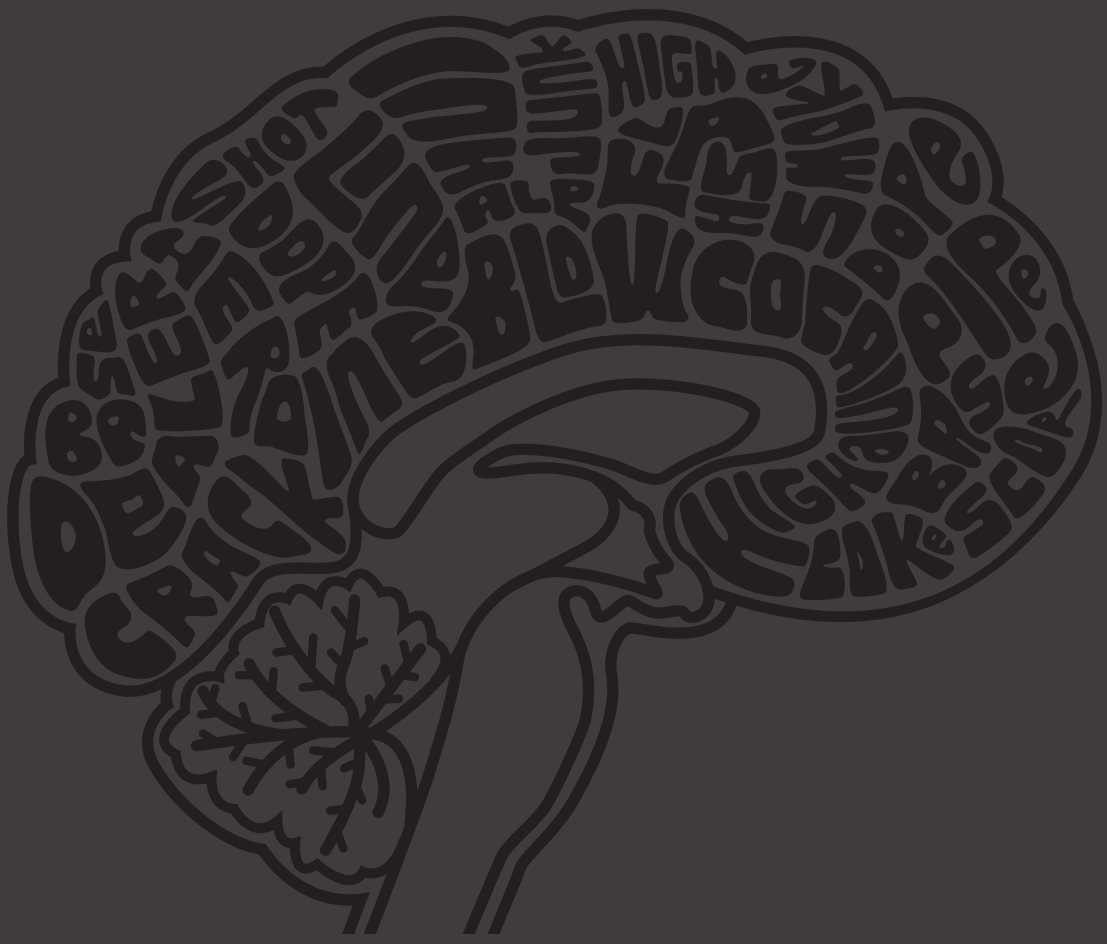

NEUROCOGNITIVE PREDICTORS OF DRUG RELAPSE

RESHMI MARHE

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Cover by: Sidney Latuperissa
Layout by: Sidney Latuperissa
Printed by: GVO drukkers & vormgevers B.V. | Ponsen & Looijen, Ede, The Netherlands

ISBN: 978-90-6464-648-5

The research described in this thesis was financially supported by grants from the Netherlands Organisation for Health Research and Development (Chapter 2 and 3: ZonMw 31180001 to IHA Franken; Chapter 4 and 5: ZonMw 31160203 to IHA Franken) and the National Institute on Drug Abuse, US (Chapter 2 and 3: R01 DA020436-S3 to AJ Waters). The contributing authors of all studies in this thesis have no financial competing interests.

NEUROCOGNITIVE PREDICTORS OF DRUG RELAPSE

Neurocognitieve voorspellers van terugval in druggebruik

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

prof.dr. H.G. Schmidt

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
22 maart 2013 om 11.30 uur

door

Reshmi Marhe

geboren te Paramaribo
Suriname

ERASMUS UNIVERSITEIT ROTTERDAM

Promotiecommissie

Promotor

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Prof. dr. W. van den Brink

Contents

Chapter 1

General introduction

Addiction: a relapsing disorder

Worldwide, about 35 million people, that is 0.8% of the world's adult population, use heroin and/or cocaine and more than 10-13% of these drug users are or will become drug dependent (UNODC, World Drug Report, 2012). Drug dependency is characterized as a chronic relapsing disorder (Leshner, 1997; McLellan et al., 2000). Substance dependent individuals often relapse, despite their efforts to stay abstinent (APA, 1994). Hence, the major goal of treatment facilities is to prevent treatment dropout and subsequent relapse. Unfortunately, about 50% of heroin and cocaine dependent patients already dropout in the first phase of clinical treatments, which is the detoxification phase. These dropout rates are consistent across several countries and remained steady over the years (the Netherlands: Franken and Hendriks, 1999; Switzerland: Hättenschwiler et al., 2000; United Kingdom: Gossop et al., 2002; Day and Strang, 2011). In addition, treatment dropout is associated with higher relapse rates (Gossop et al., 1987, 2002). There is ample room for improving these dropout and relapse rates of substance dependent patients. To improve treatment for these patients we first have to know the factors predicting relapse.

Predictors of substance relapse: from explicit to implicit cognitive measures

Over the years, several variables have been studied in relation to treatment compliance and substance relapse. Among these variables are demographical characteristics such as race, age, education, and gender; and other variables such as drug use severity, medical problems, and psychopathology (for reviews see Stark, 1992; Poling et al., 2007). In addition, self-report (or explicit) measures of emotional states such as negative affect (Shiffman and Waters, 2004), and drug-related states such as attitude towards drug use (Burden and Maisto, 2000) and craving (Weiss et al., 2003; Preston et al., 2009) have also found to be predictive of substance relapse. However, while craving plays an important role in theories of addiction and relapse (e.g., Robinson and Berridge, 1993; Franken, 2003 described in detail below), some studies report no relationship with substance relapse (Weiss et al., 1995; Bordnick and Schmitz, 1998). These mixed findings might depend on differences in the assessment of craving (Sayette et al., 2000; Rosenberg, 2009; McKay, 1999), for example single laboratory measures versus repeated (real-time) measures in a natural environment using ecological momentary assessment (EMA).

The use of hand-held computers (Personal Digital Assistants; PDAs) in an EMA setting has facilitated longitudinal data collection of fluctuating drug-related processes such as craving (Shiffman et al., 1996). EMA involves assessing phenomena at the moment they occur ("momentary") in a person's natural environment ("ecological"). Assessments are done at

random times and/or when participants experience heightened emotions (e.g., feeling particularly stressed or experience cravings). The data are highly detailed and can reveal patterns of change within a day, or even within a few hours (e.g., Shiffman and Waters, 2004), that cannot be obtained using standard retrospective techniques. Recent EMA studies in heroin and cocaine dependent patients have reported that self-reports of mood, temptations to use and cue exposure are elevated in the hours before craving and use (Epstein et al., 2009) and, most interestingly, that craving is elevated in the hours preceding drug use (Preston et al., 2009).

Although EMA is beneficial to measure changes over time in self-reported craving levels, an important limitation of using self-report measures is that people – and particularly drug dependent individuals – may have low insight in their motivations and misrepresent their thoughts and feelings, or their reports may be biased due to social desirability (Hammersley, 1994; Marissen et al., 2005). This is less of a problem in cognitive measures (i.e., reaction time tasks) because participants are often unaware of the purpose of the assessment. Most importantly, automatic (or fast) cognitive processes that are unavailable to conscious introspection ("implicit processes") can influence behavior (e.g., Fazio and Olson, 2003). These implicit processes cannot be assessed by self-reports, which can only measure more conscious/controlled processes ("explicit processes"), but can be assessed by cognitive-psychological assessments. In addition, such assessments have been successfully implemented on PDAs for assessment in the natural environment (Waters and Li, 2008).

In addiction research, there has been much recent interest in the use of behavioral and neurobiological measures to examine implicit cognitive processes underlying addiction. Additionally, implicit cognitive and physiological measures hold some promise in predicting drug relapse and may even be able to better predict outcomes than explicit measures (e.g., Marissen et al., 2006; Brewer et al., 2008) perhaps by bypassing conscious or subconscious processes. Before elaborating upon the association between cognitive processes and substance relapse, an overview of important theories on implicit cognition in addiction will be described.

Cognitive and neurobiological processes in addiction

Automatic "drive" processes

In the early '90s, theories of addiction started highlighting the role of automatic cognitive processes. Tiffany (1990) proposed that in heavy drug dependents, drug use behavior has become an entirely automatic process (like brushing your teeth) and only if this automatic behavior is interrupted, non- automatic processes such as craving emerge. Another

influential cognitive-biological theory of addiction is the incentive-sensitization theory (Robinson and Berridge, 1993). According to this theory, repetitive drug use sensitizes dopaminergic neurotransmission in the brain's mesolimbic reward system up to a point that merely the perception (and not only the use) of drugs or drug cues becomes salient. Because of this incentive salience that is being attributed to drug-related stimuli, attention is automatically oriented to these stimuli. The automatic attention capture of drug cues, or attentional bias, is the focus of Franken's model (2003). This model illustrates that enhanced attentional bias for drug-related stimuli can elicit and increase subjective craving and vice versa, and that the excitatory relationship between the two processes can cause drug use and relapse. Reaction time tasks that have generally been used to measure attentional bias are substance use-versions of the Stroop task and visual dot-probe task (Cox et al., 2006; Robbins and Ehrman, 2004). The key idea behind both measures is that substance dependent people are distracted from task performance (i.e., color naming or locating the dot) when their attention is captured by the substance-related content of the stimuli, indicated by a slower response to substance-related stimuli than to neutral stimuli. The presence of an attentional bias to substance cues in dependent individuals has been confirmed by a wide range of empirical studies (for a review see Cox et al., 2006) and its association with self-reported craving has also been supported (for a meta-analysis see Field et al., 2009).

Recently, there has been much interest for investigating the neurobiological substrates of attentional bias. Functional magnetic resonance imaging (fMRI) studies have showed that attentional bias to substance cues (contrasted against neutral cues) is associated with activity in prefrontal brain areas such as the anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (DLPFC; Hester and Garavan, 2009; Luijten et al., 2011a, 2012; Nestor et al., 2011; Völlstadt-Klein et al., 2012; Janes et al., 2010b), other cortical areas such as the insula (Luijten et al., 2011a; Vollstädt-Klein et al., 2012; Janes et al., 2010b) and also in subcortical areas such as the nucleus accumbens (Nestor et al., 2011) and amygdala (Janes et al., 2010a; Völlstadt-Klein et al., 2012). It is suggested that these brain regions play a role in the cycle of drug addiction; that is, the nucleus accumbens and amygdala are evidently involved in the bottom-up process of salience attribution to substance related stimuli while at the same time top-down attentional resources of the prefrontal executive areas might be impaired or depleted when focusing on cognitive tasks in the presence of distracting drug-related cues (Goldstein and Volkow, 2002; 2011).

Another important automatic cognitive process in addiction is implicit affective asociations in memory (Wiers and Stacy, 2006). The premise of this process is that drug dependent individuals develop several associations with the use of drugs (e.g., reinforcing effects). Consequently, when drugs or drug-related stimuli are perceived, these associations in memory automatically activate (Stacy and Wiers, 2010). A widely used task to measure these automatic memory associations is the Implicit Association Test (IAT; Cunningham et

al., 2001; Greenwald et al., 2003). The IAT (at least the version that is used in the present thesis) is comprised of two tasks. In task 1, participants are asked to respond rapidly with a specific key press to items representing two concepts (e.g., drugs + positive), and with a different key press to items from another two concepts (e.g., not drugs + negative). In task 2, the assignments for one of the concept pairs is switched (such that not drugs + positive share a response, likewise drugs + negative). The key idea behind the IAT is that it is easier to map two concepts onto a single response when those concepts are more strongly associated in memory than when the concepts are unrelated or dissimilar (De Houwer, 2002). The critical measure (the IAT effect) is the difference in response times on task 1 compared to task 2. In studies that use substance-related stimuli and valence (i.e., positive and negative) as concepts, the IAT effect is an index of the relative strength of implicit positive or negative attitudes towards drugs. The IAT has been used to investigate associative memory in psychopathology, including substance use disorders (for a review see Roefs et al., 2011). While it is expected that substance users generally exhibit a significantly more positive (less negative) implicit attitude with substance-related stimuli, studies in alcohol dependents and smokers have shown that they experience a more negative implicit attitude with the substance of abuse, while cocaine dependents have showed more positive, arousing and sedative associations with drugs. In addition, several studies reported an association between more self-reported use and exhibiting more positive implicit attitudes towards the substance of abuse (Roefs et al., 2011).

In sum, automatic substance-related cognitions such as attentional bias and implicit memory associations are related to substance use and these processes might contribute to the motivation to continue using the substance. In addition, the ability to control drives or urges is also important for optimal behavior. Recent views posit that this ability is diminished in addiction (see figure 4 in Volkow et al., 2004) which will be discussed next.

Control processes

Cognitive control processes, or executive functions, such as behavior monitoring, inhibitory and attentional control are essential functions in order to pursue goal-directed behavior. Consider the example of a person entering a bar on a hot summer day whose attention is drawn to a glass of beer on the table and who remembers that a beer is a nice thirst-quencher. This drives the person towards drinking a beer. However, the individual realizes that (s)he cannot have too many beers because (s)he has to attend an important meeting early the next morning and too many beers always give him/her a headache. Hence, the individual will not drink more than one beer and controls his/her urge to drink more (Volkow et al., 2004). This might be the case in non-substance dependent people, however concerning addiction recent theories stress the disability of substance dependent patients to exert cognitive control over their behavior in particular in conditions that deplete recourses, like

craving or cue-elicited drug-taking scenarios (Goldstein and Volkow, 2002; Garavan and Hester, 2007; Field and Cox, 2008). Prefrontal areas including the ACC and DLPFC are believed to be important areas for executive cognitive functions regulating cognitive control functions (Botvinick et al., 2001; Carter and Van Veen, 2007). There are indications that these control processes are compromised in substance dependent patients, suggesting impaired prefrontal functions (Goldstein and Volkow, 2011; Hester and Garavan, 2004).

