs to be taken into account is the cognitive load imposed on SDI during treatment. The findings presented in *Chapter 3* indirectly suggest that impulsive SDI do not seem to benefit from (empirically validated) cognitively oriented treatment programs (e.g., cognitive behavioral therapies; CBTs) to the same extent as their less impulsive counterparts (Stevens et al., 2014). These modalities are often predicated on the ability of the client to attend to treatment and to understand, remember and implement behavioral change strategies (Ersche & Sahakian, 2007; Fals-Stewart & Bates, 2003). Impulsivity however, does not exist in a vacuum but is often part of a wider set of higher-order executive impairments, including poor working memory, planning and attention deficits (Noël et al., 2011; Winstanley, Olausson, Taylor, & Jentsch, 2010). Impairment in these and other areas of executive functioning may substantially hamper the ability of these individuals to successfully participate in cognitively demanding treatment programs. Attentional deficits or poor cognitive inhibition for instance, may hamper their ability to allocate attentional resources to treatment goals or actions that can be used to override habitual behavior (e.g., relapse prevention strategies) (Klein, 2000). Consequently, individuals with compromised attention or inhibitory control may abandon treatment goals or activities within a short period of time (Aharonovich et al., 2006; Brewer et al., 2008; Streeter et al., 2008). The cognitively demanding nature of certain treatment formats may even increase impulsive behavior. Studies indicate that imposing a working memory load increases impulsive responding on delay discounting tasks (Hinson, Jameson, & Whitney, 2003) and SDI under high cognitive demands have difficulties restricting the processing of salient drug-related cues (Kane & Engle, 2003). Impulsive SDI may be particularly prone for this depletion of self-control resources (Klein, 2007; Salkovskis & Reynolds, 1994).

A significant amount of time in cognitively oriented treatment modalities is also devoted to homework and the acquisition of new coping skills, activities which place high demands on the capacity to plan and remain focused. However, impulsive individuals are often less inclined to engage in planned, consistent and cognitively demanding behaviors (Dom, De Wilde, Hulstijn, & Sabbe, 2007; Kahler, Spillane, Metrik, Leventhal, & Monti, 2009), which makes the aforementioned therapeutic strategies particularly challenging. Corroborating this notion, Carroll and colleagues (2011) found that SDI with poorer decision-making skills were less likely to complete their homework assignments during CBT, which in turn was related to worse CBT outcomes. Similarly, a study in smokers found that those with higher levels of sensation seeking were less likely to make use of strategies learned during treatment (e.g., planning for high risk situations, thinking about the benefits of quitting), which in turn led to poorer treatment outcomes in high sensation seekers (Kahler et al., 2009). These findings reinforce the view that cognitively oriented treatment modalities might need to be modified to better meet impulsive drug users' cognitive needs and capacities. At minimum, impulsive SDI need to be monitored more closely with respect to their active treatment engagement in these programs or modalities. Again, we do not imply that cognitively oriented modalities should not be considered as a part of the treatment of highly impulsive SDI. On the contrary: an emphasis on top-down control and strengthening executive functions might be specifically indicated in this subgroup of SDI. However,

targeting executive top-down processes should be distinguished from *imposing* high demands on top-down functions during a time that these skills are still developing.

Stepped care approaches

Recently, there has been a surge of interest in the development of adaptive algorithms that guide ongoing modifications to treatment content and intensity in response to the client's progress or the lack thereof (McKay & Hiller-Sturmhöfel, 2011; McLellan, Lewis, O'Brien, & Kleber, 2000). For SDI with inflated impulsivity, it might be interesting to consider stepped care approaches in which these subjects initially receive less intensive levels of care to minimize frustration and demoralization. More positive experiences in the early stages of treatment can potentially increase treatment motivation or readiness in these subjects, and counteract their initial propensities to leave treatment prematurely. After an initial period of abstinence and acute withdrawal, some spontaneous recovery of cognitive functioning and decision-making skills may occur (De Wilde, Bechara, Sabbe, Hulstein, & Dom, 2013; Goldman, 1995; Pfefferbaum et al., 1995). If neurocognitive assessments reveal such improvements in cognitive functioning, the intensity of treatment can be progressively increased, and clients can begin to engage in more demanding cognitive or interpersonal interventions (McCrady & Smith, 1986).

Considering impulsive personality traits when modifying addiction treatment programs

Contemporary conceptualizations of personality highlight the dynamic interplay between personality traits and the environmental context, in that relatively stable personality traits will influence an individual's response to particular situations (Staiger, Kambouropoulos, & Dawe, 2007). Although we did not examine whether personality traits of impulsivity were predictive of poor treatment retention or drop-out in the present dissertation, there is growing evidence to support such a relationship (Alvarez-Moya et al., 2011; Moeller et al., 2001; Patkar et al., 2004). In CDI, higher sensation seeking has been found to negatively correlate with the number of days in treatment (Patkar et al., 2004). Perhaps even more interesting, Helmus and colleagues (2001) found that SDI with higher levels of novelty seeking were more likely to remain in treatment during the early phase of a CM program, but dropped out more frequently during the later stages of treatment (Helmus, Downey, Arfken, Henderson, & Schuster, 2001). These data indirectly suggest that, at the outset, treatment in general and voucher-based treatment programs in particular may be viewed as novel or exciting, which facilitates the success of high novelty seekers early in treatment. However, as soon as the novelty fades away, novelty seekers may become bored and experience a drop in their treatment involvement. To the extent that enduring impulsive tendencies interact with program characteristics to result in treatment drop-out, treatment content and environment need to be better aligned with these personality traits. Introducing more novelty in the treatment protocol for example may help to better meet novelty or sensation seekers' persistent need for stimulation and novel experiences (Reichel & Bevins, 2010). For SDI who have difficulties to focus attention or concentrate (i.e., attentional impulsivity), possible adaptations might include decreased session length, the use of multi-modal presentation of material (visual, verbal, experiential) or repeated presentation of therapeutic material. If these and other issues can be better aligned with the particular profile of highly impulsive SDI, treatment motivation and retention might be enhanced. As yet, these suggestions must remain tentative. For future studies, it will be important to

identify the core cognitive, behavioral and emotional demands of specific treatment programs and explore which of these components are most challenging for SDI with inflated impulsivity. Exploring clients' own perceptions of program-related barriers to completing treatment may be a worthwhile prospect in this regard.

7.3.1.3. Targeting impulsivity: a focus on clinical model-based interventions

In contrast to predictive variables that are generally stable, impulsivity is malleable by treatment. Accordingly, impulsivity *can* and *should* serve as a target for manipulation as part of the treatment process. Indeed, there is growing evidence indicating that neurocognitive indices of impulsivity reflect the behavioral markers of the core mechanisms that support the maintenance of drug addiction (Belin, Mar, Dalley, Robbins, & Everitt, 2008; Diergaarde et al., 2008; Koob & Kreek, 2007). Extending these lines of evidence, the data presented in this doctoral thesis lend support for a significant contribution of these indices in predicting relapse susceptibility *(cf. Chapters 3 & 6)*. Accordingly, interventions that target the core mechanisms involved in impulsivity might help to promote sustained recovery. In this regard, our findings suggest that interventions that improve interference control over drug-related words (i.e., attentional biases) and those that reduce delay discounting and impulsive decision-making may represent the most valuable therapeutic strategies for reducing relapse propensity in SDI.

In *Chapter 1 (cf. Section 1.2.2.)*, we emphasized that poor interference control, delay discounting and impulsive decision-making (as well as the maintenance of drug addiction) may emerge from abnormal functioning in at least two key neural systems; a PFC-dependent top-down system important for cognitive/executive control and forecasting the future consequences of a behavior or choice, and an amygdala-striatum dependent bottom-up system mediating immediately rewarding, automatic and habitual behaviors (Bechara, 2005; Bickel & Yi, 2008). Recent models moreover emphasize the relevance of a third, insula-dependent system implicated in the reception of interoceptive signals and their translation into affective states (Noël, Brevers, & Bechara, 2013). Abnormal functioning in this latter system is relevant to impulsivity in that it may induce attentional biases and compromise advantageous decision-making (by affecting feedback reactivity and metacognitive capacity) (Noël et al., 2013; Paulus, 2007). Accordingly, interventions that (1) strengthen the supervisory top-down system, (2) retrain automatic bottom-up processes (e.g., attentional biases) and/or (3) train (re)appraisal of bodily feedback to guide decision-making may eventually help SDI to become less governed by immediate situations and automatic responses and more influenced by systems involved in the pursuit of future valued goals. Whereas a detailed overview and description of such interventions is beyond the scope of this dissertation, some of the more exciting developments in addiction treatment research will be briefly discussed here. More information on these novel developments and interventions can be found in a number of recent publications (Noël et al., 2013; Sofuoglu, DeVito, Waters, & Carroll, 2013).

- *Strategies aimed at boosting the supervisory top-down system and cognitive control*

In accordance with the notion that impulsivity and the maintenance of compulsive drug use partially result from a failure in top-down executive control, directly strengthening the influence of prefrontal cortical and executive control processes on behavior may have utility for the treatment of impulsivity in

SDI. A particularly promising strategy in this regard is cognitive rehabilitation training, which aims to enhance functioning in several cognitive domains, including executive functioning, (working) memory, planning, organization, decision-making and attention (Sofuoglu et al., 2013). Although the effectiveness of cognitive training programs has only recently been evaluated in addicted populations, first outcome data are promising: effects of general cognitive trainings appear to generalize to neurocognitive functions involved in impulse control (Alfonso, Caracuel, Delgado-Pastor, & Verdejo-García, 2011; Bickel et al., 2011). Working memory training in stimulant-dependent subjects for instance, has been found to result in a significant decrease in discounting of delayed rewards (Bickel et al., 2011). Working memory training may also decrease alcohol consumption in problem drinkers, possibly by strengthening cognitive control over automatic alcohol preferences (Houben, Wiers, & Jansen, 2011). These data extend the rapidly growing evidence demonstrating that training-induced improvements in working memory capacity can transfer to other cognitive skills and clinically-relevant behavior (Morrison & Chein 2011). A combination of Goal Management Training (GMT; Robertson, Levine, & Manly, 2005) – aimed at improving participants' organization and ability to achieve goals – and mindfulness-based meditation has shown promise in improving SDI's performance on tasks of working memory, response inhibition and decision-making (Alfonso et al., 2011). Recent technological advances in computer-delivered cognitive rehabilitation moreover allow for a greater level of individualization of these interventions to account for clients' cognitive strengths or weaknesses (Carroll et al., 2011; Sofuoglu et al., 2013).

The accumulating data on cognitive deficits among SDI has also led to an increased focus on the use of cognitive-enhancing medications (e.g., atomoxetine, modafinil) as a part of addiction treatment. A remarkable but relatively consistent finding is that differences in baseline impulsivity levels seem to moderate the effect of these cognitive enhancing agents on cognition. In particular, it appears that SDI with elevated impulsivity seem to benefit from these agents, whereas no effects or even worsening of cognitive control occurs in low impulsive subjects (Eagle et al., 2007; Economidou, Dalley, & Everitt, 2011; Joos et al., 2013; Zack & Poulos, 2009). These findings are consistent with an inverted U-shaped relationship between catecholamine neurotransmitter levels and cognitive performance (Levy, 2009). The use of cognitive enhancement strategies may be particularly useful during the early stages of treatment by improving the ability to learn, remember, and/or to implement new skills.

A promising line of research has begun to explore the use of noninvasive brain stimulation techniques in improving cognition in general and decision-making specifically. Consistent with the well-established role of the DLPFC in modulating decision-making, bilateral transcranial stimulation of the DLPFC has been found to reduce risky and impulsive decision-making in healthy subjects, possibly by assisting them in suppressing riskier responses (Fecteau et al., 2007a, 2007b). Recent studies applying this technique in SDI suggest that modulation of the DLPFC can improve decision-making in addicted populations (Fecteau et al., 2014; Fecteau, Fregni, Boggio, Camprodon, & Pascual-Leone, 2010). Given that impulsive decision-making emerged as a reliable predictor of drop-out and relapse in the current dissertation, neuromodulation-based approaches that improve decision-making might be particularly interesting in the treatment of impulsive SDI.

Ultimately, these findings indirectly support the notion that training of executive functions or neuromodulation-based approaches may help to improve several aspects of impulsivity in SDI. 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 the aforementioned findings.

- *Attentional bias modification and mindfulness training*

SDI exhibit an intensified automatic attentional processing of addiction-relevant cues (i.e., attentional bias), which emerged as a relatively consistent predictor of relapse in the present dissertation *(cf. Chapter 3)*. In an attempt to desensitize such automatic attentional responses, attentional bias modification (ABM) trains SDI to direct their attention away from drug-related cues (Fadardi & Cox, 2009). Preliminary evidence supports the clinical usefulness of ABM in clinical samples of alcoholics (Schoenmakers et al., 2010): ABM appears to be effective in increasing alcoholics' ability to disengage attention from alcohol-related cues and can delay the occurrence of relapse in these subjects (Schoenmakers et al., 2010). However, replication of these findings in larger samples is clearly needed.

Another intervention that has received growing attention in recent years and appears to target the pathogenic mechanisms that maintain addictive behaviors is mindfulness. Mindfulness training can result in improvements in response inhibition and decreases in attentional biases in alcohol-dependent individuals (Garland, Gaylord, Boettiger, & Howard, 2010). At least part of these effects may be caused by decreases in thought suppression following mindfulness training, a maladaptive strategy many persons recovering from drug addiction use in an attempt to suppress cravings (Garland et al., 2010; Wegner, Schneider, Carter, & White, 1987). Paradoxically, thought suppression tends to result in a rebound effect, i.e., an increase rather than a decrease in the rate and intensity of the very thoughts and emotions it is directed against (Garland et al., 2010; Wegner et al., 1987; Wenzlaff & Wegner, 2000). As thought suppression decreases, cognitive top-down processes can be more effectively deployed to inhibit habitual responding, resulting in decreased attentional capture by alcohol or drug-related cues. Mindfulness-training also promotes adaptive decision-making (Alfsono et al., 2011), potentially by increasing awareness of interoceptive emotional inputs that serve to anticipate the prospective outcomes of potential decisions (e.g., Bechara, Damasio, Tranel, & Damasio, 1997; Weller, Levin, Shiv, & Bechara, 2007).

7.3.2. We are only at the beginning of a journey, rather than at the end…

In the aforementioned sections, we have argued that screening for impulsivity at treatment entry and enhancing treatment retention and readiness in SDI with increased levels of impulsivity should be a priority. We have highlighted several interventions that might be promising in this respect, including the use of monetary incentives, motivational interventions and the implementation of treatment modifications to better meet the needs and profile of SDI with increased impulsivity. We have also briefly discussed some clinical interventions that might be effective in targeting attentional biases (e.g., ABM), delay discounting (e.g., working memory training) and/or impulsive decision-making (e.g., GMT+mindfulness). However, we are only at the beginning of a journey, rather than at the end. First,

there is currently insufficient evidence that these interventions will be effective at promoting treatment retention and improving impulsivity in SDI with inflated impulsivity specifically. Indeed, the findings presented in this dissertation suggest that impulsivity moderates the effectiveness of several empirically validated, evidence-based treatment interventions, including CM and CBT: SDI with higher levels of impulsivity do not seem to benefit from these treatment modalities to the same extent as do their less-impulsive counterparts, pointing out the importance of assessing whether a given treatment is working for a particular individual, not just whether it tends to work for addicted individuals as such.

Moreover, and consistent with the *orthopedagogical orientation* of the present dissertation, the clinical recommendations outlined above need to form an integrated entity (Broekaert, Autrique, Vanderplasschen, & Colpaert, 2010). Only by a fruitful interaction and integration of different treatment approaches – including pharmacotherapy, cognitive training, motivational enhancement and treatment modification efforts – it will be possible to optimize treatment outcomes for highly impulsive SDI. For instance, cognitive enhancers or neuromodulation-based approaches aimed at upregulating brain functioning might act as a successful adjunct for increasing the effectiveness of cognitive training programs in these individuals. These interventions influence neuronal plasticity, may temporarily enhance working memory capacity and facilitate the deployment of cognitive control in the early phases of treatments, when these skills are still developing (Fregni et al., 2005; Nitsche et al., 2003; Sofuoglu et al., 2013). Accordingly, they may provide SDI with neurocognitive deficits related to impulsivity with a stronger ability to benefit from cognitively oriented treatment programs. Adherence to these cognitive rehabilitation trainings (e.g., working memory training) can further be facilitated by integrating CM procedures offering high-magnitude vouchers (Bickel et al., 2011).

The extensive focus on client factors involved in drop-out and relapse may obscure the fact that poor treatment motivation or drop-out might also result from a dynamic interplay between client and treatment-related characteristics. In fact, some of the evidence presented in this doctoral dissertation indicates that neurocognitive deficits associated with impulsivity may result in poor treatment motivation/outcomes only under particular environmental conditions (Passetti et al., 2011). Therefore, a deliberate selection of the treatment environment and setting in which the aforementioned strategies or interventions are being applied needs to be part of such an integral approach. Creating a supportive and facilitative environment that can be adapted to the changing cognitive/motivational status of SDI can play an important role in increasing the effectiveness of the aforementioned strategies. Ideally, the selection of these different strategies, treatment environments and of their combination should be based upon each individual's impulsivity profile by adopting a multidimensional approach (e.g., delay discounting/working memory training vs. poor interference control/ABM).

Only through an integrated and comprehensive system of treatment modalities, we can transcend postulated and presupposed solutions and tailor services according to individuals' needs and expectations. However, this integration of different strategies and approaches will not happen without substantial efforts, since they are underpinned by distinct methodological and scientific paradigms (e.g., pharmacotherapy/empirical-analytical paradigm of care versus drug-free therapeutic communities/phenomenological-existential paradigm of care), which are still too often seen as competing (Broekaert et al., 2010). From an orthopedagogical perspective however, different

paradigms do not exclude, but rather complement each other: various treatment approaches may all have their value for someone with substance abuse problems at a certain moment in a certain situation throughout their lifespan (Broekaert et al., 2010). In the search for the best answer in a given situation, we try to find the most suitable treatment combination and do the best for mankind. This is what Broekaert and colleagues (2010) label the *human prerogative*, i.e., the human dedication to achieve the best solution for persons with substance (ab)use problems, free of dogmatic premises. As a human being, the client is also an interconnected and integral part of this 'best' choice.