A basic neurocognitive index of cognitive control is error processing. Error processing is an element of behavior monitoring and refers to the ability to adequately process negative consequences in order to appropriately adapt subsequent behavior. One of the hallmark characteristics of addiction is that substance dependent individuals continue to use substances despite the negative consequences such as social, interpersonal or physical problems (APA, 1994). Paradigms that are typically used to measure error processing are the Flanker task and the Go-Nogo task; both fast reaction-time tasks where it is inevitable to make errors. There are several studies showing that substance use and dependence is associated with deficits in error processing. For example, it has been observed that cocaine dependent patients have a reduced error processing on a behavioral and neurophysiological level (Franken et al., 2007). Recordings of event-related potentials (ERPs) during performance on an Eriksen flanker task (Eriksen and Eriksen, 1974) revealed that cocaine dependent patients showed reduced error related negativity (ERN) and error positivity (Pe) components - both electrophysiological indices of error processing - as compared to a control group. On the behavioral level, patients showed reduced post- error accuracy improvement. In contrast, another study among active cocaine users found that they do adjust their behavior correctly after an error is made, however they have poor awareness of their errors (Hester et al., 2007). Regarding electrophysiological measures, reductions in the ERN component – which represents the brain's automatic detection of an error – have also been found by Sokhadze et al. (2008) in cocaine dependents and by Luijten et al. (2011) in smokers during the presence of task-irrelevant smoking cues. Furthermore, ACC functioning – which is also associated with error processing and has assumed to be the neural generator of the ERN (e.g., Miltner et al., 2003) – has also found to be diminished in opiate dependence (Forman et al., 2004), cocaine dependence (Kaufman et al., 2003), cannabis dependence (Hester et al., 2009), and nicotine dependence (De Ruiter et al., 2012). In contrast, it has been reported that alcohol dependent individuals show increased ERN amplitudes (Padilla et al., 2011; Schellekens et al., 2010) which is supposedly due to comorbid anxiety disorder in this specific population (Schellekens et al., 2010). Indeed, the ERN has found to be differentially associated with internalizing and externalizing psychopathology. That is, patients with internalizing psychopathology such as anxiety disorder and depression, show an enhanced ERN, while patients with externalizing psychopathology such as substance dependency show a reduced ERN (Olvet and Hajcak, 2008).

Theories regarding the ERN imply that besides representing the automatic detection of an error (e.g., Falkenstein et al., 1991) its magnitude reflects the ability to monitor ongoing behavior and is subsequently used to correctly adjust behavior (Holroyd and Coles, 2002; Yeung et al., 2004). A theory that speaks more to the individual differences in ERN magnitude proposes that it is involved in the emotional or motivational significance one attributes to an error (Hajcak et al., 2005). The reduced ERN found in most of the addictions arguably represents that errors are perceived as less meaningful or motivationally-relevant in substance dependent individuals, which may underlie their persistence of drug taking despite the adverse consequences.

Above mentioned studies have provided more insight in the fundamental processes that are involved in addictive behaviors. More clinically relevant is that a few studies have reported that cognitive and neurobiological measures of automatic and control processes in substance dependent individuals are prospectively associated with treatment outcome and substance relapse. These studies are described next.

Neurocognitive predictors of treatment outcome and relapse

Regarding automatic motivational processes there are number of studies that have examined whether behavioral attentional bias is a predictor of treatment outcome or substance relapse. In contrast, and to our best knowledge, there are no studies that have examined whether implicit associations (measured with the IAT) are predictive of treatment outcome or relapse in a clinical substance dependent sample. Regarding nonclinical samples it has been reported that implicit associations predict alcohol use at 1- month follow-up in heavy drinkers (Wiers et al., 2002) and marijuana use in a high-risk adolescent population (Ames et al., 2007). Results of the studies that have examined attentional bias are discussed below.

Attentional bias

Most studies have reported significant associations between attentional bias and outcome in several addictions (see Table 1 for an overview). In smokers most studies point to a significant association between smoking abstinence and attentional bias, as measured with the Stroop task (Waters et al., 2003a; Powell et al., 2010; Janes et al., 2010b). However, one study did not find this effect when using a visual dot-probe task (Waters et al., 2003b).

Concerning drug dependence, the results of Marissen et al. (2006) showed that attentional bias in heroin dependent patients, measured before the start of a clinical trial, was an adequate predictor of relapse at 3 month follow-up. Attentional bias was even a better pre-

dictor than self-reported craving. However, Carpenter et al. (2006) failed to show an effect of attentional bias on outpatient treatment outcome in heroin dependent patients, while in cocaine and in marijuana dependent individuals it was found that attentional bias was associated with treatment retention and positive urines. Surprisingly, in marijuana users attentional bias for cocaine and heroin, but not for marijuana, was predictive of their outcome.

In alcohol dependent patients pre-treatment attentional bias was not predictive of treatment outcome (Cox et al., 2002; Field et al., 2012). Cox et al. (2002) did find that, compared with control subjects and successful patients, unsuccessful patients showed an increase in attentional bias from pre-treatment to post-treatment assessment, suggesting that attentional bias might underlie recovery from alcohol dependence. In a study with excessive alcohol drinkers (not in treatment) it was found that participants with low attentional bias at baseline had a greater reduction in alcohol consumption on the long-term (6 months) than participants with high attentional bias at baseline (Cox et al., 2007) which might point to differences in motivational processes in alcohol abuse vs. dependence.

All studies that have examined the role of attentional bias in the identification of relapse vulnerable substance dependents have been conducted in a laboratory setting. However a drawback of this setting is that the relationship between attentional bias and relapse might diminish due to the large delay between the assessment of attentional bias and treatment outcomes/relapse. This might explain why the studies of Cox et al. (2002) and Powell et al. (2010) did not find associations with pre-treatment attentional bias and long term outcomes. Only the study by Marissen et al. (2006) reported an association between attentional bias and relapse on the longer term (3 months after treatment). Other studies suggest that it is a better predictor of relapse on the short term (1-week; Waters et al., 2003a; Powell et al., 2010). Another disadvantage of assessing attentional bias in a laboratory setting is that it cannot provide information on how this cognition is experienced in the natural environment of an individual or for example, during heightened feelings of craving and temptation. By using EMA methodology we are able to collect longitudinal data in the natural (or clinical) environment of a substance dependent patient and consequently examine possible changes in attentional bias over time. In addition, we can examine whether "momentary" attentional bias can predict relapse on the short- term. As previous research has reported that increases in craving levels can precede a relapse (Preston et al., 2009; Shiffman et al., 1997) it is possible that increases in attentional bias – which is associated with craving (Franken, 2003; Field et al., 2009) – also precede relapse.

A number of fMRI studies have used attentional bias paradigms to examine associated neural patterns in substance dependence (e.g., Hester and Garavan, 2009; Luijten et al., 2011a, 2012; Nestor et al., 2011). Yet, we are not aware of any fMRI studies that have

prospectively examined brain-activity during an attentional bias paradigm in relation to treatment outcome or relapse. There are however fMRI studies that have examined whether cue-reactivity to substance related stimuli vs. neutral stimuli (i.e., by means of passive viewing) might predict substance use outcomes (Table 1). Overall, these studies showed that mainly enhanced activity in prefrontal, sensory, motor and limbic (sub)cortical areas are associated with substance relapse (Kosten et al., 2006; Janes et al., 2010b; Beck et al., 2012; however no significant associations were reported in Heinz et al., 2007). Only Janes et al. (2010b) has examined to what extent both behavioral attentional bias for smoking-related words (measured with a Stroop task outside of the scanner) and reactivity of the brain to smoking cues (measured in the scanner) were predictive of smoking relapse and found that both measures were predictive of smoking lapse. In addition, anterior insula and dACC activation strongly correlated with respectively larger interference of drug-related words and low accuracy during the Stroop task, suggesting that these regions might be neural correlates of attentional bias important for identifying individuals at risk of relapse.

Cognitive control

Several studies have reported that substance dependency is associated with cognitive impairments in executive functions such as attention, inhibitory control and working memory and a few studies propose that these impairments are related to treatment dropout and substance relapse (for recent reviews see Garavan and Weierstall, 2012; Sofuoglu et al., 2013; Stevens et al., in revision). There are a number of behavioral studies that have examined associations with treatment outcome and relapse using classic executive tasks such as the Stroop color word interference task and the WCST (see above mentioned reviews for a detailed overview). A few of these studies are displayed in Table 1. For example, Aharonovich et al. (2006) found that impaired performance on several cognitive tests – but not the WCST – was associated with treatment non-completion in cocaine dependent patients. In contrast, Turner et al. (2009) did find associations between cocaine dependence treatment outcome and perseverative errors on the WCST, suggesting that individuals who repeated mistakes and did not benefit from feedback were less compliant to treatment. Speculatively, it might be that poor error processing on a neurophysiological level found in cocaine dependent patients (Franken et al., 2007; Sokhadze et al., 2008) is also related to poor treatment outcome or relapse. Note however that the results of Turner et al. (2009) were based on zero-order correlations between cognitive performance and treatment retention while Aharonovich et al. (2006) controlled for demographic variables (e.g., age, sex), cocaine use severity and comorbid depression and thus provided more information on the unique contribution of cognitive assessments to the prediction of treatment outcome. To our best knowledge, only studies by Passetti and colleagues have examined whether treatment compliance is as-

sociated with response inhibition using the Go-Nogo task, but they failed to find an association. There are no studies that have measured performance on the flanker task as possible predictor of treatment outcome.

Both the studies of Passetti et al. (2011) as well as Paulus et al. (2005) indicate that, respectively on the behavioral and neurological level, decision-making is associated with either treatment outcome or relapse into substance use. Interestingly, Paulus et al. (2005) were the first to report that brain-activity during a simple cognitive task (measured with fMRI) can predict relapse in methamphetamine addiction with high accuracy. In a study with cocaine dependent patients it was found that interference on the classical Stroop task was associated with treatment outcome, even after controlling for mild depressive symptoms (Streeter et al., 2008). Brewer et al. (2008) also found an association between behavioral performance on the Stroop and treatment outcome in cocaine dependent patients (though this was a moderate effect). Most interestingly, they showed that prefrontal and striatal brain activations during Stroop interference (i.e., involved in cognitive control) were associated with several measures of treatment outcome (although it should be noted that these results were also based on zero-order correlations, thus not pertaining to possible overlapping variance between these variables).

Together the majority of these studies indicate that basic cognitive and motivational processes might help to identify substance dependent patients that are at risk of treatment failure or relapse into substance use. The present thesis will add to this existing literature by examining whether implicit cognitive processes in real-time, attentional bias on the behavioral and neural level, and brain activity related to error processing are adequate predictors of relapse.

Outline of the present thesis

The general aim of this thesis is to investigate the neurocognitive mechanisms of addiction and associations with treatment processes and treatment outcomes. All studies reported in the upcoming four chapters have included heroin and/or cocaine dependent patients who are within their first week of detoxification treatment. Also, besides studying neurocognitive mechanisms, all studies have examined the influence of self-reported craving. In the first two chapters we used ecological momentary assessment (EMA) with self-report measures (e.g., level of craving) and reaction time tasks (i.e., drug Stroop task and IAT) implemented on hand-held computers (PDAs) to study these mechanisms in heroin and cocaine dependent patients during their first week of detoxification treatment.

In **chapter 2** we examined whether real-time measures of explicit (i.e., craving and explicit attitudes to drugs) and implicit drug-related cognitions (i.e., attentional bias and implicit associations) during the first week of detoxification treatment were associated with drug relapse during (1st week) and after (3 weeks) treatment. In addition, we investigated whether drug-related cognitions were elevated in the days preceding relapse. It was hypothesized that relapsers would exhibit elevated levels of self-reported craving, more positive explicit attitudes toward drugs, elevated levels of attentional bias and more positive implicit associations with drugs than nonrelapsers. In addition, given that previous studies found that craving is increased in the moments before a relapse (Preston et al., 2009; Shiffman et al.,1997) it was expected that attentional bias (which is associated with craving, Franken, 2003; Field et al., 2009) is also increased in the days before relapse.

In **chapter 3** we further examined the natural history of temptation episodes during the first week of detoxification treatment and whether real-time measures of self-reported negative affect, craving and explicit attitudes to drugs and implicit cognitive processes (i.e., attentional bias and implicit associations) were associated with temptations to use drugs. In addition, we investigated whether these measures were elevated in the hours preceding a temptation episode. We expected that drug dependent patients would exhibit elevated negative affect and drug-related cognitions during temptations compared to random assessments.

The last two chapters investigated whether the neural substrates of attentional bias and the neurophysiological marker of error processing - measured with respectively fMRI and EEG during the first week of detoxification treatment - are predictive of relapse to cocaine use 3 months after treatment.

In **chapter 4** it was examined to what extent brain activity in specific regions of interest related to attentional bias for drugs (i.e., anterior cingulate cortex, dorsolateral prefrontal cortex, insula, nucleus accumbens, and amygdala) was associated with cocaine use outcome, in addition to self-report measures (i.e., craving and addiction severity) and behavioral attentional bias. Cocaine dependent patients completed a cocaine Stroop task during fMRI acquisition. We hypothesized that enhanced brain-activation associated with attentional bias for cocaine-related stimuli would be an adequate predictor of days of cocaine use after treatment.

In **chapter 5** the predictive value of the ERN component for cocaine use outcome was tested in addition to addiction severity and self-reported craving in the week before treatment. The ERN was measured with ERPs during an Eriksen Flanker task. It was expected that reduced amplitude of the ERN component (reflecting diminished error processing) would be associated with more days of cocaine use after treatment. Furthermore, since

only two studies have examined the ERN in cocaine dependent patients (Franken et al., 2007; Sokhadze et al., 2008) we also examined whether cocaine dependent patients have a reduced ERN compared to healthy controls, in order to reconfirm results of these previous studies.

Finally, in **chapter 6** the main findings of this thesis are summarized and discussed as well as the limitations of the present studies. Furthermore, possible implications for treatment and suggestions for future research are provided.