7.4. Limitations of this dissertation and directions for future research

The studies included in the present dissertation had several notable strengths. Most importantly, we adopted a multidimensional impulsivity approach to elucidate the relative importance of each impulsivity dimension in the prediction of poor addiction treatment outcomes. In addition, studies were conducted in real-world operating addiction treatment programs using a naturalistic sampling approach, which increases the generalizability of our findings. Finally, attention was given to indirect pathways by which impulsivity may negatively affect treatment retention or post-treatment relapse, which helps to translate findings into recovery-oriented services. The findings presented in this dissertation however, should also be considered in light of some weaknesses. Whereas the most important limitations of each particular study have been discussed in the different chapters, this section focuses on some overall limitations of the doctoral thesis. In addition, we propose how future studies may address these limitations and contribute to further progress in this area.

7.4.1. Focus on and measurement of impulsivity

In the present dissertation, we selectively focused on impulsivity as a potential factor contributing to the variability in treatment outcomes among SDI. Obviously, treatment drop-out and relapses are complex and multidimensional processes, influenced by a combination and interaction of biological, psychological, social and treatment-related factors (for reviews on this topic, see Adamson, Sellman, & Frampton, 2009; Bradizza, Stasiewicz, & Paas, 2006; Brorson, Arnevik, Rand-Hendriksen, & Duckert, 2013; Ciraulo, Piechniczek-Buczek, & Iscan, 2003; Reske & Paulus, 2008). Identifying additional predictors of poor addiction treatment outcomes and examining how these interact with impulsivity to promote treatment drop-out or relapse may be an interesting avenue for future research. Perhaps even most important, there is a need for studies to explore whether and how impulsivity interacts with specific treatment-related characteristics to predict premature treatment drop-out. Such a paradigm shift from an exclusive focus on client characteristics to the dynamic interplay between client and treatment-related components may facilitate implementation of changes in program design and service delivery.

In the present dissertation, some relatively complex neurocognitive paradigms – which rely on multiple cognitive and motivational functions – were used (e.g., IGT or CGT). Whereas these tasks may be argued to have a high ecological validity, their complexity clearly interferes with the ability to elucidate and distinguish the different processes that may be implicated. Accordingly, when interpreting the findings presented in this dissertation, readers should bear in mind that compromised performance on these tasks is not necessarily or uniquely 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, Dalgleish, & Lawrence, 2006; Winstanley et al., 2010).

While widely used and believed to index some of the core facets of impulsivity commonly impaired or elevated in SDI, the impulsivity measures used did not constitute a comprehensive assessment. For instance, it is important to consider that cognitive inhibition was not measured in the empirical studies of this dissertation. We also recommend future studies on the relationship between motor disinhibition and addiction treatment outcomes to include tasks in which neutral stimuli (e.g., letters or airplanes) are substituted by motivationally relevant stimuli, which permit analyses of performance in response to cues of affective valences.

We did not examine the association between trait impulsivity and treatment retention or drop-out. Still, a cursory review of the literature seems to support the notion that more enduring impulsive tendencies which are manifest across a range of situations may predict inadequate treatment engagement and premature drop-out (Alvarez-Moya et al., 2011; Moeller et al., 2001; Patkar et al., 2004). Replication of these findings would provide support for the notion that general indicators (i.e., trait impulsivity) better predict general behaviors (i.e., treatment retention), whereas specific indicators (i.e., neurocognitive tasks indexing control over motivationally-relevant components) better predict specific behaviors (i.e., relapse).

In the present dissertation, we did not establish the threshold of neurocognitive impairment associated with relapse or drop-out vulnerability, which may be necessary if one wishes to translate findings into guidelines for treatment matching. 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 cutoff values and to select the optimal cut-off.

7.4.2. Selection of and operationalization of addiction treatment outcome indicators

In this doctoral thesis, treatment retention, drop-out and relapse were used as the treatment outcome indicators of interest. Obviously, relevant treatment outcomes extend to other areas of functioning as well, including employment status, criminal involvement, health and well being, family relations, quality of life, treatment status, and so forth (De Maeyer et al., 2011; Vanderplasschen et al., 2013). Growing evidence moreover suggests that impulsivity is associated with poorer functioning in these various life domains (see Albein-Urios, Pilatti, Lozano, Martinez-Gonzalez, & Verdejo-Garcia, 2013). Accordingly, future studies may benefit from focusing on a broader range of outcome indicators while examining the effects of impulsivity on addiction treatment outcomes.

In the study discussed in *Chapter 6*, relapse was coded as a dichotomous variable, i.e., any use of an illicit substance during the follow-up period. It should be noted that this is a relatively stringent definition of relapse, and that not all SDI may want to adopt the goal of total abstinence. Regrettably, we did not collect information regarding the severity of the relapse(s) reported by the participants or

other potentially relevant information, such as the number of relapse episodes, duration, number of substances involved, and consequences. The study discussed in *Chapter 6* also relied solely on self-reported abstinence. Whereas previous research suggests that clients' self-reports of drug use are reasonably reliable when events are recent and clients do not face negative consequences for their answers (Zanis, McLellan, Canaan, & Randall, 1994), future investigations of relapse may benefit from incorporating biological markers to verify abstinence (e.g., hair analyses).

Although complete abstinence is the ultimate goal of detoxification, it is widely recognized that these programs are rarely effective by themselves. In fact, the biggest challenge for detoxification programs is to provide effective linkages to continuing care services. Therefore, abstinence outcomes may be contingent in large degree upon whether clients enter long-term treatment after they leave the detoxification facility. Future studies examining the relationship between impulsivity and treatment outcomes within the context of detoxification programs may focus on whether and how impulsivity affects transition or transfer to continuing care.

In this dissertation, we did not examine whether the weight of impulsivity as a risk factor for poor treatment outcomes varied as a function of time in treatment. It is possible that impulsive SDI are more likely to remain in treatment during the early phases of treatment but drop out more frequently during the later stages (Helmus et al., 2001). Moreover, impulsivity variables associated with drop out early in treatment may not be the same ones as those associated with dropping out during the middle phase or towards the end of treatment. Some aspects of impulsivity (e.g., decision-making skills) may improve during treatment (Aklin, Tull, Kahler, & Lejeuz, 2009; De Wilde et al., 2013) and, accordingly, their relative impact may be undermined as retention in treatment increases.

7.4.3. Sample characteristics

Although the sample sizes of the studies discussed in *Chapters 2*, *5* and *6* were rather large compared to those of previous studies in this research area (De Wilde et al., 2013; Goudriaan et al., 2008; Passetti et al., 2008), subtle differences in performance between the clinical groups may not have been detected. Larger samples would have resulted in greater statistical power to identify group differences.

Participants in the studies discussed in *Chapters 2*, *4*, *5*, and *6* were recruited at inpatient addiction treatment settings. SDI attending treatment in inpatient settings generally present with increased severity of symptoms and incidence of psychiatric co-morbidity relative to outpatients (Budde, Rounsaville, & Bryant, 1992). Accordingly, findings may not apply to clients treated in outpatient settings. Whereas there is currently no evidence suggesting that the relationship between impulsivity and addiction treatment outcomes differs according to the primary substance of abuse (see Winhusen et al., 2013), it should be noted that the majority of the SDI included in this dissertation reported cocaine as their primary substance of abuse. However, this limitation is partially offset by the inclusion of studies focusing on highly heterogeneous groups of SDI in our literature review *(cf. Chapter 3)*. In addition, a large majority of the subjects included were poly-drug users. This naturalistic sampling approach matches groups that are encountered in real clinical contexts and as such, may be argued to increase the ecological validity of the study results.

7.4.4. Study design

The cross-sectional design of the studies included in this doctoral thesis precludes any causal interference regarding the observed relationships. The proposed pathogenetic mechanisms for the emergence of impulsivity in drug addiction have been broadly separated into two potentially interacting processes: (1) impulsivity acting as a premorbid vulnerability factor underlying the development of substance use disorders (SUDs), and (2) impulsivity as a consequence of exposure to the neurotoxic effects of drug use (de Wit, 2009). Unfortunately, cross-sectional study designs do not permit us to disentangle the causality of impulsivity in drug addictions. In humans, such evaluations necessitate longitudinal studies with long-term follow-up assessments that start from the early years of childhood or adolescence and continue into adulthood (see Tarter et al., 2003). Alternatively, animal studies have the potential to quantify impulsivity prior to drug initiation and therefore, also provide a valuable means to prospectively evaluate the influence of impulsivity on drug use or conversely, the effects of drug use on impulsivity (see Perry, Larson, German, Madden, & Carroll, 2005). In the study discussed in *Chapter 5*, treatment readiness emerged as a partial mediator of the relationship between delay discounting and treatment retention. However, treatment readiness and delay discounting were measured at the same time (i.e., at treatment entry) and therefore, no causal interferences can be made regarding the nature of their relationship.

We did not examine during treatment changes in motivation or treatment readiness. It should be noted however, that motivation is a dynamic state that can fluctuate over time and in relation to different situations, rather than a static personal attribute (Cahill, Adinoff, Hosig, Muller, & Pulliam, 2003; Simoneau & Bergeron, 2003). It would be interesting for future studies to explore whether delay discounting or other facets of impulsivity are associated with different motivation trajectories among SDI.

In the present dissertation, we argued that highly structured, inpatient detoxification programs or TCs may be suboptimal in retaining impulsive drug users in treatment, potentially due to the high demands that are placed on the ability to postpone immediate gratification. Similarly, we argued that poor treatment outcomes in impulsive SDI in cognitively oriented treatment modalities may result from the comparatively high cognitive demands associated with these treatment formats. However, in the absence of a control condition, we cannot ascertain whether poor treatment readiness or outcomes in impulsive SDI reflect particular challenges for specific treatment programs or modalities, or rather, a general response to treatment. A worthwhile prospect for future studies in this regard may be to investigate the actual reasons why impulsive SDI drop out of treatment prematurely or relapse soon afterwards. These reasons could be related both to intrinsic barriers (e.g., motivation or self-efficacy) and to extrinsic barriers (e.g., components of the treatment environment). More explicit information in this area would help to better tailor existing treatment programs to the needs of this vulnerable subgroup of SDI. In order to elucidate the particular conditions and clinical contexts under which aspects of impulsivity are associated with treatment failure, future studies may also examine the strength and the nature of the relationship between aspects of impulsivity and outcomes in various treatment modalities simultaneously (see Passetti et al., 2011). Similarly, 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 would provide valuable information for clinical decision-making. Such studies would allow us to determine more accurately which clients would benefit most from which types of interventions and at which intensity. This would ensure maximum effectiveness while creating minimal burden for both the client and treatment providers. Phrased differently, future research on impulsivity needs to extend the scope from what predicts treatment response, into why and under what conditions. 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.

Final conclusion

Substance-dependent individuals show considerable variability in treatment outcomes. Whereas some individuals successfully complete treatment and are able to initiate/maintain abstinence following treatment, others drop out of treatment prematurely and/or relapse soon following treatment discharge. Identification of client characteristics (i.e., impulsivity) and treatment process components (i.e., motivation) that have direct linkages to drop-out, retention and relapse carries important clinical significance. In particular, the implication is that intervention strategies that improve one or more of these elements represent enhancements to treatment effectiveness.

The findings presented in the current dissertation yield convincing evidence to suggest that individual differences in neurocognitive expressions of impulsivity across addicted individuals may account for part of this variability in treatment outcomes: inflated impulsivity in SDI is associated with poor treatment retention, premature treatment drop-out and a greater propensity to relapse. The negative effects of impulsivity on addiction treatment outcomes appear to operate across a variety of existing, empirically validated treatment programs, modalities and settings. Accordingly, current addiction treatment programs may be suboptimal for SDI with more pronounced levels of impulsivity. One of the key clinical implications of these findings is that existing treatment services need to be tailored to the specific profile of SDI with inflated impulsivity, so that remaining in treatment becomes a more feasible and appealing proposition. Enhanced treatment retention may in turn enable the implementation of more specialized interventions directly aimed at targeting impulsivity. The translation of this knowledge into clinical practice will ideally become increasingly apparent in the coming years. In line with the orthopedagogical orientation of this dissertation, we emphasize the need to strive towards integrated treatment systems, which give full opportunity and access to a broad spectrum of interconnected treatment modalities, approaches and services.

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Nederlandstalige samenvatting

Introductie

Verslaving is een ernstig en wijdverspreid probleem, met een aanzienlijke impact op het verslaafde individu, diens omgeving en de samenleving als geheel (Degenhardt & Hall, 2012; Degenhardt et al., 2013). De laatste decennia hebben er zich drastische veranderingen voorgedaan in het denken over verslaving (van den Brink, 2005), waarbij de medisch-biologische aspecten van het breed gedragen biopsychosociale model een steeds prominentere rol lijken te spelen. Recent neurobiologisch onderzoek toont aan dat verslaving gepaard gaat met moleculaire, cellulaire, structurele en functionele hersenafwijkingen (Feil et al., 2010). Deze hersenafwijkingen uiten zich onder meer in neurocognitieve dysfuncties, die voornamelijk prominent zijn in het domein van impulscontrole (Verdejo-Garcia, Lawrence, & Clark, 2008). Uit beeldvormend onderzoek blijkt bovendien dat deze neurale afwijkingen en gebrekkige impulscontrole een centrale rol spelen in de chroniciteit en compulsiviteit die centraal staan bij verslaving (Feil et al., 2010). Parallel met deze nieuwe inzichten wordt verslaving in toenemende mate geconceptualiseerd als een *chronische hersenziekte* (Leshner, 1997).

Consistent met de chroniciteit van verslaving, blijkt een aanzienlijk percentage drugafhankelijke individuen herhaaldelijke episodes van herval door te maken (Sinha, 2011). Bovendien wordt een adequate behandeling van verslaving bemoeilijkt door hoge drop-outcijfers (Brorson, Arnevik, Rand-Hendriksen, & Duckert, 2013). Vroegtijdige behandelingsdrop-out is bijzonder problematisch vanuit een klinisch perspectief, gezien de behandelingsduur of retentie één van de meest consistente voorspellers is van positieve uitkomsten; d.w.z., de kans op succes na de behandeling stijgt wanneer men de behandeling afrondt of naarmate men langer in het behandelingsprogramma verblijft. Omgekeerd blijkt een kortere behandelingsduur of vroegtijdige behandelingsdrop-out geassocieerd te zijn met een verhoogd risico op herval en geassocieerde problemen (Brorson et al., 2013; Smyth, Barry, Keenan, & Ducray, 2010).

Het ontwikkelen van een beter zicht op cliëntfactoren die geassocieerd zijn met behandelingsdrop-out en herval bij personen met een verslavingsproblematiek is dan ook essentieel. Een identificatie van dergelijke determinanten zou kunnen bijdragen aan een vroegtijdige detectie van de meest kwetsbare individuen, zodat deze vervolgens extra ondersteund/begeleid kunnen worden, dan wel worden toegewezen aan meer gerichte interventies. Een focus op dynamische voorspellers (die beïnvloedbaar zijn door interventie) kan bovendien leiden tot de identificatie van cruciale behandelingstargets.

Voorliggend doctoraatsonderzoek dient dan ook geïnterpreteerd te worden vanuit deze achtergrond. Het doctoraatsonderzoek richt zich specifiek op een exploratie van de rol van *impulsiviteit* in het voorspellen van drop-out en herval bij individuen met een verslavingsproblematiek. De keuze voor een focus op impulsiviteit werd ingegeven door zowel theoretische als klinische overwegingen. Impulsiviteit hangt, zoals eerder aangegeven, sterk samen met het controleverlies dat centraal staat bij verslaving, en speelt een belangrijke rol in de instandhouding van verslavingsgedrag (Dalley, Everitt, & Robbins, 2011). Deze samenhang manifesteert zich zowel op neurobiologisch als gedragsmatig niveau. De neurobiologische basis van impulsiviteit vertoont een sterke overlap met de neurobiologische

processen die betrokken zijn bij de persistentie van verslaving (Dalley et al., 2011; Feil et al., 2010). Bovendien blijken individuen die hoger scoren op impulsiviteit een groter risico te lopen om de controle over het druggebruik te verliezen en compulsief verslavingsgedrag te ontwikkelen (Economidou, Pelloux, Robbins, Dalley, & Everitt, 2009; Hogarth, 2011; Tarter et al., 2003). Gezien deze duidelijke samenhang, lijkt het niet onlogisch te veronderstellen dat impulsiviteit ook een aanzienlijke invloed op het herstelproces, en dus, de behandelingsuitkomsten zal hebben. Een focus op de rol van impulsiviteit in het voorspellen van drop-out en herval is bovendien klinisch relevant. Impulsiviteit is beïnvloedbaar door interventie, en gezien de overlap tussen impulsiviteit en de neurobiologische basis van compulsief verslavingsgedrag, kan een behandeling van impulsiviteit wellicht bijdragen aan het doorbreken van de chroniciteit van verslaving.

Impulsiviteit: definiëring en meetinstrumenten

De ontwikkeling van een precies begrip omtrent de relatie tussen impulsiviteit en verslavingsgedrag is de voorbije jaren bemoeilijkt door de afwezigheid van een consensus betreffende de conceptualisatie van impulsiviteit. Ondanks het wijdverspreide gebruik van de term, blijkt het begrip 'impulsiviteit' vaak gehanteerd te worden om te verwijzen naar kwalitatief uiteenlopende gedragspatronen. Inmiddels is er een breed gedragen consensus tussen onderzoekers dat impulsiviteit een multidimensioneel construct is, bestaande uit verschillende componenten (Whiteside & Lynam, 2001). Bovendien toont steeds meer onderzoek aan dat deze verschillende componenten beïnvloed worden door uiteenlopende neurobiologische substraten (Broos, Diergaarde, Schoffelmeer, Pattij, & De Vries, 2012; Diergaarde et al., 2008).