Table 1. Overview of studies relevant for the present thesis investigating neurocognitive predictors of treatment outcome and substance relapse

Study	Participants	Task measures	Assessment Time	Outcome measures	Main results and Analysis		Main conclusion
Attentional bias – Behavior							
Marissen et al. (2006)	110 detoxified heroin dependents	Addiction Stroop task	- Pre-clinical treatment trial (duration of 3 weeks) - Post-treatment (immediately after 3 weeks)	Self-reported relapse vs. nonrelapse within 3 months after treatment	↑ 0	Logistic regression	Attentional bias at pre-treatment predicted relapse, but attentional bias post-treatment did not. Results persisted when controlling for self-reported craving during assessment.
Carpenter et al. (2006)	45 cocaine dependents 25 marijuana dependents 10 detoxified heroin dependents	Addiction Stroop task	Pre-outpatient treatment trial	- Self-reported average days of drug use per week during treatment - Proportion of positive urines during treatment - Proportion of treatment weeks completed	0 ↑ ↑	Zero-order Correlation	Attentional bias for cocaine - but not for marijuana or heroin - was associated with higher proportion of urines testing positive for drugs in cocaine and marijuana dependents. Low treatment retention was associated with attentional bias to cocaine in cocaine dependents and attentional bias to heroin in marijuana dependents. No associations between attentional bias and outcome in heroin dependents were found.
Cox et al. (2002)	14 alcohol dependents 16 controls	Addiction Stroop task	- Pre-clinical detoxification treatment - Shortly prior to discharge from treatment	Successful vs. unsuccesful treatment outcome 3 months after discharge (alcohol use measured with KAT)	0 ↑	RM-ANOVA: Group (successful, unsuccessful, control) x Stimulus Type (alcohol, neutral) RM-ANOVA: Group (successful, unsuccessful, control) x Assessment Time	Baseline attentional bias for alcohol did not predict treatment outcome. Unsuccessful patients had a strong increase in attentional bias from the start of treatment to discharge, while successful patients showed a similar pattern to controls: no change in attentional bias scores from pre-treatment to post-treatment.

Table 1. continued

Study	Participants	Task measures	Assessment Time	Outcome measures	Main results and Analysis		Main conclusion
Field et al. (2013)	28 detoxified alcohol dependents	- Addiction Stroop task - Visual probe task	During 1st week of follow-up treatment	Treatment compliance vs. non-compliance during 6-week treatment program (verified by breath tests)	0 0	Point-biserial Correlation	Neither attentional bias measured with the Stroop task nor with the visual probe task was associated with treatment compliance. Treatment compliance was associated with self-reported severity of alcohol dependence and craving.
Waters et al. (2003a)	122 smokers	Addiction Stroop task	Pre-smoking cessation treatment, on quit day	- 1-week continuous abstinence - Time to first lapse (daily self-reports on hand-held computer and verified by breath tests at clinic visits)	↑ ↑	Logistic regression Cox proportional-hazards analysis	Acute attentional bias predicted both outcome measures. Results persisted when controlling for pretask-smoking urge.
Waters et al. (2003b)	141 smokers	Visual probe task	Pre-smoking cessation treatment, 2 weeks before quit day	Time to first lapse (daily self-reports on hand-held computer and verified by breath tests at clinic visits)	0	Cox proportional-hazards analysis	Attentional bias was not associated with time to first lapse.
Powell et al. (2010)	141 smokers	Addiction Stroop task	Pre-smoking cessation	- 1-week abstinence - 1-month abstinence - 3-month abstinence (self-reports verified by breath tests)	↑ 0 0	Logistic regression	Attentional bias predicted abstinence on the short term (first week), but not on the long term.

Table 1. continued

Study	Participants	Task measures	Assessment Time	Outcome measures	Main results and Analysis		Main conclusion
Janes et al. (2010b)[a]	21 smokers	Addiction Stroop task	Pre-smoking cessation treatment	Lapse vs. abstinence during 8-week smoking cessation (weekly self-reports verified by breath tests)	↑	RM-ANCOVA: Group (lapse, abstinence) x Stimulus Type (smoking, neutral) corrected for FTND score	Attentional bias (both accuracy and reaction time measures) was associated with lapse during smoking cessation.
Attentional bias/ cue reactivity – Neuroimaging							
Kosten et al. (2006)	17 cocaine dependents	Passive viewing of cocaine-related (3-min) and neutral video (60-sec)	During a 2-week in-patient stay prior to a 10-week outpatient clinical trial	- Proportion of all cocaine negative urines during 10-week outpatient clinical trial - relapsers vs. nonrelapsers (verified by urine tests)	↑ ↑	fMRI contrast: first 30-sec of cocaine tape vs. 60-sec of neutral tape. Correlations between outcome measures and contrasted brain activity	Increased brain activation during cocaine cue exposure in precentral gyrus, posterior cingulate, superior temporal gyrus, lingual gyrus and inferior occipital gyrus was associated with lower proportion of urines testing negative for cocaine. Relapse was associated with higher posterior cingulate activation (extended anteriorly) during cue exposure.
Heinz et al. (2007)	12 detoxified alcohol dependents	Passive viewing of alcohol-related and neutral pictures and positive and negative pictures	1-week after 3-week detoxification program	Alcohol intake during 6-month follow-up period (biweekly assessment of alcohol intake using Form 90)	0	fMRI contrast: alcohol vs. neutral stimuli. Correlations between outcome measures and contrasted brain activity	Brain activation elicited by briefly presented alcohol-associated stimuli vs. neutral stimuli was not associated with relapse to alcohol intake.

Table 1. continued

Study	Participants	Task measures	Assessment Time	Outcome measures	Main results and Analysis		Main conclusion
Beck et al. (2012)	46 detoxified alcohol dependents	Passive viewing of alcohol-related, neutral and scrambled pictures	1-week after detoxification treatment	Relapsers vs. abstainers during 3-month follow-up (biweekly assessment of alcohol intake using Form 90)	↑ ↑[b]	fMRI contrast: alcohol vs. neutral stimuli. Correlations between outcome measures and contrasted brain activity	Increased brain activation in the left medial prefrontal cortex during processing of alcohol-related stimuli is associated with relapse and not with abstinence. In contrast, increased brain activation in the right ventral tegmental area and left and right ventral striatum during processing of alcohol-related stimuli is associated with abstinence and not with relapse.
Janes et al. (2010b)	21 smokers	Passive viewing of smoking and neutral pictures while occasionally responding to prompt animal pictures (to avoid study fatigue)	Pre-smoking cessation treatment	Lapse vs. abstinence during 8-week smoking cessation (weekly self-reports verified by breath tests)	↑ ↓	fMRI contrast: smoking vs. neutral stimuli. Correlations between outcome measures and contrasted brain activity Functional connectivity analyses in lapsers vs. abstainers Discriminant analysis	Lapsers had increased brain activation for smoking-related versus neutral stimuli in the insula, ACC, posterior cingulate cortex, amygdala, primary motor cortex, premotor cortex, inferior parietal cortex, parahippocampal gyrus, thalamus, putamen, cerebellar hemispheres and vermis, prefrontal cortex, and striate and extrastriate cortex. Lapsers had reduced connectivity in an insula-containing network and dACC. A prediction model including behavioral Stroop effect and anterior insula and dorsal ACC activation to smoking-related vs. neutral stimuli predicted outcomes with 79% accuracy.

Table 1. continued

Study	Participants	Task measures	Assessment Time	Outcome measures	Main results and Analysis		Main conclusion
Cognitive control/ executive functions – Behavior							
Aharonovich et al. (2006)	56 cocaine dependents	- MicroCog test battery assessing cognitive functioning - WCST	Pre-clinical treatment trial	Treatment compliance vs. non-compliance during 12-week program	↓ 0	Logistic regression per task measure	Treatment non-completers showed poorer cognitive functioning on attention, memory, spatial ability, speed, accuracy, global functioning, and cognitive proficiency. Mental reasoning and performance on the WCST was not associated with treatment compliance.
Turner et al. (2009)	84 cocaine dependents	- Test battery assessing cognitive functioning - WCST % perseverative errors	Pre-clinical treatment trail	Treatment compliance and proportion of negative urines during 12-week program	0 ↓	Zero-order Correlation	Percentage of perseverative errors from the WCST was negatively associated with treatment compliance. Other measures of cognitive functioning were not associated with treatment compliance.
Streeter et al. (2008)	74 cocaine dependents	Classic Stroop task	Pre-clinical treatment trail	Treatment compliance vs. non-compliance during 12- or 17-week program	↓	Logistic regression	Poor performance on the Stroop interference subtest is associated with treatment dropout, even after controlling for depressive symptoms. The classical Stroop task can predict treatment dropout with 91% accuracy and treatment retention with 78% accuracy.
Passetti et al. (2011)	80 opiate dependents	- Go/No-Go task - IST - DDT - IGT - CGT	Pre-clinical treatment trail	Relapsers vs. abstainers at 3-month follow-up (self-report verified by urine tests)	0 0 0 0 ↓	Logistic regression	Relapse was associated with impaired performance on the CGT (i.e., decision-making) but was not associated with other measures such as response inhibition.

Table 1. continued

Study	Participants	Task measures	Assessment Time	Outcome measures	Main results and Analysis		Main conclusion
Cognitive control/ executive functions - Neuroimaging							
Brewer et al. (2008)	20 cocaine dependents	Classic Stroop task	Pre-clinical treatment trail	- Proportion of cocaine-negative urines - Self-reported longest abstinence from cocaine (days) - Weeks in treatment	↑ ↑ ↓	fMRI contrast: Incongruent Stroop trials vs. congruent Stroop trials Correlations between outcome measures and contrasted brain activity	Brain regions involved in cognitive control are differentially associated with specific treatment outcomes; cocaine free urines was associated with hyperactivity in the right putamen. Self-reported abstinence was associated with hyperactivity in the left posterior cingulate cortex and left ventromedial prefrontal cortex. Treatment retention was associated with hypoactivity in de DLPFC. Treatment retention was also associated with behavioral Stroop interference.
Paulus et al. (2005)	46 meth-amphetamine dependents	2-choice prediction task	1-month after inpatient treatment	- Self-reported Relapse vs. nonrelapse within 1-year follow-up - Self-reported time to relapse (by means of structured interview)	↓ ↓	fMRI contrast: choice prediction vs. simple response Stepwise discriminant function analysis with the areas of differences between relapsers and nonrelapsers as predictor variables and relapse status as dependent variable Stepwise Cox regression analysis	Relapse was associated with reduced activity in right insula, right posterior cingulate, and right middle temporal gyrus during the 2-choice prediction task. Time to relapse was best predicted by low activation in right middle frontal gyrus, right middle temporal gyrus, and right posterior cingulate cortex activation. There were no associations between relapse and behavioral measures.

Note. 0 = no association between neurocognitive measures and outcome; ↑= elevated levels of cognition/brain activity is associated with worse treatment outcome or relapse; ↓= reduced levels of cognition/brain activity is associated with worse treatment outcome or relapse. [a]This study was also included in the attentional bias/cue reactivity neuroimaging subsection. [b]elevated brain activity was associated with abstinence. KAT, the Khavari Alcohol Test; FTND, Fagerstrom Test for Nicotine Dependence; ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; WCST; Wisconsin Card Sorting Test; IST, Information Sampling Task; DDT, Delay Discounting Task; IGT, Iowa Gambling Task; CGT, Cambridge Gamble Task.

Chapter 2

Implicit and explicit drug-related cognitions during detoxification treatment are associated with drug relapse: An ecological momentary assessment study

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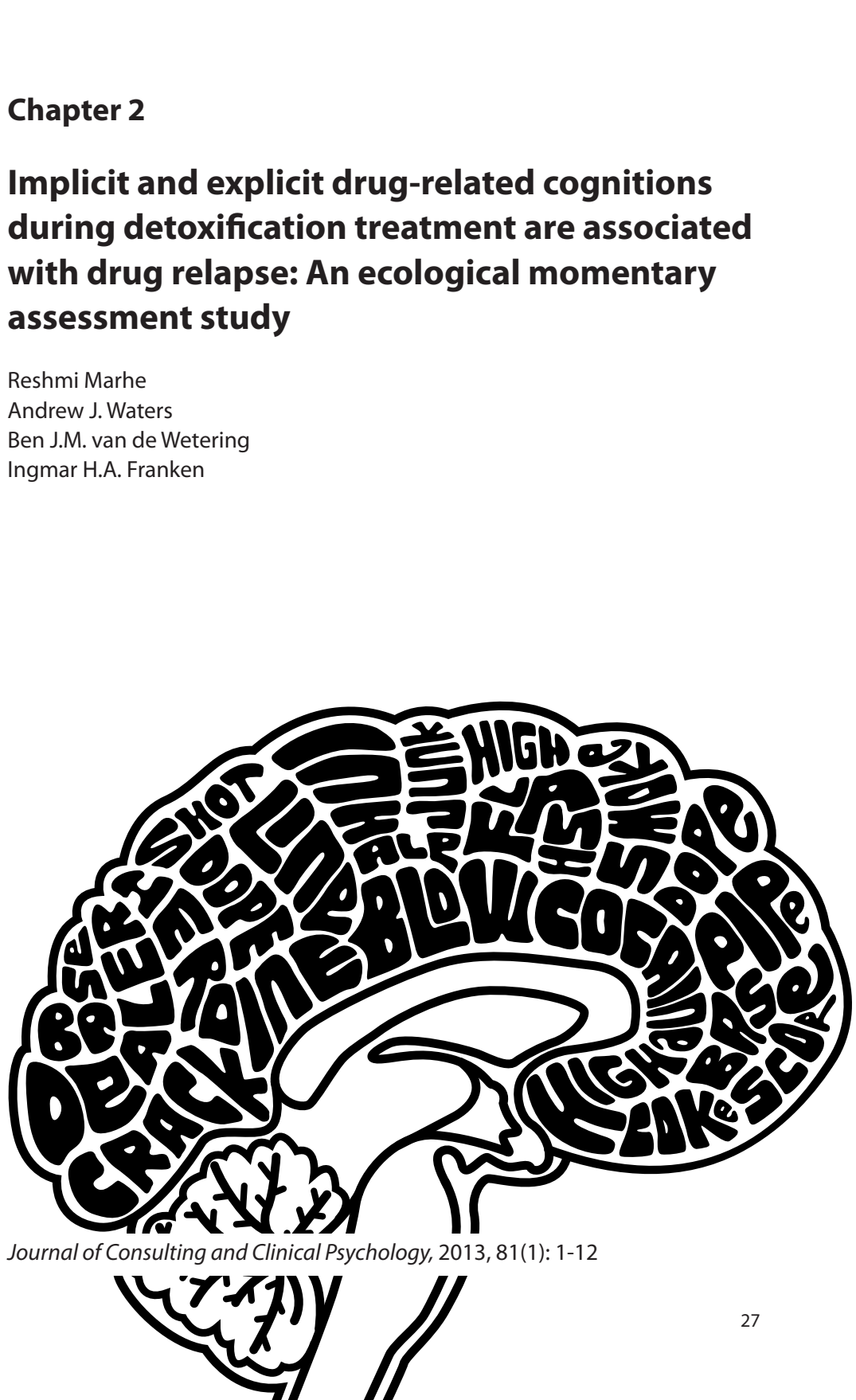

Journal of Consulting and Clinical Psychology, 2013, 81(1): 1-12

Abstract

Objective

Relapse is a major problem in drug addiction treatment. Both drug craving and drug-related cognitions (e.g., attentional bias and implicit attitudes to drugs) may contribute to relapse. Using ecological momentary assessments, we examined whether craving and cognitions assessed during drug detoxification treatment were associated with relapse.