Doorgaans wordt een onderscheid gemaakt tussen neurocognitieve en persoonlijkheidsgerelateerde impulsiviteitdimensies (Verdejo-Garcia et al., 2008). Binnen persoonlijkheidsonderzoek wordt impulsiviteit benaderd als een stabiel persoonlijkheidskenmerk dat zich manifesteert over verschillende situaties heen. Neurocognitieve onderzoekers daarentegen, benaderen impulsiviteit doorgaans als een transitoire staat, die fluctueert in reactie op cognitieve- of omgevingsinvloeden. In wat volgt worden enkele concepten en meetinstrumenten uit beide onderzoekstradities kort toegelicht.

- *Impulsiviteit vanuit een neurocognitieve invalshoek: definities en meetinstrumenten*

Binnen neurocognitieve onderzoekstradities wordt er doorgaans een onderscheid gemaakt tussen twee mogelijke uitingsvormen van impulsiviteit: *impulsive action* en *impulsive choice*[9] (Dalley et al., 2011; Winstanley, Eagle, & Robbins, 2006). De eerste component, *impulsive action*, kan worden opgedeeld in motor en cognitive disinhibition. *Motor disinhibition* uit zich als een onvermogen om automatische of geconditioneerde gedragingen te onderdrukken of te inhiberen. Deze neurocognitieve impulsiviteitdimensie wordt typisch gemeten met behulp van taken waarin een gedragsmatige onderdrukking van automatische of prepotente reacties wordt vereist, zoals de Stop Signal Task (SST; Logan, Cowan & Davis,1984), de Go/No-Go Task (Donders, 1969; zie ook Luce, 1986) en de Continuous Performance Test (CPT; Mackworth & Taylor, 1963). *Cognitive disinhibition* verwijst naar

[9] Om de vergelijkbaarheid met de in de internationale literatuur gehanteerde concepten voor de lezer te verzekeren, worden Engelstalige termen zonder duidelijk Nederlandstalig equivalent in hun oorspronkelijke vorm vermeld.

moeilijkheden met interferentiecontrole, of het onderdrukken van irrelevante informatie. De Stroop Kleur-Woord Test (Stroop, 1935) is wellicht het meest gehanteerde instrument om disfuncties op het niveau van interferentiecontrole in kaart te brengen. Moeilijkheden met het onderdrukken van irrelevante informatie blijken met name uitgesproken te zijn wanneer de informatie betrekking heeft op de kernpathologie van een stoornis. Zo ziet men bij personen met een verslavingsproblematiek vaak een preoccupatie met druggerelateerde stimuli (i.e., aandachtsbias), die interfereert met het uitvoeren van cognitieve taken die een beroep doen op responsinhibitie (Field & Cox, 2008). Eén van de meest gebruikte indicatoren voor deze zogenaamde aandachtsbias is de mate van interferentie op 'emotionele' versies van de Stroop test. In deze taak worden emotionele (stoornisgerelateerde) en neutrale woorden één voor één in verschillende kleuren in beeld gebracht. Aan de proefpersoon wordt gevraagd zo snel mogelijk de kleur van het woord te benoemen en de betekenis van het woord te negeren. Aangenomen wordt dat de betekenis van de druggerelateerde woorden automatisch wordt verwerkt en interfereert met de snelheid waarmee de kleur van de woorden kan worden benoemd. Net zoals het begrip impulsive action, dekt de term *impulsive choice* diverse uitingsvormen van impulsiviteit. Vooreerst wordt de term vaak gebruikt om te verwijzen naar een devaluatie van uitgestelde beloningen, gekoppeld aan een uitgesproken voorkeur voor onmiddellijk beschikbare beloningen. De term *delay discounting* verwijst daarbij naar de vaststelling dat de subjectieve waarde van een beloning daalt wanneer de tijd gekoppeld aan het verkrijgen van deze beloning toeneemt. Deze impulsiviteitdimensie wordt typisch gemeten door een persoon te vragen naar zijn voorkeur voor een kleine, onmiddellijke beloning dan wel een grotere, uitgestelde beloning, zoals in de Delay Discounting Task (DDT; Richards, Zhang, Mitchell & De Wit, 1999). De term *reflection impulsivity* verwijst naar de vaststelling dat impulsieve individuen vaak minder informatie verzamelen of evalueren vooraleer een complexe beslissing te nemen (Kagan, 1966). Deze tendens wordt bestudeerd aan de hand van neurocognitieve taken zoals de Information Sampling Task (IST; Clark, Robbins, Ersche & Sahakian, 2006) en de Matching Familiar Figure Test (MFFT; Kagan, 1966). Bij impulsieve personen ziet men ook vaak keuzegedrag waarbij mogelijke risico's gekoppeld aan het nastreven van een beloning niet of weinig in acht worden genomen. Vaak wordt de term *impulsive decision-making* gehanteerd om te verwijzen naar dit soort keuzepatronen. Deze tendens wordt gemeten met behulp van taken waarin het individu een keuze kan maken tussen conservatieve of risicovollere opties, waarvan de laatste naast een aanzienlijk risico doorgaans ook een aantrekkelijk voordeel met zich meebrengen (Bechara, 2003). Voorbeelden van taken die deze impulsiviteitdimensie in kaart brengen zijn de Iowa Gambling Task (IGT; Bechara, Damasio, Damasio & Anderson, 1994) en de Balloon Analogue Risk Task (BART; Lejuez et al., 2002). Neurocognitieve prestaties worden doorgaans beschouwd als endofenotypische indicatoren van impulsiviteit, aangezien ze fungeren als een intermediaire factor tussen de klinische symptomatologie enerzijds en de onderliggende genetische, neurobiologische basis van een stoornis anderzijds (Gottesman & Gould, 2003).

- *Impulsiviteit vanuit een persoonlijkheidsperspectief: definities en vragenlijsten*

Impulsiviteit kan zich echter ook manifesteren als een relatief stabiel persoonlijkheidsconstruct. Termen als *non-planning impulsivity* en *lack of premeditation* verwijzen daarbij naar een gebrek aan planning, toekomstoriëntatie, of het afwegen van consequenties op de lange termijn (Whiteside &

Lynam, 2001). Enigszins in eenzelfde lijn wordt de term *motor impulsivity* gehanteerd om te refereren naar een afwezigheid van aan het handelen voorafgaande reflectie (Patton, Stanford & Barratt, 1995). In aansluiting op de notie dat impulsiviteit vaak samengaat met aandachts- en concentratiestoornissen, worden de begrippen *attentional impulsivity* en *lack of perseverance* gehanteerd om te verwijzen naar moeilijkheden op het vlak van volgehouden aandacht of doorzettingsvermogen bij complexe of cognitief veeleisende taken (Patton et al., 1995; Whiteside & Lynam, 2001). Een frequent gehanteerde vragenlijst om de zojuist genoemde impulsiviteitdimensies in kaart te brengen is de Barratt Impulsiveness Scale-11 (BIS-11; Patton et al., 1995). Deze schaal, die bestaat uit 30 items, meet drie verschillende componenten van impulsiviteit: *non-planning-, motor-* en *attentional impulsivity*. In de UPPS-impulsiviteitschaal (Whiteside & Lynam, 2001) worden de begrippen *lack of premeditation* en *lack of perseverance* gehanteerd om te verwijzen naar problemen op het niveau van respectievelijk planning en doorzettingsvermogen. Deze vragenlijst, die bestaat uit 45 items, meet daarenboven nog twee bijkomende impulsiviteitdimensies, die in tegenstelling tot de eerdergenoemde cognitieve en motorische componenten meer emotioneel/motivationeel van aard zijn. Zo wordt de term *negative urgency* gehanteerd om te verwijzen naar een tendens om snel en ondoordacht te reageren in reactie op negatieve gevoelens. De observatie dat sommige individuen ook geneigd zijn om impulsief gedrag te stellen naar aanleiding van positieve gevoelens, heeft meer recent geleid tot de introductie van het begrip *positive urgency* (Cyders & Smith, 2007). Impulsiviteit kan zich ook voordoen als een neiging om voortdurend nieuwe situaties of prikkels op te zoeken die een kick opleveren. Deze tendens kan gemeten worden aan de hand van de *sensation seeking*-subschaal van de UPPS en de Zuckerman-Kuhlman Personality Questionnaire (SSS; Zuckerman, 1993). In tegenstelling tot neurocognitieve dimensies van impulsiviteit, die typisch in kaart worden gebracht met behulp van gedragstaken, worden persoonlijkheidsconstructen met andere woorden gemeten door middel van zelfrapportagevragenlijsten.

Probleemstelling

Studies naar de relatie tussen impulsiviteit en behandelingsuitkomsten binnen het veld van verslavingsonderzoek zijn schaars, doch aan een duidelijke opmars begonnen. De beschikbare evidentie wijst uit dat impulsiviteit wellicht een belangrijke rol speelt in het voorspellen van behandelingsdrop-out of herval (Moeller et al., 2001; Patkar et al., 2004). Desalniettemin wordt voorgaand onderzoek gekenmerkt door een aantal belangrijke beperkingen.

Wellicht de meest belangrijke beperking verbonden aan eerder onderzoek is de doorgaans eenzijdige benadering van het concept impulsiviteit. Ondanks de toenemende erkenning dat impulsiviteit een multidimensioneel concept is, hebben de meeste voorgaande studies slechts één impulsiviteitdimensie onderzocht in relatie tot drop-out en/of herval. Bovendien zijn persoonlijkheids- en neurocognitieve onderzoekstradities naar impulsiviteit historisch sterk gescheiden gebleven, wat zich weerspiegelt in een gebrek aan integratie van zelfrapportage-vragenlijsten en neurocognitieve impulsiviteitstaken binnen eerder onderzoek (Enticott & Ogloff, 2006). Het blijft daardoor actueel ook onduidelijk of één van beide benaderingen meer of minder geschikt is in het voorspellen van behandelingsuitkomsten.

Een tweede beperking verbonden aan eerder onderzoek naar de relatie tussen impulsiviteit en behandelingsuitkomsten heeft betrekking op de geringe generaliseerbaarheid. Een belangrijke meerderheid van voorgaande studies in dit domein werd verricht in het kader van gerandomiseerde gecontroleerde trials (RCTs) naar de effecten van diverse farmacologische interventies. Hoewel RCTs doorgaans beschouwd worden als de gouden standaard binnen behandelingonderzoek, is de generaliseerbaarheid van dergelijke studies naar de dagelijkse klinische praktijk vaak beperkt. Een belangrijke reden betreft onder meer de strenge exclusiecriteria, waardoor cliënten met comorbiditeit vaak niet worden opgenomen. Deelnemers aan deze RCTs maken doorgaans slechts een zeer beperkte subgroep uit van de cliënten die men aantreft in de gangbare klinische praktijk. Bovendien blijkt de aard van de relatie tussen impulsiviteit en behandelingsuitkomsten mede bepaald te worden door het specifieke behandelingsprogramma waarin deze relatie bestudeerd wordt. Bijgevolg is het actueel moeilijk voor bestaande behandelingsprogramma's om uit te maken of en hoe de beschikbare evidentie betrekking heeft op hun eigen setting. Onderzoekers benadrukken dan ook de behoefte aan kleinschalige studies die verricht worden in klinische settings die een heterogene groep van druggebruikers behandelen.

Ten slotte hebben eerdere studies geen aandacht gehad voor mogelijke indirecte effecten van impulsiviteit op de behandelingsuitkomsten bij personen met een verslavingsproblematiek. Studies uit andere onderzoeksdisciplines suggereren dat de invloed van neurocognitieve dysfuncties op de behandelingsuitkomsten of het functioneren van de cliënt doorgaans indirect is, i.e., gemedieerd wordt door inter-persoonlijke factoren (Bates, Buckman, & Nguygen, 2013). Mogelijk relevant in dit opzicht is een recente studie van Peters en collega's (2013), waarin een associatie tussen impulsiviteit en een zwakkere behandelingsmotivatie bij verslaafde individuen werd gedocumenteerd (Peters, Petry, Lapaglia, Reynolds, & Carroll, 2013). Behandelingsmotivatie op zijn beurt, is een belangrijke voorspeller van de behandelingsretentie (Simpson, & Joe, 1993). Desalniettemin zijn er actueel geen studies die beide aspecten van mediatie hebben onderzocht: met name dat impulsiviteit gerelateerd is aan een zwakkere behandelingsmotivatie, en dat deze zwakkere behandelingsmotivatie resulteert in een kortere behandelingsduur. Evidentie voor een dergelijk indirect verband zou kunnen leiden tot het opstellen van specifieke richtlijnen omtrent de behandeling van de meest impulsieve drugafhankelijke individuen.

Voorliggend doctoraatsonderzoek tracht aan bovengenoemde tekortkomingen tegemoet te komen door een meer diepgaand onderzoek naar de relatie tussen impulsiviteit, drop-out en herval. Bijzondere aandacht gaat uit naar de multidimensionele aard van impulsiviteit. De relatie tussen impulsiviteit en behandelingsuitkomsten wordt bovendien onderzocht in de context van diverse klinische settings. Ten slotte wordt aandacht gegeven aan twee indirecte verbanden tussen impulsiviteit en behandelingsuitkomsten.

Inhoud van het proefschrift

In een eerste hoofdstuk *(cf. Hoofdstuk 1)* werden de belangrijkste begrippen van het doctoraat toegelicht (i.e., impulsiviteit, verslaving). Vervolgens werden beperkingen van eerder onderzoek naar de relatie tussen impulsiviteit en behandelingsuitkomsten bij drugafhankelijke individuen besproken, en werd aangegeven hoe er met voorliggend doctoraatsonderzoek getracht wordt hieraan tegemoet te

komen. Het hoofdstuk eindigde met een kort overzicht van de verschillende studies die deel uitmaken van het doctoraatsonderzoek.

De eerste studie van dit doctoraatsonderzoek, waarvan de resultaten beschreven werden in *Hoofdstuk 2* van dit proefschrift, kan gezien worden als een introductie in het thema impulsiviteit bij verslaving. In deze studie werden cocaïneafhankelijke individuen met en zonder een ADHD diagnose en een groep van gezonde controles vergeleken in hun scores op diverse impulsiviteitmaten, i.e., BIS-11, SST, DDT en IST. Dit onderzoeksopzet liet toe om na te gaan of (1) impulsiviteit bij cocaïneafhankelijke individuen (in vergelijking met gezonde controles) specifiek geassocieerd is met een comorbide ADHD-problematiek, en (2) of de aanwezigheid van een comorbide ADHD-problematiek bij cocaïneafhankelijke individuen gepaard gaat met hogere scores op bepaalde impulsiviteitdimensies. Uit deze studie bleek vooreerst dat impulsiviteit bij cocaïneafhankelijke individuen niet enkel het gevolg is van of samenhangt met een comorbide ADHD-problematiek. Ook cocaïnegebruikers zonder ADHD (1) rapporteerden een hogere mate van motor, non-planning en attentional impulsivity op de BIS-11, (2) hadden meer tijd nodig om geautomatiseerde motorische reacties te onderdrukken op de SST (i.e., motor disinhibition) en (3) verzamelden minder informatie alvorens een beslissing te nemen op de IST (i.e., reflection impulsivity) in vergelijking met een groep van gezonde controles. De enige uitzondering hierop werd gevonden op de DDT: in vergelijking met gezonde controles bleken enkel cocaïneafhankelijke individuen met ADHD een significant meer uitgesproken devaluatie van uitgestelde beloningen te vertonen op deze taak.
Een vergelijking tussen cocaïnegebruikers met en zonder ADHD toonde aan dat de comorbide groep hoger scoorde op twee specifieke impulsiviteitdimensies: delay discounting en non-planning impulsivity. Cocaïnegebruikers met een comorbide ADHD-problematiek lijken zich m.a.w. te onderscheiden van cocaïnegebruikers zonder ADHD door een sterkere ‘bias’ ten aanzien van het heden, en een meer uitgesproken ‘ongevoeligheid’ voor de toekomst (of uitgestelde gevolgen). Deze verschillen bleven significant wanneer er gecontroleerd werd voor de aanwezigheid van poly-druggebruik. De twee klinische groepen verschilden niet significant op het niveau van een aantal andere druggerelateerde variabelen (e.g., duur cocaïnegebruik, beginleeftijd, frequentie druggebruik gedurende de 30 dagen voorafgaand aan de behandeling). Bijgevolg zouden de hogere impulsiviteitscores in de comorbide groep aan het cocaïnegebruik vooraf zijn kunnen gegaan, en als een kwetsbaarheidfactor hebben kunnen gefungeerd voor de ontwikkeling van een cocaïneafhankelijkheid. Een alternatieve interpretatie is dat cocaïnegebruik bij individuen met een ADHD-problematiek interageert met de pathosfysiologie onderliggend aan deze stoornis, en aanleiding geeft tot meer uitgesproken wijzigingen in fronto-striatale en limbische hersenregio’s (Preller et al., 2013). Het cross-sectionele opzet van deze studie laat echter geen precieze conclusies toe met betrekking tot de causaliteit van de vastgestelde impulsiviteitverschillen en bijgevolg is meer onderzoek nodig.

In een tweede studie *(cf. Hoofdstuk 3)* werd de beschikbare literatuur betreffende de relatie tussen neurocognitieve impulsiviteitdimensies en behandelingsuitkomsten bij verslaving systematisch geanalyseerd. Uit deze literatuurstudie bleek vooreerst dat de rol van motor disinhibition in het

voorspellen van abstinentie/herval bij personen met een verslavingsproblematiek wellicht beperkt is: vijf van de zes geselecteerde studies die deze relatie onderzochten vond geen verband. Consistent met deze bevinding toont dierenonderzoek aan dat motor disinhibition minder betrokken is bij de persistentie van verslavingsgedrag, en wellicht eerder een rol speelt in de initiële stadia van het verslavingsproces (Broos et al., 2012; Diergaarde et al., 2008). De literatuurstudie leverde verder relatief consistente evidentie op voor de rol van interferentiecontrole over druggerelateerde woorden in het voorspellen van herval. Meer specifiek werd er in alle geselecteerde studies die deze impulsiviteitdimensie onderzochten (n=5) een relatie met herval/abstinentie gerapporteerd.