Method

Participants were 68 heroin-dependent inpatients undergoing clinical detoxification at an addiction treatment center. Participants carried around a personal digital assistant for 1 week. Participants completed up to 4 random assessments (RAs) per day. They also completed an assessment when they experienced a temptation to use drugs (TA). At each assessment, participants reported their craving and attitudes to drugs. Implicit cognitions were assessed with a drug Stroop task (attentional bias) and an Implicit Association Test (implicit attitudes).

Results

Individuals who relapsed during the study week exhibited a larger attentional bias and more positive implicit attitudes to drugs than did nonrelapsers at TAs (but not RAs). In addition, compared to nonrelapsers, relapsers reported higher levels of craving and more positive explicit attitudes to drugs at TAs than at RAs. Additional within-subject analyses revealed that attentional bias for drugs at TAs increased before relapse.

Conclusions

Drug-related cognitive processes assessed with ecological momentary assessments were associated with relapse during drug detoxification. Real-time assessment of craving and cognitions may help to identify which individuals are at risk of relapse and when they are at risk of relapse.

Introduction

Relapse prevention is arguably the most important problem in substance dependence treatment. Generally, drug-dependent patients start substance abuse treatment with detoxification. However, more than 50% of patients do not complete detoxification treatment (Day and Strang, 2011; Franken and Hendriks, 1999; Hättenschwiler et al., 2000) and usually relapse to drug use soon afterward (Gossop et al., 1987; Gossop et al., 2002). It is therefore critical to understand the psychological processes underlying treatment dropout and relapse so that more effective interventions can be developed.

Several theories on the maintenance of substance use and relapse focus on the role of craving (e.g., Ludwig et al., 1974; Wise, 1988). Many studies have reported that self-reported craving is a predictor of treatment outcome and relapse (see McKay, 1999). However, not all studies have demonstrated this, and its role seems to be dependent on how it is measured (Rosenberg, 2009; Sayette et al., 2000). Studies have also examined the role of self-reported attitudes toward substance use; in the current context this refers to feelings or cognitions toward substance use. Studies that have examined the association between self-reported attitudes toward substances and substance use behavior have yielded mixed findings. For example, Burden and Maisto (2000) reported that self-reported positive attitudes toward alcohol consumption predicted heavier drinking behavior at 1-month follow- up, whereas De Leeuw et al. (2008) reported that self-reported positive attitudes toward smoking did not predict smoking behavior of adolescents at 1-year follow-up.

Much recent research has also focused on the role of drug-related cognitive processes underlying addiction and relapse (e.g., Franken, 2003). According to these models, both implicit (or automatic) and explicit (or controlled) cognitive processes play a role in drug use and relapse. Implicit cognitions are automatic, fast processes that can be measured indirectly using behavioral measures, usually reaction time tasks. Explicit cognitions are more controlled, slower processes and can be measured via self-report (Wiers and Stacy, 2006). An advantage of using implicit measures is that participants are generally unaware of the purpose of the assessment. The implicit measures may therefore be a more objective measure of internal processes (e.g., Fazio and Olson, 2003). In contrast, self-report measures require a certain level of insight into one's own motivational and cognitive processes. Therefore, self-report measurements can be biased by limited insight into these motives or processes and by other biases such as social desirability (Marissen et al., 2005).

In addiction research, the two most studied implicit cognitive processes are attentional bias and implicit memory associations (Wiers and Stacy, 2006). Attentional bias refers to exaggerated attentional processing of drug-related stimuli. It is often assessed with the drug Stroop task, in which participants are required to classify the colors of drug-related and

neutral words; slower responses on the former indicate an attentional bias to drug-related stimuli (Cox et al., 2006). Heroin- and cocaine dependent patients exhibit a robust attentional bias to drug-related words on this task, whereas control subjects do not (Constantinou et al., 2010; Franken et al., 2000; Hester et al., 2006). Implicit memory associations are usually measured with the Implicit Association Test (IAT; Greenwald et al., 2003). Drug users tend to exhibit more positive (less negative) automatic associations with drug-related cues than do nonusers (see Roefs et al., 2011, for a review of IAT and addiction literature).

Most pertinent to the present study, it has been hypothesized that both attentional bias (e.g., Franken, 2003) and implicit associations (e.g., Wiers and Stacy, 2006) can contribute to relapse. Several studies have examined the prospective association between implicit cognitions and substance use or relapse. It has been reported that attentional bias predicts substance use and/or relapse in nicotine dependence (Janes et al., 2010b; Powell et al., 2010; Waters et al., 2003a), alcohol abuse (Cox et al., 2002; Cox et al., 2007), and heroin or cocaine dependence (Carpenter et al., 2006; Marissen et al., 2006). In nonclinical populations it has been reported that implicit attitudes predict use of alcohol (e.g., Wiers et al., 2002), cigarettes (McCarthy and Thompsen, 2006), and cannabis (Ames et al., 2007). However, no studies have examined the role of implicit associations in relapse during or after treatment (see also Roefs et al., 2011).

The aforementioned studies were conducted in laboratory settings. A limitation of laboratory settings is that there may be a long lag between the assessment of cognition (and craving) and the occurrence of relapse. This lag might diminish the reported associations (Field et al., 2009; Shiffman, 2000). Moreover, it is uncertain whether craving or cognitions assessed in the laboratory accurately capture craving and cognitions experienced in the natural environment. Finally, in laboratory studies it is difficult to collect extensive longitudinal data from participants, making it difficult to understand how craving and cognition change over time.

Ecological momentary assessment (EMA) is an emerging methodology that can obviate these concerns (Stone et al., 2007). EMA can assess fluctuating and context dependent phenomena in real time, and it has been used successfully in a variety of psychiatric populations including the addictions (e.g., Epstein et al., 2009; Shiffman and Waters, 2004). In EMA, assessments are typically completed at random times and when participants experience heightened emotions or motivational states. In addiction research, assessments taken during temptation episodes can be highly informative, as there may be commonalities in the psychological processes underlying temptation episodes and relapse episodes (Shiffman, 2009; Shiffman et al., 1996; Waters et al., 2012). EMA studies also yield rich longitudinal data sets, allowing researchers to investigate how variables such as craving (Shiffman et al., 1997) and negative affect (Shiffman and Waters, 2004) change in the days leading up to relapse.

The recent development of portable electronic devices has facilitated the collection of EMA data in the addictions (e.g., Freedman et al., 2006). For example, Preston et al. (2009) reported an EMA study that examined the association between cocaine craving and cocaine use. During the five hours prior to cocaine relapse, ratings of cocaine craving at random assessments significantly increased. This study provided real-time evidence for the association between self-reported craving and subsequent relapse.

As noted before, implicit cognitions might also be important predictors of relapse (e.g., Marissen et al., 2006). Although it is feasible to administer reaction time tasks on electronic devices in EMA studies (e.g., Tiplady et al., 2009; Waters and Li, 2008), no previous study has assessed the predictive utility of implicit cognitions administered during EMA.

In sum, our main goal in the study was to examine whether implicit cognitive measures (i.e., attentional bias and implicit associations) and/or self-reported craving and explicit attitudes assessed with EMA were associated with relapse during heroin detoxification treatment. In doing so we also examined whether implicit and explicit cognitions were elevated in the days preceding relapse. We hypothesized that relapsers would report higher levels of self-reported craving and more positive explicit attitudes toward drugs than nonrelapsers. We also hypothesized that relapsers would exhibit higher levels of attentional bias for drugs and a more positive implicit association with drugs than nonrelapsers. Previous research has revealed that increases in craving are observed during the five hours before a relapse (Preston et al., 2009) and on the morning of the relapse day (Shiffman et al., 1997). Given that attentional bias may precede (and contribute to) craving (Franken, 2003), we hypothesized that attentional bias may be elevated in the days prior to relapse.

Method

Participants

Sixty-eight heroin-dependent inpatients (58 men) were recruited from a large addiction treatment center in an urban area (Bouman GGZ, Rotterdam, the Netherlands). Inclusion criteria for this study were (a) age between 18 and 65 years; (b) presence of the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; American Psychiatric Association, 1994) diagnosis for heroin dependence (assessed by both a physician and a research psychologist); and (c) the ability to speak, read, and write in Dutch at an eighth- grade literacy level. Exclusion criteria were (a) indications of severe psychopathology (i.e., psychosis, severe mood disorder, as assessed by a physician); (b) self-reported color blindness or (noncorrected) defective vision; and (c) pregnant or breast-feeding.

The mean age of the participants was 40.9 years (SD = 7.7). Of the total 68 participants, 14.9% completed primary education, 56.7% completed junior secondary education, 25.4% completed senior secondary education, and 3% completed higher education. Of all participants, 51.5% reported Dutch nationality and origin, 33.8% reported Dutch nationality but other origin, and 14.7% reported other nationality and origin. All participants were heroin dependent. Although cocaine dependence was not an inclusion criterion, most participants were also cocaine dependent (88.1%), and those who were not had used cocaine regularly for an average of 10.1 years. Additionally, 95% of all participants had used heroin in the week prior to intake in the detoxification treatment. During the past month, participants reported using heroin on an average of 21.3 days (SD = 9.1) and cocaine on 19.0 days (SD = 10.1). The mean reported age of first heroin use was 22.3 years (SD = 6.7), and the mean reported total years of heroin use was 14.1 years (SD = 8.7). The mean reported age of first cocaine use was 22.3 years (SD = 8.5), and the mean reported total years of cocaine use was 12.4 years (SD = 7.9). Inhalation was endorsed as the main administration route for both heroin (85.3% of all participants) and cocaine (86.8% of all participants).

The study was approved by the Ethics Committee of the Erasmus Medical Center, Rotterdam, the Netherlands. All procedures were carried out with the adequate understanding and written informed consent of the participants.

Treatment Setting

The inpatient detoxification unit where the study was carried out consists of two living and dining rooms, a nicotine smoking room, a small kitchen, and a garden. All patients had their own private bedroom. The usual duration of a detoxification treatment in this setting is 3 weeks. The specific goal of this detoxification treatment is to reduce physical and mental withdrawal symptoms, in this case heroin withdrawal symptoms. In the present study, 63 participants (95%) of participants (n = 66, as there were missing data from 2 participants) were placed on methadone maintenance at admission (mean starting dose = 58.9 mg, SD = 26.8). The mean number of days of methadone use (n = 65; there were missing data from 3 participants) during the study was 6.57 days (SD = 1.51). After the 3-week detoxification treatment, the patients started a follow-up treatment. This is a rehabilitation program with a duration of between one month and two years, depending on the severity of the problems. Occasionally, the detoxification treatment staff decided to discharge patients after 3 weeks if they had successfully finished detoxification and did not need further treatment.

Procedure

Participants were informed about the study on the second day of detoxification treatment. They had 24 hours to decide whether to participate. Volunteers signed the informed consent form on the third day of detoxification treatment. They then completed several questionnaires (data from questionnaire assessments are reported elsewhere) and were trained to use the personal digital assistant (PDA). Participants carried the PDA around for 7 days; that is, from the third day of detoxification treatment until the ninth day of treatment. All study materials were written in Dutch.

The PDA was programmed to beep four times each day at random times (random assessment; RA). Participants were also instructed to press a PDA button whenever they experienced an acute rise in urge to use heroin or cocaine or when they felt they were on the brink of acquiring and using heroin or cocaine (temptation assessment; TA). At each RA or TA assessment, participants responded to items assessing subjective (e.g., craving), pharmacological (e.g., use of coffee, alcohol and cigarettes), and contextual variables (e.g., the present environment/room, light conditions, presence of others). Subsequently, the PDA administered either a drug Stroop task or a drug IAT (detailed below; see Figure 1). The PDA was programmed to administer the two tasks in an alternating sequence to each participant. After completion of the study, the participant returned the PDA and received financial compensation. Compensation was contingent on the number of completed RAs (max. 50 euro).

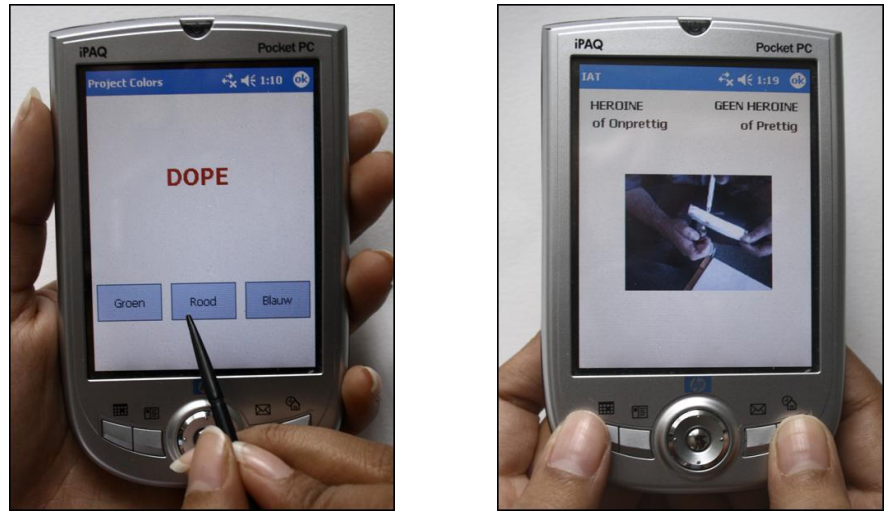

Figure 1. PDA versions of the drug Stroop task (left) and the IAT (right). PDA = personal digital assistant; IAT = Implicit Association Test.

During treatment, a patient was permitted to go on leave for a couple of hours upon staff approval. Therefore, participants could lapse (take heroin or cocaine) while offsite (away from the clinic). All reported relapses occurred offsite. To prevent PDA loss, participants were not permitted to take the PDA with them offsite. Therefore, all PDA assessments were completed at the detoxification unit.

EMA Measures

Because most participants were cocaine dependent or had used cocaine regularly (as noted previously), we used both heroin and cocaine versions of all behavioral tasks and subjective measures (where appropriate; see below). Both versions were administered to all participants.