Het literatuuronderzoek leverde ook relatief consistente evidentie op ter ondersteuning van een relatie tussen delay discounting en abstinentie/herval bij individuen met een verslavingsproblematiek. Een meerderheid van de geselecteerde studies (10/13) toonde aan dat drugafhankelijke individuen die sterker geneigd zijn om uitgestelde beloningen te devalueren meer problemen ondervinden bij het initiëren, bereiken of behouden van abstinentie.

Ten slotte bevestigde het literatuuronderzoek ook de klinische/prognostische relevantie van impulsive decision-making. Meer specifiek vonden zes van de zeven geselecteerde studies een relatie tussen impulsive decision-making en abstinentie/herval. Inadequaat of suboptimaal keuzegedrag blijkt m.a.w. een belangrijke risicofactor te zijn voor herval.

Uit een analyse van enkele recente studies bleek dat het negatieve effect van impulsiviteit op de behandelingsuitkomsten bij individuen met een verslavingsproblematiek 'gebufferd' kan worden door bepaalde behandelingskenmerken (Passetti et al., 2011; Washio et al., 2011). Passetti en collega's (2011) vonden bijvoorbeeld dat dysfuncties op het niveau van besluitvorming (decision-making) gepaard gingen met een ongunstige behandelingsrespons in een ambulante, maar niet in een residentiële behandelingssetting. Confirmatie van deze en andere bevindingen zou in de toekomst kunnen leiden tot zeer concrete richtlijnen met betrekking tot het 'matchen' van bepaalde drugafhankelijke individuen aan specifieke behandelingssettings of interventies.

Uit het literatuuronderzoek bleek dat studies naar de relatie tussen impulsiviteit en behandelingsdrop-out of retentie uiterst schaars zijn. Om aan deze beperkingen tegemoet te komen, werd er in een derde studie *(cf. Hoofdstuk 4)* aandacht besteed aan de relatie tussen impulsive decision-making en behandelingsdrop-out binnen de context van drugvrije therapeutische gemeenschappen (TGs). Twee neurocognitieve taken die verschillende aspecten van decision-making in kaart brengen, de IGT en Cambridge Gamble Task (CGT), werden voorgelegd aan een groep van cocaïneafhankelijke individuen (n=150) tijdens de eerste weken van hun behandelingsdeelname. Cocaïnegebruikers die de behandeling vroegtijdig verlieten (n=84) werden geclassificeerd als 'drop-outs'. Cocaïnegebruikers die de behandeling succesvol afrondden (n=66) werden daarentegen geclassificeerd als 'treatment completers'. In tegenstelling tot de typisch normatieve trend op de IGT (gezonde individuen leren doorheen het verloop van deze taak systematisch vaker kaarten te selecteren van de voordelige stapels), vertoonde de drop-out-groep geen duidelijk leerpatroon doorheen de taak: deze groep bleef een voorkeur vertonen voor kaarten uit de nadelige stapels, zoals onder meer geïllustreerd in de (nog steeds) negatieve scores van deze groep tijdens de laatste 20 trials van de IGT (blok 5). Verder bleek de drop-out-groep minder vaak de meest waarschijnlijke optie te selecteren tijdens het uitvoeren van

de CGT, ondanks de aanwezigheid van expliciete kansinformatie. Zowel scores op blok 5 van de IGT als de kwaliteit van de beslissingen op de CGT droegen bij aan het voorspellen van behandelingsdrop-out. Suboptimaal keuzegedrag, waarbij geen rekening wordt gehouden met eerdere ervaringen en/of kansinformatie, lijkt m.a.w. gepaard te gaan met een hoger risico op drop-out.

In *Hoofdstuk 5* werd aandacht gegeven aan de rol van delay discounting in het voorspellen van de behandelingsretentie in een heterogene groep van drugafhankelijke individuen. Een tweede doelstelling van deze studie was om na te gaan of de relatie tussen delay discounting en de behandelingsduur gemedieerd werd door behandelingsmotivatie. De DDT en een Nederlandstalige versie van de TCU Motivation for Treatment (MfT) schaal (De Weert-Van Oene, Schippers, De Jong, & Schrijvers, 2002) werden voorgelegd aan een groep drugafhankelijke individuen (n=84) tijdens de eerste week van hun deelname aan een sterk gestructureerd residentieel ontwenningsprogramma. De MfT meet drie aspecten van behandelingsmotivatie: problem recognition, desire for help en treatment readiness. Hoewel delay discounting niet correleerde met de eerste twee dimensies, werd een significante (negatieve) correlatie tussen delay discounting en treatment readiness gevonden. Deze dimensie verwijst naar de mate waarin de gebruiker bereid is om zich actief te engageren in de behandeling. Een mogelijke verklaring voor deze negatieve correlatie is dat drugafhankelijke individuen die hoger scoren op delay discounting sterk gestructureerde behandelingsprogramma's als te veeleisend ervaren, of minder vertrouwen hebben in hun vermogen om het gebruik stop te zetten. Dit zou kunnen leiden tot minder optimistische verwachtingen betreffende de voordelen van een behandelingsdeelname. Een dergelijke verklaring zou in lijn liggen met de vaststelling dat minder hoop op verandering één van de vaakst vernoemde redenen is voor een vroegtijdige behandelingsdrop-out bij individuen met een verslavingsproblematiek (Ball, Carroll, Canning-Ball, & Rounsaville, 2006). Bovendien kan ook verwacht worden dat een expliciete toekomstoriëntatie een noodzakelijke voorwaarde is om de voordelen verbonden aan een behandelingsdeelname voldoende te valueren. Deze voordelen, zoals een verbeterde gezondheid of tewerkstelling, treden doorgaans immers pas op na een zeker tijdsinterval (i.e., uitstel). Een regressieanalyse toonde aan dat delay discounting significant bijdroeg aan de voorspelling van drop-out en een kortere behandelingsduur, ook wanneer gecontroleerd werd voor een aantal andere (eerder gevestigde) voorspellers van retentie of drop-out (e.g., leeftijd, ADHD).
Een mediatie-analyse met delay discounting als predictor, treatment readiness als mediator en behandelingsretentie als uitkomstindicator wees uit dat het negatieve effect van delay discounting op de behandelingsduur gedeeltelijk indirect was, i.e., gemedieerd door treatment readiness. Meer specifiek bleek dat een sterkere devaluatie van uitgestelde beloningen geassocieerd was met een zwakkere treatment readiness, en bleek deze zwakkere treatment readiness vervolgens aanleiding te geven tot een kortere behandelingsduur.

In een vijfde studie *(cf. Hoofdstuk 6)* werd de relatie tussen diverse impulsiviteitdimensies en herval onderzocht. Eén van de doelstellingen van deze studie was om na te gaan of bepaalde impulsiviteitdimensies meer relevant zijn in het voorspellen van herval dan anderen. Conform met de groeiende evidentie voor een samenhang tussen impulsiviteit en een kortere behandelingsduur

enerzijds, en een kortere behandelingsduur en herval anderzijds (Stevens et al., 2014; Zhang, Friedmann, & Gerstein, 2003), werd bovendien onderzocht of de relatie tussen impulsiviteit en herval gemedieerd werd door behandelingsretentie. De UPPS impulsiviteitschaal en 4 neurocognitieve taken (SST, DDT, IGT, IST) werden voorgelegd aan drugafhankelijke individuen (n=70) tijdens de eerste week van hun deelname aan een residentieel ontwenningsprogramma. Drie maanden na deze baselinemeting vond een telefonisch follow-up interview plaats, waarin gepeild werd naar de herval- of abstinentiestatus van iedere deelnemer. Herval werd gedefinieerd als ieder gebruik van een illegaal middel tijdens de maand voorafgaand aan het follow-up gesprek. Op basis van deze definiëring werden 29 deelnemers geclassificeerd als abstinent, en werden 41 deelnemers geclassificeerd als hervallen. In vergelijking met de groep die abstinent was op het ogenblik van het follow-up interview, vertoonde de groep hervallers bij aanvang van de behandelingsdeelname (1) hogere scores op de UPPS-dimensie 'sensation seeking', (2) een sterkere devaluatie van uitgestelde beloningen op de DDT, en (3) negatievere net scores op de IGT. Parallel met de bevindingen van het literatuuronderzoek *(cf. Hoofdstuk 3),* verschilden beide groepen niet in hun prestaties op een taak die de mate van motor (dis)inhibition meet (i.e., SST).