Subjective measures

Participants were asked to respond according to how they felt "at this moment." Unless otherwise indicated, participants made their responses on 7-point Likert scales (1 = strongly disagree to 7 = strongly agree). Craving for heroin, craving for cocaine (e.g., "At this moment, I am craving heroin"), explicit attitude to heroin ("At this moment, please indicate your overall attitude to heroin"; 1 = strongly negative to 7 = strongly positive), explicit attitude to cocaine, and difficulty concentrating were assessed with single items. Explicit attitudes were administered only on those assessments during which an IAT was administered. Several additional items, not reported here, assessed affect, contextual variables, pharmacological variables, and number of interruptions (Waters et al., 2012).

Drug Stroop Task

The PDA version of the Stroop task has been described in detail elsewhere (see Waters and Li, 2008; Waters et al., 2012). Briefly, the instructions on the PDA stated that words written in different colors would be presented on the PDA screen one after the other and that the task was to indicate as rapidly and as accurately as possible which color the word was written in by pressing one of the three response buttons on the PDA using the stylus. The response buttons were boxes with color names within them (green, red, and blue). Participants were informed that they should ignore the meaning of the (target) word itself and just respond to the color. At each assessment, participants responded to a practice sequence of letter strings (33 trials), followed by two test blocks of 33 trials each. Each word was presented in capital letters and remained on the screen until the participant responded or a timeout of three seconds.

Stimulus materials

Participants completed either a heroin Stroop or a cocaine Stroop at each Stroop assessment. The Stroop task was randomly selected (without replacement) from one of 24 sequences of words ("lists"). Twelve lists (1–12) contained heroin words and matched neutral words (heroin Stroop), and the other twelve (13–24) contained cocaine words and matched neutral words (cocaine Stroop). The positions of the response buttons on the screen varied across lists (e.g., on List 1 they were ordered [Blue] [Green] [Red]; on List 2 they were ordered as [Green] [Red] [Blue]). Order of presentation of neutral words and drug words was counterbalanced across lists.

In the heroin Stroop, each list contained 11 heroin-related words (score, flash, smack, dope, dealer, junk, shot, ball, heroin, inhale, high) and 11 neutral words drawn from the category "transport" (ticket, metro, tram, moped, bike path, scooter, zebra crossing, asphalt, gasoline, freeway, racing), matched on word length and word frequency from the CELEX database (Baayen et al., 1995). In the cocaine Stroop, each list contained 11 cocaine words (pipe, puff, crack, smoke, cocaine, blow, line, coke, snort, powder, base) and 11 neutral words drawn from the category "indoor features" (rug, blanket, sofa, oven, lamp, attic, cabinet, armchair, tap, couch, stove), matched on word length and word frequency.

Scoring

Reaction times (RTs) from incorrect responses were discarded (3.5% of trials), as were RTs < 100 ms (0.01% of trials). To reduce the influence of RT outliers caused by interruptions, up to four RTs from assessments with reported interruptions were discarded (0.68% of trials), as described elsewhere (Waters and Li, 2008). A difference score between mean RT on drug Stroop words and mean RT on linked neutral words was computed to create a drug Stroop effect on each assessment. The estimated internal (split-half) reliabilities of the heroin Stroop and cocaine Stroop effects were $r = .72$ and $r = .68$, respectively (Waters et al., 2012).

Drug IAT

The IAT consists of two tasks. On Task 1, participants are required to respond rapidly with a keypress to items representing two concepts (e.g., heroin + pleasant) and with a different keypress to items from two other concepts (e.g., no heroin + unpleasant). In Task 2, the assignment of one concept is switched. In the current case, no heroin + pleasant shared a response, and heroin + unpleasant shared the other response. The main idea is that it is easier to perform the keypresses when the two concepts are strongly associated in memory than when the two concepts are unrelated. The IAT

effect is a measure of the difference in response times on Task 1 versus Task 2. The IAT effect is an index of the relative strength of automatic associations. In the example above, it indicates whether associations are stronger between heroin and pleasant and no heroin and unpleasant than between no heroin and pleasant and heroin and unpleasant.

The heroin IAT consisted of four blocks: (a) first block of Task 1 (e.g., heroin + pleasant/no heroin + unpleasant); (b) second block for Task 1; (c) first block of Task 2 (e.g., no heroin + pleasant/heroin + unpleasant); (d) second block for Task 2. At each assessment, participants were randomly assigned to complete one of four IATs: (a) heroin + pleasant first, pleasant on left; (b) heroin + pleasant first, unpleasant on left; (c) heroin + unpleasant first, pleasant on left; (d) heroin + unpleasant first, unpleasant on left. Analogous procedures were used for cocaine IAT. There were no practice blocks.

On each trial, a stimulus (picture or word) was presented in the center of the PDA screen. On the top of the screen were labels (on each side of the screen) to remind participants of the categories assigned to each key for the current task. Participants responded to the categorization task by pressing either the left or the right key under the screen on the PDA. They were instructed to respond as quickly and as accurately as possible. The program randomly selected items such that the sequence of trials alternated between the presentation of a (heroin/no heroin or cocaine/no cocaine) picture and the presentation of a (pleasant/unpleasant) word. If the participant made an error, a red X appeared below the stimulus and remained there until the participant responded correctly. Participants were instructed to correct their errors as quickly as possible. The intertrial interval was 150 ms.

IAT stimulus materials

Ten heroin and 10 neutral pictures were used in the heroin IAT and 10 cocaine and 10 (different) neutral pictures were used in the cocaine IAT. Twelve words were used for pleasant (Dutch equivalents of nice, pleasant, cool, relaxing, soothing, restful, smooth, peaceful, positive, friendly, satisfying, calm) and unpleasant (nasty, unpleasant, dirty, foul, smelly, unhealthy, ugly, negative, antisocial, depressing, harmful, revolting).

Scoring.

The error rate on the IAT was 13.0%. The IAT D score recommended by Greenwald et al. (2003; Table 4) was used to derive the IAT effect. The untransformed IAT effect (in ms) is also reported to assist in interpretation. The estimated internal (split-half) reliability of the IAT effect was .64 (ms score) and .72 (D score) for the heroin IAT and .72 (ms score) and .77 (D score) for the cocaine IAT (Waters et al., 2012).

Relapse Measures

The primary relapse measure was relapse during the PDA study week (i.e., from Day 3 to Day 9 of treatment; termed "early relapse"). On the fourth day of the study week and at the end of the study week, a researcher asked the participant to report whether or not he or she had used heroin or cocaine during the study. If participants reported use, they were asked to recall on which day or days of the study week they had used heroin or cocaine. Participants were assured that their report was confidential and was to be used only for research purposes. Early relapse was defined as at least one reported heroin or cocaine use during the PDA study week and was coded dichotomously (early relapsers vs. non-EMA relapsers). Treatment dropouts were coded as early relapsers, because research has shown that dropouts from residential treatment usually relapse to drug use soon afterward (Gossop et al., 1987, 2002).

The secondary relapse measure was relapse after the study (termed "late relapse"). Late relapse was assessed until the end of detoxification treatment (i.e., 2 weeks after the PDA study). Selfreported relapse was assessed for 1 week after the PDA study. Late relapse was defined as at least one reported heroin or cocaine use during detoxification treatment but occurring after the PDA study week, or as the presence of at least one positive urine screen, and was coded dichotomously (late relapsers vs. never relapsers). Treatment dropouts during this period (between the end of the PDA study and end of detoxification) were also coded as late relapsers (Gossop et al., 1987, 2002).

PDA Hardware and Software

Study procedures were implemented on a HP iPAQ Pocket PC running the Microsoft Windows Pocket PC operating system (Waters et al., 2012). The iPAQ uses a pen-based, touchscreen system. Participants could prevent the PDA from presenting RAs for up to 2 hours ("suspend" function). Participants could also delay RAs by 5 minutes (up to four times per RA). Participants were encouraged to use the suspend and delay functions as infrequently as possible.

Data Reduction and Analysis

Of the 68 participants, 64 contributed data to the study. Data from two participants were lost due to PDA error. One participant dropped out immediately following the PDA training because he did not comprehend the procedures, and one participant relapsed prior to completing any assessments. Of the remaining 64 participants, 10 were early relapsers (relapsed during study) and 54 were non-EMA relapsers (did not relapse

during study).[1] The 10 early relapsers completed 147 assessments prior to relapse (38 TAs, 109 RAs). The 54 non-EMA relapsers completed 1290 assessments (301 TAs, 989 RAs). A relapse (or dropout) date was known for all 10 early relapsers. Of the 54 non-EMA relapsers, 25 participants were late relapsers (relapsed after study). They completed 583 assessments (118 TAs, 465 RAs). A relapse date was known for nine late relapsers. There were 29 never relapsers. They completed 707 assessments (183 TAs, 524 RAs).

We used linear mixed models (LMM) for the relapse analyses using SAS PROC MIXED. LMM analyses take into account the dependence between observations due to clustering of the data by participants. The analyses also allow for different numbers of observations across participants. To select an appropriate working correlation structure, we first ran LMM analyses under two commonly used correlation structures (compound symmetry and first-order autocorrelation) and compared the resulting Akaike/ Schwartz information criteria (AIC/ BIC). On the basis of the reported AIC/BIC (smaller is better), we selected the more appropriate working correlation structure for each dependent variable. For significant results, parameter estimates from the mixed model were reported as an (unstandardized) measure of effect size (Wilkinson and the APA Task Force on Statistical Inference, 1999). For the analyses of relapse status, the dependent variables were craving for heroin; craving for cocaine; difficulty concentrating; explicit attitude to heroin; explicit attitude to cocaine; drug Stroop; and drug IAT.

First, we examined the associations between relapse and the number of temptations reported. The dependent variable was the number of temptations reported on each day. In separate models using data from 400 days (n = 64 participants) and 358 days (n = 54 participants), respectively, we examined whether early relapse status and late relapse status were associated with number of temptations. To control for the effect of time, we included day in study as a covariate in these models. These analyses address the question "Do individuals who subsequently relapse report more temptations than those who do not relapse?"

Second, we examined the association between early relapse status and the dependent variables listed above (n = 64 participants, 1437 assessments). Assessment type (TA vs. RA) was entered as a class (categorical) variable. Day in study was entered as a continuous variable to control for the effect of time. Number of assessments within each day was entered as a continuous variable. For analyses on the drug Stroop or drug IAT, drug type (heroin vs. cocaine Stroop; heroin vs. cocaine IAT) was entered as a class variable. The primary independent variable, early relapse status, was entered as a class variable (early relapser vs. non-EMA relapser). Given that many study measures were significantly elevated during temptation episodes (Waters et al., 2012) and given that relapse risk might arguably be best assessed from responses in temptation episodes, we tested the interaction term between early relapse status and assessment type (a detailed analysis of the comparison between TAs and RAs is reported in Waters et al., 2012). If a significant early relapse status and assessment type was observed, follow-up analyses tested the effect of early relapse status at TAs and RAs separately (using LMM). If a significant interaction was not observed, the interaction term was dropped from the model and the *F* values from the reduced model were reported. The analyses described above address the question "Do individuals who subsequently relapse (during the PDA study) differ in craving and cognition at TAs and RAs from individuals who do not relapse?" To bolster the LMM analyses, for the variables where a significant interaction or main effect was observed with LMM, we used logistic regression to test whether craving and cognition at TAs and RAs were associated with relapse. In these subject-level analyses, measures of craving and cognition (aggregated over all TAs and RAs) were the independent variables, and relapse was the dependent variable. These analyses address the question "Is craving and cognition at TAs and RAs (during the PDA study) prospectively associated with relapse (during the PDA study)?"

Third, we examined the association between late relapse status and dependent variables listed above (n = 54 participants, 1290 assessments). Thus, these analyses used data from the 54 participants who did not relapse during the PDA study. As before, day in study, number of assessments, and drug type were entered into the model. The primary independent variable, late relapse status (late relapser vs. never- relapser), was entered as a class variable. As above, using LMM, we tested the Late Relapse × Assessment Type interaction term. If a significant Late Relapse Status × Assessment Type interaction was observed, follow-up analyses tested the effect of late relapse status at TAs and RAs separately (using LMM). If a significant interaction was not observed, the interaction term was dropped from the model and the F values from the reduced model were reported. These analyses address the question "Do individuals who subsequently relapse (after the PDA study) differ in craving and cognition at TAs and RAs from individuals who never relapse?" As before, for the variables where a significant interaction or main effect was observed, we used logistic regression to test whether craving and cognition at TAs and RAs were associated with subsequent relapse. These analyses address the question "Is craving and cognition at TAs and RAs (during the PDA study) prospectively associated with relapse after the study?"

The analyses described above are between-subject analyses that compared craving and cognition in relapsers and nonrelapsers. The analyses examine who is at risk of relapse. Additionally, to examine the precipitants of relapse during the PDA study, we used mixed model logistic regression analyses. These analyses compared craving and cognition at

[1] Of the 10 early relapsers, nine reported at least one relapse and one dropped out of treatment during the study week. Of the 25 late relapsers, nine reported at least one relapse during the first week after the PDA study; of the remaining 16, 11 dropped out of treatment and five had at least one positive urine during the last week of treatment.

the RA and TA most proximal to the relapse with craving and cognition at all other RAs and TAs completed by the participant (control cases that were not followed by relapse). In these analyses, relapse was the dependent variable, and the measures of craving and cognition were the predictor variables.

This was a within-subjects comparison that addressed the question "Is relapse more likely to occur following elevated craving and cognition at RAs and TAs?" They examine when an individual is at risk of relapse. Following the methods of Cooney et al. (2007), we used generalized estimating equations (GEE; PROC GENMOD in SAS) and restricted analyses to data from the 10 PDA relapsers, who completed 76 and 71 assessments on the drug Stroop and drug IAT tasks respectively. We selected the appropriate working correlation structure based on the reported QIC (smaller is better), a goodness-of-fit statistic for GEE models. For TAs, the proximal assessment occurred on average 2.11 days and 2.14 days before relapse for the drug Stroop and drug IAT assessments respectively; for RAs the proximal assessments occurred on average 0.20 days and 0.78 days before relapse. Consistent with the LMM analyses, assessment type and the interaction term between assessment type and the predictor variable were included in the GEE models, as were the variables day, number of assessment (in day), and drug material type (if appropriate). If a significant interaction was not observed, the interaction term was dropped from the model, and the chi-square values from the reduced model were reported.

In secondary analyses, we recomputed LMMs when including three study methadone-related variables as covariates: starting dose of methadone (a subject-level continuous variable); detoxification status (a subject-level dichotomous variable that indicated whether or not the participant underwent detoxification during the PDA study); and methadone status (an assessment-level dichotomous variable that indicated whether or not the assessment occurred while the participant was on methadone). Due to missing data for methadone-related variables, these analyses used data from 62 and 53 participants for the early relapse and late relapse analyses, respectively. These analyses yielded similar findings to the primary analyses and are not reported here.

For all analyses, only assessments completed before reported relapse were included. Given the study focus on two implicit measures and given the large number of tests, alpha was set at .025 for the multilevel analyses (LMMs and GEEs); p values < .025 are interpreted, and p values < .05 are also noted. For logistic regression analyses, which were fewer in number because they were only conducted following significant effects in LMMs, alpha was set at .05. All tests were two-tailed.

Results

Number of Temptations

Early relapsers (n = 10) reported on average 0.90 temptations per day (SD = 1.10) prior to relapse (n = 42 days). Non-EMA relapsers (n = 54) reported on average 0.84 temptations per day (SD = 1.29; n = 358 days). The effect of early relapse status on number of temptations was not significant ($p > .1$). Late relapsers (n = 25) reported on average 0.70 temptations per day (SD = 1.17; n = 169 days). Never relapsers (n = 29) reported on average 0.97 temptations per day (SD = 1.38; n = 189 days). The effect of late relapse status on number of temptations was not significant ($p > .1$).

Primary Outcome: Early Relapse

Summary statistics are reported in Table 1, and results from LMMs are reported in Table 2. The Early Relapse Status × Assessment Type interaction was significant for the following variables: craving for heroin; craving for cocaine; explicit attitude to heroin; explicit attitude to cocaine; drug Stroop effect; and drug IAT effect (ms score and D score).[2] For the drug Stroop effect, the Early Relapse Status × Assessment Type interaction remained significant when craving for heroin and craving for cocaine were added as covariates to the model, $F(1, 688) = 5.61$, parameter estimate (PE) = 108.0, SE = 45.6, $p = .025$. For the drug IAT effect, the Early Relapse Status × Assessment Type interaction remained significant when explicit attitude to heroin and explicit attitude to cocaine were added as covariates to the model: ms score, $F(1, 610) = 8.52$, PE = 490.5, SE = 168.0, $p < .01$; D score, $F(1, 610) = 4.98$, PE = 0.30, SE = 0.13, $p < .05$. Explicit attitudes were associated with craving ratings across subjects (heroin craving and explicit attitude to heroin, $r = .73$ and .50, ps < .001 at RAs and TAs respectively; cocaine craving and explicit attitude to cocaine, $r = .79$ and .59, ps < .001, at RAs and TAs, respectively) and within subjects (mean within-subject correlation: heroin craving and explicit attitude to heroin: $r = .44$, $p < .001$, cocaine craving and explicit attitude to cocaine, $r = .47$, $p < .001$). However, the Early Relapse status × Assessment Type interaction for explicit attitude to heroin, $F(1, 612) = 11.67$, PE = 1.27, SE = 0.37, $p < .01$, and cocaine, $F(1, 612) = 9.94$, PE = 1.22, SE = 0.39, $p < .01$, persisted when controlling for the craving for heroin and craving for cocaine, respectively.

[2] For the implicit assessments, we also examined whether the Early Relapse Status × Assessment Type interaction was moderated by drug type (heroin vs. cocaine Stroop and heroin vs. cocaine IAT). There were no significant Drug Type × Early Relapse Status × Assessment Type interactions ($p > .1$).

Because the Early Relapse Status × Assessment Type interaction was significant for the aforementioned variables, we tested the effect of early relapse status at TAs and RAs separately (see Table 2). At TAs, the effect of early relapse status was significant for the drug Stroop effect (see Figure 2), indicating that the attentional bias of early relapsers (at TAs) was 111 ms greater than the attentional bias of non-EMA relapsers (at TAs). Similarly, at TAs the effect of early relapse status was significant for the drug IAT effect (see Figure 2), indicating that the IAT effect of early relapsers (at TAs) was 654 ms (ms score) more positive than the IAT effect of non-EMA relapsers (at TAs). At TAs, the effect of early relapse status was not significant ($p > .1$) for the other variables (i.e., craving for heroin, craving for cocaine, explicit attitude to heroin, and explicit attitude to cocaine). At RAs, the effect of early relapse status was not significant ($p > .1$) for any of the following variables: craving for heroin; craving for cocaine; explicit attitude to heroin; explicit attitude to cocaine; drug Stroop effect; and drug IAT effect.

The Early Relapse Status × Assessment Type interaction was not significant for difficulty concentrating (see Table 2). Similarly, the main effect of early relapse status (reduced model) was not significant ($p > .1$) for this variable.

Using logistic regression, the drug Stroop effect at TAs was prospectively associated with relapse (PE = 0.0053, SE = 0.0027, Wald = 3.95, $p < .05$). The effect remained significant when craving for heroin and craving for cocaine were added as covariates to the model (PE = 0.0056, SE = 0.0030, Wald = 3.98, $p < .05$). The IAT ms score at TAs was also prospectively associated with relapse (PE = 0.0012, SE = 0.00055, Wald = 4.65, $p < .05$). The effect remained significant when explicit attitude to heroin and explicit attitude to cocaine were added as covariates to the model (PE = 0.0014, SE = 0.00062, Wald = 4.94, $p < .05$). The association for the IAT D score approached significance (PE = 1.42, SE = 0.82, Wald = 3.00, $p = .08$). There were no significant effects at TAs for the following variables: craving for heroin; craving for cocaine; explicit attitude to heroin; explicit attitude to cocaine ($ps > .1$). There were no significant effects for any variable at RAs ($ps > .1$).

Table 1. Explicit and Implicit Measures by Early Relapse Status and Assessment Type

	Early Relapsers (n = 10)						Non-EMA relapsers (n = 54)					
	TAs			RAs			TAs			RAs		
	n	M	SD	n	M	SD	n	M	SD	n	M	SD
Heroin Craving (1-7)	38	4.32	1.73	109	2.48	1.50	301	3.79	2.26	989	2.65	1.84
Cocaine Craving (1-7)	38	4.29	2.25	109	2.26	1.48	301	3.49	2.46	989	2.39	1.91
Difficulty Concentrating (1-7)	38	4.34	1.60	109	3.83	1.31	301	4.44	1.91	989	3.86	1.87
Heroin Explicit Attitude (1-7)	19	4.05	1.35	52	2.27	1.27	143	3.20	1.93	464	2.65	1.79
Cocaine Explicit Attitude (1-7)	19	4.26	1.56	52	1.94	1.07	143	2.97	2.10	464	2.47	1.90
Drug Stroop (ms)	19	159.0	171.7	57	26.3	179.0	158	57.8	178.3	525	36.4	156.1
Drug IAT (ms)	19	686.9	969.7	52	185.3	565.9	143	106.0	809.3	464	84.8	628.4
Drug IAT (D score)	19	0.50	0.62	52	0.26	0.70	143	0.12	0.58	464	0.13	0.54

Note. n = number of observations; M and SD were computed by aggregation across observation. Drug stroop data were aggregated over heroin and cocain Stroop tasks. Similarly, drug IAT data were aggregated over heroin and cocaine IAT tasks. Mixed-model based estimates of the mean and standard deviation, which account for the fact that participants differ in the number of observations they contribute, are available on request. EMA = ecological momentary assessments; RAs = random assessments; TAs = temptation assessments; IAT = Implicit Association Test.

Table 2. Results of LMMs for Early Relapse Status

	Interaction				TAs				RAs			
	dfs	F	PE	SE	dfs	F	PE	SE	dfs	F	PE	SE
Heroin Craving	1, 1368	8.19***	0.75	0.26	1, 277	0.04	-0.12	0.60	1, 1032	0.64	0.41	0.51
Cocaine Craving	1, 1368	6.82***	0.61	0.23	1, 277	0.06	-0.18	0.78	1, 1032	0.09	0.18	0.59
Difficulty Concentrating	1, 1368	0.56	0.21	0.28	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Heroin Explicit Attitude	1, 612	11.67***	1.27	0.37	1, 111	0.92	-0.61	0.64	1, 453	1.86	0.69	0.51
Cocaine Explicit Attitude	1, 612	9.94***	1.22	0.39	1,111	1.69	-0.94	0.72	1, 453	0.99	0.53	0.54
Drug Stroop	1, 690	5.63**	108.1	45.5	1, 120	5.70**	-111.0	46.7	1, 517	0.16	17.3	24.9
Drug IAT (ms score)	1, 612	9.34***	508.2	166.3	1, 111	5.19**	-654.2	287.1	1, 453	0.67	-120.8	140.1
Drug IAT (D score)	1, 612	5.26**	0.30	0.13	1, 111	4.02*	-0.41	0.20	1, 453	0.36	-0.09	0.15

Note. Column labeled Interaction reports Early Relapse Status × Assessment Type interaction term from LMM. Column Labeled TAs reports effect of early relapse status at TAs; negative parameter estimates mean higher (more positive) values for relapsers vs. non-EMA relapsers. Column labeled RAs reports effect of early relapse status at RAs; positive parameter estimates mean lower (more negative) values for relapsers vs. non-EMA relapsers. LMM = linear mixed models; TAs = temptation assessments; RAs = random assessments; df = degrees of freedom; PE = parameter estimate; SE = standard error; n/a = not assessed, due to absence of significant interaction term; IAT = Implicit Association Test.

*$p < .05$, ** $p < .025$, ***$p < .01$.

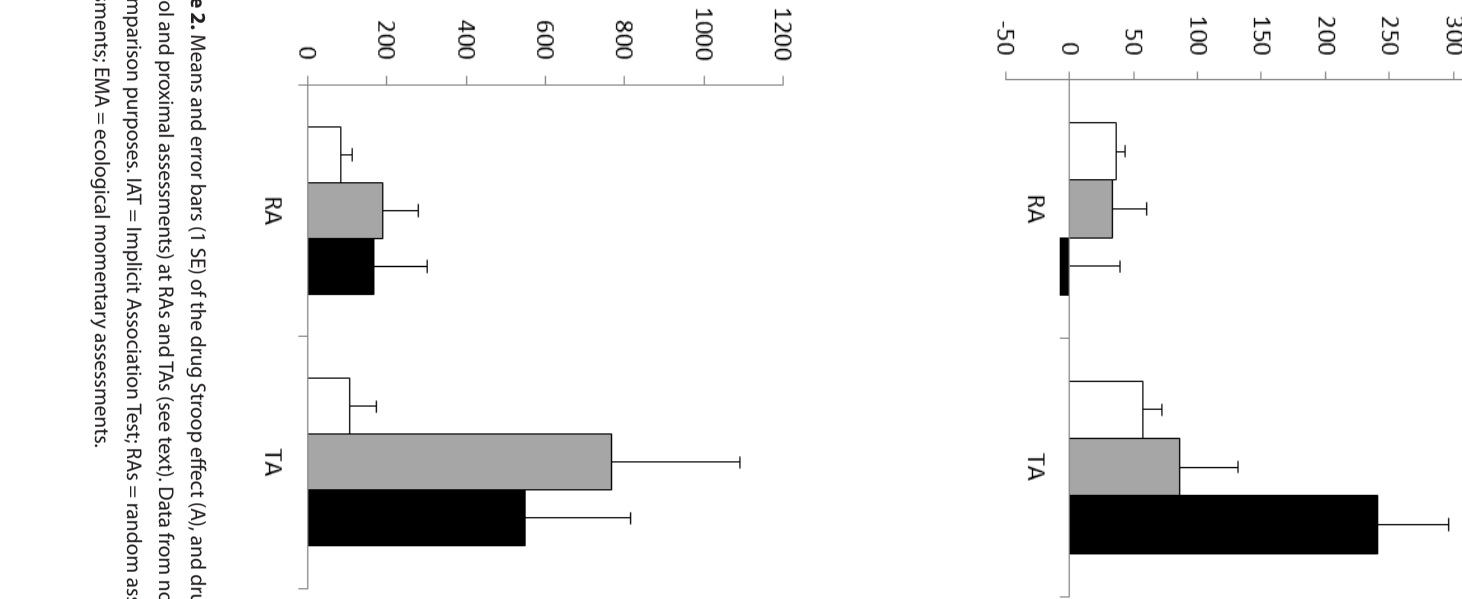

Figure 2. Means and error bars (1 SE) of the drug Stroop effect (A), and drug IAT effect (B) for early relapsers (control and proximal assessments) at RAs and TAs (see text). Data from non-EMA relapsers are also shown for comparison purposes. IAT = Implicit Association Test; RAs = random assessments; TAs = temptation assessments; EMA = ecological momentary assessments.

Secondary Outcome: Late Relapse

Summary statistics are reported in Table 3, and results from LMMs are reported in Table 4. The Late Relapse Status × Assessment Type Status interaction was significant for the following variables: explicit attitude to heroin and explicit attitude to cocaine. Follow-up analyses revealed that there were no significant effects of late relapse status (no differences between late and never relapsers) at TAs or RAs (see Table 4).

The Late Relapse Status × Assessment Type Status interaction was not significant ($p > .1$) for the other variables: craving for heroin; craving for cocaine; difficulty concentrating; drug Stroop effect; and drug IAT effect (see Table 4). Similarly, the main effect of late relapse status (reduced model) was not significant ($ps > .1$) for any of these variables.

With logistic regression used, there were no significant effects at TAs or RAs for any study variable ($ps > .1$).

Within-Subject Analyses

Results from GEE analyses (see Table 5) revealed that the Assessment Type × Drug Stroop interaction was significant. As the drug Stroop effect increased, the risk of subsequent relapse increased following TAs relative to the risk of subsequent relapse following RAs. This effect persisted when including self- reported craving for heroin and craving for cocaine in the model, Wald statistic (1) = 5.61, PE = -0.009, SE = 0.004, $p < .025$. As the drug Stroop effect increased at TAs (but not RAs), the risk of subsequent relapse tended to increase (see Table 5). This finding is illustrated in Figure 2. Although early relapsers generally exhibited elevated drug Stroop effect at TAs compared to nonrelapsers (as reported earlier), the drug Stroop effect of early relapsers was particularly elevated at the proximal assessment.

For the drug IAT, the Assessment Type × Drug Stroop interaction was not significant. The same was true for craving for heroin, craving for cocaine, difficulty concentrating, explicit attitude to heroin, and explicit attitude to cocaine (see Table 5). Similarly, the main effect of the predictor variable (reduced model) was not significant ($ps > .1$) for any of these variables.