Met als doelstelling na te gaan of persoonlijkheidsdimensies van impulsiviteit unieke variantie in herval kunnen verklaren bovenop de variantie in herval die verklaard wordt door neurocognitieve impulsiviteitdimensies, werd een multiple, stapsgewijze logistische regressieanalyse uitgevoerd. In een eerste stap werd enkel sensation seeking (persoonlijkheidsdimensie) ingevoerd. In een tweede stap werden delay discounting en decision-making (neurocognitieve impulsiviteitdimensies) aan dit model toegevoegd. Hoewel sensation seeking in een univariate logistische regressie significant bijdroeg aan de predictie van herval, werd dit effect non-significant eens de neurocognitieve variabelen aan het regressiemodel werden toegevoegd. Bijgevolg blijkt sensation seeking geen unieke variantie in hervalstatus te verklaren bovenop de variantie die verklaard wordt door delay discounting en decision-making. Deze bevinding is consistent met duale procesmodellen van verslaving, waarin geponeerd wordt dat de instandhouding van verslaving het gevolg is van een verstoorde balans tussen twee neurale systemen: een impulsief/automatisch bottom-up systeem en een cognitief/controlerend top-down systeem (Wiers, Ames, Hofmann, Krank, & Stacy, 2010). De dynamische interactie tussen of de relatieve invloed van beide systemen wordt wellicht beter in kaart gebracht door neurocognitieve taken die een beroep doen op de wisselwerking tussen beide systemen (McClure, Laibson, Loewenstein, & Cohen, 2004). Zelfrapportage-vragenlijsten daarentegen, meten doorgaans slechts de invloed van één van beide systemen. Bovendien kunnen vragen gesteld worden bij de validiteit en betrouwbaarheid van vragenlijsten: de aanwezigheid van een impulsieve persoonlijkheidsstijl kan het invullen van deze vragenlijsten beïnvloeden, wat een betrouwbare interpretatie bemoeilijkt. Het voordeel van neurocognitieve taken is dat ze nauw samenhangen met onderliggende neurobiologische functionele circuits en wellicht een objectievere invalshoek bieden op de aanwezigheid van impulsieve gedragstendensen.

Conform met de tweede doelstelling van deze studie werden twee mediatie-analyses uitgevoerd, met delay discounting en/of impulsive decision-making als predictoren, behandelingsretentie als mediator, en herval als de afhankelijke variabele. Deze analyses leverde overtuigende evidentie op voor een

indirect verband tussen impulsiviteit en herval. Meer impulsieve keuzepatronen op de DDT en IGT bleken geassocieerd te zijn met een minder lange behandelingsduur, en deze kortere behandelingsduur bleek samen te hangen met een hoger risico op herval. Deze studie toont aan dat de meest impulsieve druggebruikers uit het hulpverleningsnetwerk dreigen uit te vallen nog voor impulsiviteit adequaat behandeld kan worden (i.e., tijdens de eerste weken van hun deelname aan een ontwenningsprogramma). Deze vroegtijdige behandelingsdrop-out verhoogt bovendien het risico op herval, en verkleint de kans dat deze groep zal doorstromen naar het meer gespecialiseerde hulpverleningsaanbod. Het verhogen van de behandelingsretentie in de meest impulsieve drugafhankelijke individuen is dan ook een prioriteit.

In een laatste hoofdstuk *(cf. Hoofdstuk 7)* werd ten slotte ingegaan op de belangrijkste bevindingen van het doctoraatsonderzoek: impulsiviteit bij individuen met een verslavingsproblematiek blijkt een risicofactor te vormen voor een kortere behandelingsduur, vroegtijdige behandelingsdrop-out en herval. Herval bij drugafhankelijke individuen lijkt het beste voorspeld te worden door neurocognitieve taken die een beroep doen op de wisselwerking tussen automatische/impulsieve en reflectieve/controlerende hersenprocessen, zoals drugversies van de Stroop taak, de DDT en de IGT. Dit in tegenstelling tot neutrale versies van de SST of Go/No-Go taak en/of vragenlijsten, die slechts één van beide processen in kaart brengen. Het risico op herval bij druggebruikers die hoger scoren op enkele impulsiviteitdimensies (i.e., delay discounting en impulsive decision-making) wordt in belangrijke mate gemedieerd door een kortere behandelingsretentie. Een kortere behandelingsduur bij deze groep hangt bovendien (deels) samen met een zwakkere behandelingsbereidheid (treatment readiness).

Vervolgens werden de klinische implicaties van de bevindingen uit het doctoraatsonderzoek toegelicht. Er werd beargumenteerd dat impulsiviteit een prominentere plaats dient te krijgen in het klinische besluitvormingsproces en in de behandeling van verslaving. Drugafhankelijke individuen zouden bij aanvang van hun behandelingsdeelname gescreend kunnen worden met behulp van neurocognitieve impulsiviteitstaken. Slechtere prestaties op deze taken zouden vervolgens als een alarmsignaal kunnen fungeren voor hulpverleners dat deze individuen extra begeleid/omkaderd moeten worden, of eventueel dienen te worden doorverwezen naar een meer gerichte behandelingsmodaliteit. De daadwerkelijke vertaling van neurocognitieve testprestaties in concrete richtlijnen betreffende het matchen van bepaalde individuen aan specifieke interventies, vraagt echter om de beschikbaarheid van klinisch significante cut-off scores. Een tweede prioriteit in het streven naar gunstigere behandelingsuitkomsten voor de meest impulsieve druggebruikers is het verhogen van de behandelingsretentie. Het doctoraatsonderzoek toont aan dat druggebruikers met hogere impulsiviteitscores al erg vroeg in het behandelingsproces door de mazen van het net dreigen te glippen, d.w.z., gedurende hun deelname aan ontwenningsprogramma's. Ontwenningsprogramma's vormen doorgaans slechts een eerste stap binnen het bredere hulpverleningsproces, en zijn zelden effectief op zichzelf. Daarentegen fungeren ze als een bijzonder belangrijke toegangspoort naar verdere, meer gespecialiseerde behandelingsopties. Een vroegtijdige uitval uit deze programma's reduceert echter de kans dat de meest impulsieve druggebruikers zullen doorstromen naar het meer gespecialiseerde hulpverleningsaanbod. Bovendien neemt het risico op herval aanzienlijk toe *(cf.*

Hoofdstuk 6). Inspanningen gericht op het verhogen van de behandelingsretentie en het reduceren van vroegtijdige drop-out in deze individuen zijn dan ook een prioriteit.

In *Hoofdstuk 7* werden enkele interventies voorgesteld die zinvol zouden kunnen zijn in dit verband, waaronder het werken met financiële incentives of vouchers en de implementatie van strategieën gericht op het verhogen van de behandelingsmotivatie. Uitgaande van de veronderstelling dat onze huidige behandelingsprogramma's onvoldoende zijn afgestemd op het profiel van de meest impulsieve druggebruikers, werd bovendien gewezen op het belang van enkele structurele aanpassingen of modificaties. Er werd kritisch gereflecteerd op de (on)toegankelijkheid van sterk gestructureerde of cognitief intensieve behandelingsmodellen, waarin de cognitieve draaglast doorgaans hoog is en er hoge eigen worden gesteld met betrekking tot het uitstellen van onmiddellijke behoeftebevrediging. Er werd gepleit voor een meer graduele opbouw van de behandelingsintensiteit, inclusief de cognitieve draaglast.

Conform met de vaststelling dat een zwakkere interferentiecontrole over druggerelateerde woorden, delay discounting en impulsive decision-making gepaard gaan met een hoger risico op herval, werden in *Hoofdstuk 7* van dit proefschrift enkele interventies toegelicht die beloftevol lijken in het reduceren van deze neurocognitieve uitingsvormen van impulsiviteit. Meer specifiek werd gewezen op de potentiële relevantie van cognitieve training (met name werkgeheugentraining), farmacologische interventies (met name 'cognitive enhancers'), hersenstimulatie, attentional bias modification en mindfulness training. Er werd beargumenteerd dat een combinatie van bovenvermelde interventies en strategieën wellicht noodzakelijk is wil men de behandelingsuitkomsten van de meest impulsieve druggebruikers verbeteren. Een integratie van deze diverse benaderingen vraagt om een open dialoog tussen diverse wetenschapsparadigma's (empirisch-analytisch, existentieel fenomenologisch), vrij van dogma's, vanuit een onderlinge verbondenheid in het streven naar de beste oplossing voor een specifiek individu en de samenleving als geheel (Broekaert, Autrique, Vanderplasschen, & Colpaert, 2010).

Ten slotte werden in *Hoofdstuk 7* enkele beperkingen van het doctoraatsonderzoek belicht. Deze beperkingen werden gekoppeld aan aanbevelingen voor toekomstig onderzoek. Een zinvolle piste voor toekomstige studies is om na te gaan of en op welke manier impulsiviteit interageert met behandelingskenmerken in het voorspellen van drop-out. Aandacht voor het perspectief van de cliënt zelf is hierbij onontbeerlijk. In eenzelfde lijn is er een nood aan studies die de relatie tussen impulsiviteit en behandelingsuitkomsten gelijktijdig bestuderen in diverse settings (residentieel vs. ambulant). Dit soort onderzoeksdesigns laat toe om een beter inzicht te verwerven op de specifieke condities waarin of waaronder impulsiviteit geassocieerd is met een (on)gunstige behandelingsrespons. Toekomstige studies dienen bovendien na te gaan of impulsiviteit een modererende factor is voor de effectiviteit van bepaalde interventies. Verder onderzoek naar impulsiviteit kan verregaande gevolgen hebben voor de behandeling van verslaving.

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