Table 3. Explicit and Implicit Measures by Late Relapse Status and Assessment Type

	Late Relapsers (n = 25)						Never-relapsers (n = 29)					
	TAs			RAs			TAs			RAs		
	n	M	SD	n	M	SD	n	M	SD	n	M	SD
Heroin Craving (1-7)	118	4.04	2.07	465	2.41	1.67	183	3.63	2.36	524	2.87	1.96
Cocaine Craving (1-7)	118	3.81	2.43	465	2.45	1.89	183	3.28	2.46	524	2.33	1.93
Difficulty Concentrating (1-7)	118	4.32	2.08	465	3.93	1.89	183	4.52	1.79	524	3.79	1.85
Heroin Explicit Attitude (1-7)	56	3.93	1.85	217	2.49	1.75	87	2.74	1.85	247	2.78	1.81
Cocaine Explicit Attitude (1-7)	56	3.96	2.02	217	2.57	1.94	87	2.32	1.89	247	2.38	1.87
Drug Stroop (ms)	62	51.3	181.4	248	30.9	162.3	96	62.0	177.3	277	41.4	150.4
Drug IAT (ms)	56	299.7	1015.4	217	156.8	642.7	87	-18.7	618.1	247	21.6	609.9
Drug IAT (D score)	56	0.25	0.66	217	0.17	0.53	87	0.03	0.51	247	0.10	0.55

Note. n = number of observations; M and SD were computed by aggregation across observations. Drug Stroop data were aggregated over heroin and cocaine Stroop tasks. Similarly, drug IAT data were aggregated over heroin and cocaine IAT tasks. Mixed-model based estimates of the mean and standard deviation, which account for the fact that participants differ in the number of observations they contribute, are available on request. TAs = temptation assessments; RAs = random assessments; IAT = Implicit Association Test.

Table 4. Results of LMMs for Late Relapse Status

	Interaction				TAs				RAs			
	dfs	F	PE	SE	dfs	F	PE	SE	dfs	F	PE	SE
Heroin Craving	1, 1231	0.00	0.00	0.19	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Cocaine Craving	1, 1231	0.99	-0.17	0.17	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Difficulty Concentrating	1, 1231	0.40	0.13	0.21	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Heroin Explicit Attitude	1, 550	6.10**	0.69	0.28	1, 99	1.05	-0.52	0.51	1, 410	0.69	0.32	0.38
Cocaine Explicit Attitude	1, 550	5.99**	0.72	0.29	1, 99	2.08	-0.80	0.55	1, 410	0.37	-0.25	0.41
Drug Stroop	1, 624	0.11	-10.3	30.5	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Drug IAT (ms score)	1, 550	0.46	-0.01	0.10	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Drug IAT (D score)	1, 550	0.07	33.0	123.4	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

Note. Column labeled Interaction reports Late Relapse Status × Assessment Type interaction term from LMM. Column labeled TAs reports effect of late relapse status at TAs; negative parameter estimates mean higher (more positive) values for relapsers vs. nonrelapsers. Column labeled RAs reports effect of late relapse status at RAs; positive parameter estimates mean lower (more negative) values for relapsers vs. nonrelapsers. LMM = linear mixed models; TAs = temptation assessments; RAs = random assessments; df = degrees of freedom; PE = parameter estimate; SE = standard error; n/a = not assessed, due to absence of significant interaction term; IAT = Implicit Association Test.

*$p < .05$, **$p < .025$, ***$p < .01$.

Table 5. Results of GEE Within Subjects Analyses

	Interaction				TAs				RAs			
	df	Wald Statistic	PE	SE	df	Wald Statistic	PE	SE	df	Wald Statistic	PE	SE
Heroin Craving	1	1.18	0.46	0.43	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Cocaine Craving	1	1.60	0.14	0.11	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Difficulty Concentrating	1	2.23	0.30	0.20	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Heroin Explicit Attitude	1	1.46	-0.55	0.46	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Cocaine Explicit Attitude	1	0.70	0.34	0.41	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Drug Stroop	1	7.44***	-0.01	0.004	1	3.86*	0.01	0.006	1	0.05	0.0005	0.0023
Drug IAT (ms score)	1	1.07	-0.0008	0.0008	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Drug IAT (D score)	1	1.88	-1.20	0.92	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

Note. Column labeled Interaction reports the Predictor Variable × Assessment Type interaction term from GEE. Column labeled TAs reports effect of the predictor variable at TAs; positive parameter estimates mean that as values of the predictor variable become more positive there is a greater risk of subsequent relapse. Column labeled RAs reports effect of the predictor variable at RA. Predictor variables were tested in separate models. GEE = generalized estimating equations; TAs = temptation assessments; RAs = random assessments; df = degrees of freedom; PE = parameter estimate; SE = standard error; n/a = not assessed, due to absence of significant interaction term; IAT = Implicit Association Test.

*$p < .05$, ** $p < .025$, ***$p < .01$

Discussion

This study examined whether implicit and explicit cognitive assessments administered during EMA were associated with relapse during drug detoxification. The main findings were as follows. First, both early and late relapsers did not report more temptation episodes than non-EMA and never relapsers. Second and most important, early relapsers exhibited higher levels of attentional bias and more positive implicit attitudes toward drugs than non-EMA relapsers at temptation episodes (but not at random assessments). Attentional bias and positive implicit attitudes at temptation episodes were prospectively associated with relapse during the study. Third, when compared to non-EMA relapsers, early relapsers reported relatively higher levels of craving and more positive explicit attitudes toward drugs at temptation assessments compared to random assessments. Furthermore, when compared to never relapsers, late relapsers (who relapsed after the PDA study) reported relatively more positive explicit attitudes toward drugs at temptation assessments than at random assessments. Last, there was evidence from the within-subject analyses that elevated attentional bias during temptations was a precipitant of relapse.

Overall, therefore, it appears that early relapsers do not report more temptations than non-EMA relapsers. However, they experience more "severe" temptation episodes than non-EMA relapsers. The association between attentional bias at temptation episodes and relapse provides support for theoretical models that posit a relationship between attentional bias and relapse (e.g., Franken, 2003). As noted earlier, a number of laboratory studies have similarly reported prospective association between attentional bias and subsequent drug use (Carpenter et al., 2006; Cox et al., 2002, 2007; Janes et al., 2010b; Marissen et al., 2006; Powell et al., 2010; Waters et al., 2003a). The present study also revealed that individuals with more positive implicit attitudes to drugs during temptation episodes were at risk for early relapse. This finding is consistent with data from non-clinical populations. For example, McCarthy and Thompsen (2006) reported that positive implicit associations with alcohol or smoking predicted alcohol use or smoking behavior. Wiers et al. (2002) found that having less negative implicit associations with alcohol was associated with more alcohol use. In general, individuals with more positive (or less negative) implicit associations with drugs are at risk for subsequent use or relapse.

As noted above, the associations between cognition and relapse were found only at temptation assessments; they were not found at the random assessments. It seems likely that cognitive processes assessed during temptations may better reflect cognitive processes just prior to relapse than cognitions assessed at random times. For example, during both temptation episodes and relapse episodes, automatic processes such as attentional bias may drive the individual toward drug use; during temptation episodes the individual is able to prevent actual use (relapse) by inhibiting the output of these processes. However, individuals who experience more "cognitively severe" temptations may be less able to prevent drug use. Therefore, it is not surprising that cognitions assessed during temptations are more strongly related to risk of relapse than cognitions assessed at random assessments. It is noteworthy that, in some of the laboratory studies cited earlier, attentional bias was assessed under conditions of drug deprivation or shortly after cue exposure (Janes et al., 2010b; Marissen et al., 2006; Powell et al., 2010; Waters et al., 2003a). These testing conditions may have elicited temptations in some participants.

We also found that greater craving/more positive attitude at temptations (compared to random assessments) were associated with relapse. Previous EMA studies have also reported associations between craving/urge to use and substance use or relapse (e.g., Cooney et al., 2007; Preston et al., 2009; Shiffman et al., 1997). No previous study has examined associations between explicit attitudes assessed during EMA and relapse. However, several laboratory studies have reported an association between explicit attitudes and substance use or relapse (e.g., Chassin et al., 2010; McCarthy and Thompsen, 2006; Wiers et al., 2002). In the current study, a more positive explicit attitude at temptations (compared to random assessments) was associated with both early and late relapse. This suggests that the single item measure of attitudes used in this study is a useful marker for relapse risk if assessed at temptations and random assessments.

Interestingly, we did not find an association between implicit cognitions and late relapse. This may be because the EMA assessments were more proximal to early relapse episodes than the later relapse episodes (see also McKay et al., 2006). For attentional bias, confidence for this interpretation is bolstered by the observation that it was most elevated in the proximal assessment before relapse.

The present data also indicated that early and late relapsers do not report more temptation episodes than non-EMA and never-relapsers. Similarly, Shiffman et al. (1997) reported that number of temptations did not predict smoking relapse. Interestingly, duration of temptations did predict relapse, and, in lapsers, the peak reported urge during temptations (a measure of temptation intensity) increased in the days prior to lapse (Shiffman et al., 1997).

Results from the within-subject analyses suggest that elevated attentional bias during temptations – but not random assessments – is a precipitant for subsequent relapse. When an individual exhibits an elevated attentional bias during a temptation, that individual is at risk of relapse in the short term. In contrast, we did not find that more positive implicit attitudes (during temptations) were elevated just prior to relapse. This was one difference in the pattern of data for attentional bias and implicit attitudes. Individuals who exhibit an elevated IAT effect during temptations are generally at greater risk of

subsequent relapse during the study week, but there is not yet evidence that a highly positive implicit attitude at a given time point provides information about the timing of relapse.

Our findings have implications for treatment during drug detoxification. The data suggest that attentional bias (and implicit attitudes) may be an appropriate cognitive target for intervention. If further research reveals that the association between attentional bias and relapse is causal, an attentional retraining intervention, perhaps delivered on the PDA during treatment, would be a logical approach. If the association between attentional bias and relapse is not causal, the EMA data may still reveal which individuals are at risk of relapse and perhaps when they are at risk of relapse. These data may facilitate drug detoxification treatment. For example, more therapy time or instant intervention at a critical temptation period might be allocated to those individuals at greater risk of relapse.

The present study had limitations. First, because all PDA assessments occurred in the detoxification clinic and because relapses occurred offsite, we were not able to examine how craving and cognition changed in the hours and minutes before relapse. Second, due to clinic procedures, the self-reports of early relapse were not biochemically verified (late relapse was biochemically validated). Third, although we used an alpha level of .025 for the multilevel analyses, the large number of tests increases the probability that one or more of our findings are Type I errors. However, the consistency in the findings across analyses for the early relapse outcome bolsters confidence that the reported effects are real. Fourth, EMA data are correlational. It therefore remains uncertain whether cognitions cause relapse. Fifth, given that we always assessed implicit attitudes (and not the drug Stroop) after the explicit attitude measure, we cannot rule out the possibility that the explicit attitude question differentially influenced responses on the IAT (e.g., by increasing the salience of the cues in the IAT task). Last, we do not know whether the findings would generalize to users in outpatient or more naturalistic settings. However, the findings would still be of significant clinical interest if they generalized to other detoxification settings.

The study also had strengths. Most important, our methodology enabled us to measure implicit cognitions at the moment temptations occurred as well as at random times. The study revealed more specific information on the association between cognition and relapse than has been previously reported.

In sum, our data revealed that real-time assessment of implicit and explicit cognitions may help to identify those individuals who are at risk for relapse during drug detoxification and, perhaps, when they are at risk of relapse.

Chapter 3

Attentional bias to drug cues is elevated before and during temptations to use heroin and cocaine

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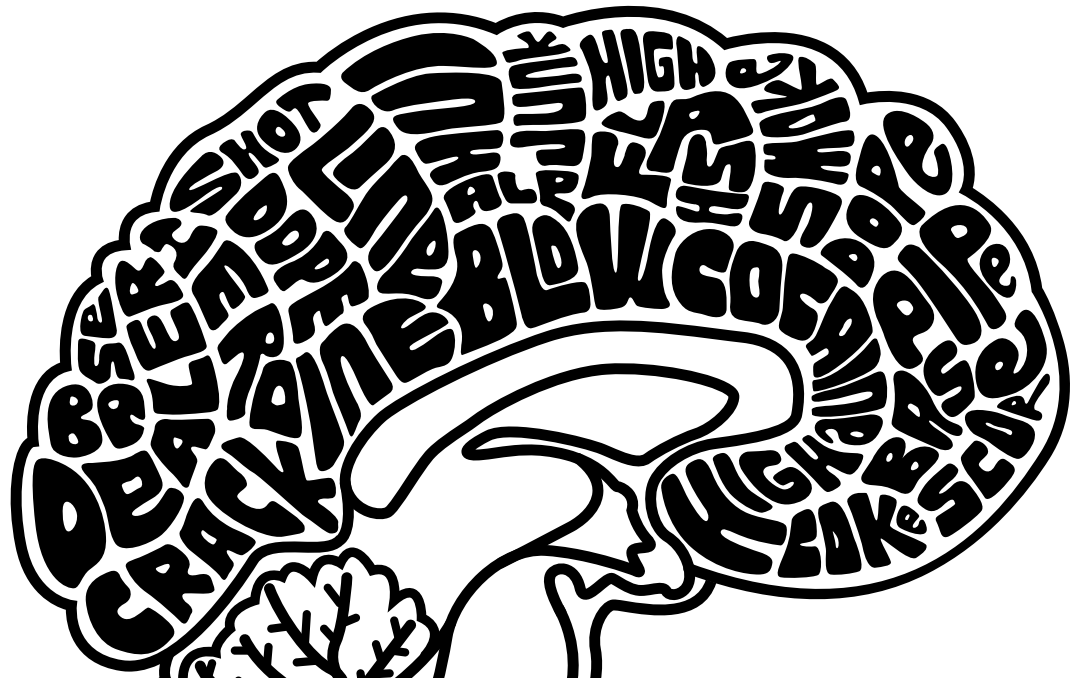

Psychopharmacology, 2012, 219(3): 909-921

Abstract

Rationale
Relapse is an important problem in substance dependence treatment. When drug users try to abstain from drug use, they often report strong temptations to use drugs. Temptation episodes have commonalities with relapse episodes, and assessment of temptation episodes may help to identify individuals at risk of relapse.

Objectives
This study aims to examine affect and cognition prior to and during temptation episodes by administering self-report and implicit cognitive assessments on a handheld computer (PDA) using Ecological Momentary Assessment.

Methods
Heroin-dependent patients (N=68) attending a drug detoxification unit completed up to four random assessments (RAs) per day on a PDA for 1 week. They also completed an assessment when they experienced a temptation to use drugs (temptation assessment; TA).

Results
Participants completed 1482 assessments (353 TAs, 1129 RAs). The rate of TAs was maximal during the first 2 days. Participants reported higher levels of negative affect, anxiety, and difficulty concentrating, and more positive explicit attitudes to drugs, at TAs compared to RAs. In addition, they exhibited elevated attentional bias to drug cues (assessed using the modified Stroop task) at TAs compared to RAs. Implicit affective associations with drug cues (assessed using the Implicit Association Test) were not different at TAs compared to RAs. Attentional bias was elevated in the 1 h prior to the entry of a temptation episode.

Conclusions
Elevated attentional bias may be a harbinger of temptation episodes. Interventions that target cognitions prior to or during temptation episodes may reduce the probability or severity of a temptation episode.

Introduction

Relapse is an important problem in substance dependence treatment. When attempting to abstain from drug use, many drug users report strong temptations to use drugs (e.g., Shiffman et al. 1997; Epstein et al. 2009). It is important to study temptation episodes because assessment of temptation episodes may help to identify individuals at risk of relapse.

A temptation episode can be defined as an occasion when a drug user, attempting to abstain from drug use, experiences an acute increase in the urge to use drugs or an occasion when the user feels that he or she has come to the brink of using drugs without actually doing so (Shiffman et al. 1996). The characteristics of temptation episodes have been examined using Ecological Momentary Assessment (EMA). EMA involves assessing phenomena at the moment they occur in a person's natural environment. Assessments may be done at random times ("random assessments"; RAs) and/or when participants experience heightened emotions or motivational states (e.g., temptations). Data from EMA studies are highly detailed and can reveal longitudinal patterns of change within a few hours (e.g., Shiffman and Waters 2004; Epstein et al. 2009).

The psychological processes that underlie temptation episodes and relapse episodes likely share some similarities (Shiffman et al. 1996). In smokers, research using EMA has shown that self-reported negative affect is most elevated just prior to lapse episodes, and it is higher just prior to temptation episodes than at random assessments (Shiffman et al. 1996). In addition, characteristics of temptation episodes have been associated with relapse. For example, duration (though not frequency) of temptations has been associated with relapse (Shiffman et al. 1997). In lapsers, the peak reported urge during temptations (a measure of temptation intensity) increased in the days prior to lapse (Shiffman et al. 1997).

EMA has also been used to study craving episodes in heroin- and cocaine-abusing outpatients treated with methadone (Epstein et al. 2009). Participants were instructed to report on a handheld computer whenever they craved heroin or cocaine without using them. In the hours preceding episodes of heroin (but not cocaine) craving, there were significant increases in endorsements (at random assessments) of a number of negative affective items, such as "feeling sad" and "feeling angry". Endorsement rates were typically maximal within 1 h of the craving episode.

The aforementioned studies relied on self-report data to examine the precipitants of temptation episodes. Self-report measures have two important limitations. First, it is easy for people to misrepresent or "fake" their mood and cognitions on self-report measures (Hammersley, 1994). Second, automatic (or implicit) processes cannot be adequately assessed using self-report measures. Automatic processes are psychological processes that are fast,

parallel, effortless, and may not engage conscious awareness (Schneider and Shiffrin 1977). Beginning with Tiffany (1990), a number of researchers have highlighted the role of automatic cognitive processes in addiction (Baker et al. 2004; Robinson and Berridge 1993; Wiers and Stacy 2006). Meta-analyses have confirmed that measures of automatic/implicit cognition are associated with substance use (Rooke et al. 2008; Cox et al. 2006).

Two widely studied automatic processes are (1) automatic attention capture (Cox et al. 2006) and (2) automatic affective associations in memory (e.g., Wiers et al. 2002). The importance of automatic attention capture (or "attentional bias") is highlighted in Franken's model (2003). Franken (2003) posits that attentional bias reflects the incentive salience of drug cues (Robinson and Berridge, 1993). The model further assumes that attentional bias can cause or increase craving, and that craving can cause or increase attentional bias. A meta-analysis has confirmed that measures of automatic/implicit cognition are associated with self-reported craving (Field et al. 2009b). The model also assumes that both craving and attentional bias can cause relapse. A number of studies have reported that attentional bias prospectively predicts outcomes in the addictions (e.g., Carpenter et al. 2006; Cox et al. 2002, 2007; Janes et al. 2010; Marissen et al. 2006; Powell et al. 2010; Waters et al. 2003).

Automatic affective associations in memory are another implicit cognitive mechanism that is important in addiction. The assumption is that drug-related choices are often influenced by associations in memory that are spontaneously activated under certain conditions (Stacy and Wiers 2010). Implicit associations are memory associations with the substance of abuse that are not revealed through introspection, self-reflection, or causal attribution (Stacy and Wiers 2010). Research has demonstrated that drug users have tended to exhibit more positive (less negative) implicit associations with drug-related cues than non-users (see Roefs et al. 2010 for review of studies using the Implicit Association Test; IAT).

In the current study, we administered both self-report and implicit cognitive assessments in temptations in heroin- and cocaine-abusing participants undergoing drug detoxification. The rationale for using this population and setting was as follows. First, attentional bias is typically robust in heroin and cocaine abusers (e.g., Franken et al. 2000; Hester et al. 2006; Liu et al. 2010). Second, there is evidence that the association between implicit cognition and craving-related variables is stronger in illicit drug users than licit drug users (Field et al. 2009b). Last, EMA methods could plausibly be used in a drug detoxification setting to determine the association between implicit and craving-related variables in a clinical setting, to determine the time course of these variables in this specific setting, and perhaps to identify those individuals at risk of treatment failure.

The goals of the study were as follows. First, we wanted to describe the natural history of temptation episodes during drug detoxification using EMA methods. Second, we examined whether self-reported negative affect, craving, and explicit attitudes were elevated in temptation episodes. Third, we examined implicit cognitive processes (attentional bias and automatic affective associations) during temptation episodes. We hypothesized that these implicit cognitions would be elevated during a temptation episode. Last, we also examined whether implicit and explicit cognitions were elevated in the hours preceding a temptation episode.

Method

Participants

Participants were 68 heroin-dependent inpatients recruited from an addiction treatment center (Bouman GGZ) in Rotterdam, The Netherlands (Table 1). Inclusion criteria were (1) aged between 18 and 65 years; (2) meeting the DSM-IV criteria for heroin dependence; and (3) the ability to speak, read, and write in Dutch at an eight-grade literacy level. Exclusion criteria were (1) indications of severe psychopathology (psychosis, severe mood disorder) as assessed by a physician, (2) self-reported color blindness or (non-corrected) defective vision, and (3) pregnant or breast-feeding. Although cocaine dependence was not an inclusion criterion, most patients attending the treatment center were dependent on cocaine. We therefore used heroin and cocaine versions of all behavioral tasks and questionnaires (see below). In the current sample, 88.1% of participants were dependent on cocaine (Table 1), and the eight participants who did not meet criteria for cocaine dependence reported that they had used cocaine regularly for an average of 10.1 years. The study was approved by the Institutional Review Board of the Erasmus Medical Center, Rotterdam, The Netherlands.

Treatment setting

The study took place at an inpatient detoxification unit of a large, urban, addiction treatment center. The inpatient detoxification unit consists of living and dining rooms, a smoking room, a small kitchen, and a garden. Patients had their own private bedroom. Detoxification treatment generally lasts 3 weeks. The goal of this treatment is to reduce physical dependency on the substances used by the patient. Ninety-five percent of the participants were placed on methadone maintenance at admission (Table 1). Methadone reduces acute heroin withdrawal and craving for heroin. Antidepressants, and/or sedative and anti-anxiety medications were administered as required. The usual procedure is that, after the detoxification treatment, patients start a follow-up treatment which is a

Table 1. Summary Statistics for Demographic Variables, Substance Use Variables, and Methadone Use

	Mean	SD
Demographic variables		
Age	40.87	7.72
Males (%)	85.3	
Education (%)[1]		
Primary education	14.9	
Junior secondary education	56.7	
Senior secondary education	25.4	
Higher education	3.0	
Race (%)		
Caucasian	51.5	
Other	48.5	
DSM GAF score[1]	47.01	5.97
Substance Use variables		
Heroin dependence (%)	100.0	
Cocaine dependence (%)[1,2]	88.1	
Heroin use one week prior to intake (%)[3]	95.0	
Age of first heroin use	22.34	6.72
Age of first cocaine use	22.32	8.50
Total years of heroin use[1]	14.13	8.73
Total years of cocaine use[1]	12.40	7.87
Number of heroin use days in last month[1]	21.28	9.10
Number of cocaine use days in last month[1]	19.00	10.08
Smoking[4] as main heroin administration route (%)	85.3	
Smoking[5] as main cocaine administration route (%)	86.8	
Alcohol Dependence (%)[1]	17.9	
Nicotine Dependence (%)	100.0	
Methadone variables		
Methadone treatment (%)[6]	95.5%	
Starting dose of methadone (mg)[7]	58.9	26.8
No. of days of methadone use during PDA study[8]	6.57	1.51

Note. Values are means (N = 68) unless otherwise indicated. [1]n = 67; [2]One participant with missing data reported they had used cocaine regularly for 12 years, and that they had used cocaine for 12 days in the past month; [3]n = 60; [4]Smoking by means of heating the substance on tin-foil ("chasing the dragon"); [5]Smoking with a crack pipe; [6]n = 66 (two participants had missing data); [7]n = 63 (participants with data who started on methadone); [8]n = 63 (participants with data who used methadone during study).

rehabilitation program that can last from 1 month to a couple of years, depending on the severity of the problems. The goal of rehabilitation treatment is to prepare the patients for reintegration into society.

Procedure

All patients were informed about the study on the second day of their detoxification treatment. They had 24 h to decide whether they wanted to participate. Participants signed an informed consent form. They were trained how to use the PDA and completed a practice assessment. Participants carried around the PDA for 1 week. The PDA beeped at random times up to four times per day (RAs). Participants were instructed to press a button on the PDA whenever they experienced a temptation to use heroin or cocaine, defined as acute rise in urge to use heroin or cocaine or an occasion when they felt they were on the brink of acquiring and using heroin or cocaine (Temptation Assessment; TA). At each assessment (RA or TA), participants first responded to items assessing subjective (e.g., mood), pharmacological (e.g., use of coffee, alcohol, and cigarettes), and contextual variables (e.g., location). They subsequently completed either a drug Stroop task or an Implicit Association Test (IAT). The PDA was programmed to administer the two tasks in an alternating sequence to each participant. After day 7 of the study, the participant returned the PDA to the researcher and received financial compensation, which was proportional to the number of RAs completed (maximum compensation was €50; approximately $65).

During treatment, a patient was permitted to go on leave for a couple of hours if the treatment staff approved. Although this was of course unwanted, participants could lapse (take heroin or cocaine) while offsite (away from the clinic). Participants were not permitted to take the PDA with them offsite. Therefore, all PDA assessments were completed at the detoxification unit. Thus, although the study involved many features of a typical EMA study (such as the use of a PDA to deliver random and participant-initiated assessments), unlike the majority of EMA studies, the data were collected in an inpatient setting rather than the patients natural environment.

Interview measure

The alcohol and drug section of the Addiction Severity Index (ASI) was used to assess drug use history and severity (McLellan et al., 1980).

PDA measures

Subjective measures

Participants were asked to respond according to how they feel "at this moment". Unless otherwise indicated, participants made their responses on seven-point Likert scales (1= strongly disagree to 7= strongly agree). Craving for heroin, craving for cocaine, hunger, and difficulty concentrating were assessed with single items. Explicit attitude toward heroin ("At this moment, please indicate your overall attitude to heroin"; 1= strongly negative to 7= strongly positive), and explicit attitudes toward cocaine were also assessed with single items (these two items were only administered on the assessments when an IAT was administered). A six-item version of the State-Trait Anxiety Inventory (STAI) (upset, worried, frightened, calm, secure, self-confident) was administered (Sayette et al. 2001). A state anxiety rating was computed from the mean of the items, reverse-scoring where appropriate (ratings from individual items are not reported). Six affect items (enthusiastic, happy, relaxed, bored, sad, angry) were presented. Two additional items assessed overall mood (My overall mood/feeling is…1= strongly negative to 7= strongly positive) and energy/arousal levels (My energy/arousal level is…1= very low to 7= very high). A negative affect rating was computed from the mean of seven items (enthusiastic, happy, relaxed, bored, sad, angry, and overall mood, reverse-scoring where appropriate; ratings from individual items are not reported).[1]

Pharmacological and contextual measures

Items assessed the number of cigarettes smoked in the past 2 h, the amount of alcohol consumed in the past 2 h, and the amount of coffee consumed in the past 2 h. One item assessed social context, and two items assessed location. After each IAT or modified Stroop assessment, the participant was asked to report the number of times that he or she was interrupted while performing the task. Response options for these items are shown in Table 2.

[1] Given that positive affect can be independent of negative affect (e.g., Watson 2000), it could be argued that two affect factors (positive affect and negative affect) might be derived. Exploratory factor analysis did not provide coWmpelling evidence for two factors. If two factors were extracted, positive affect was significantly lower at TAs than RAs, and vice versa for negative affect (*ps*<0.01).

Table 2. Summary Statistics on Subjective, Implicit, Pharmacological, and Contextual Variables.

	TAs (n = 353)	RAs (n = 1129)	All Assessments (N = 1482)
Craving			
Heroin Craving (1-7)	**3.89 (2.20)**	**2.65 (1.82)**	2.95 (1.99)
Cocaine Craving (1-7)	**3.68 (2.47)**	**2.41 (1.90)**	2.71 (2.12)
Subjective variables			
Negative Affect (1-7)[a]	**4.19 (1.24)**	**3.55 (1.22)**	3.70 (1.25)
State Anxiety (1-7)[a]	**4.01 (1.22)**	**3.36 (1.22)**	3.52 (1.25)
Mood (1-7)	**3.63 (1.70)**	**4.40 (1.59)**	4.22 (1.65)
Energy-level (1-7)	3.93 (1.85)	4.17 (1.66)	4.11 (1.71)
Difficulty Concentrating (1-7)	**4.41 (1.87)**	**3.86 (1.81)**	3.99 (1.84)
Hunger (1-7)	2.88 (1.71)	2.56 (1.62)	2.63 (1.64)
Heroin Explicit Attitude (1-7)	**3.33 (1.90)**	**2.61 (1.74)**	2.78 (1.81)
Cocaine Explicit Attitude (1-7)	**3.15 (2.10)**	**2.43 (1.85)**	2.61 (1.93)
Implicit variables			
Heroin Stroop (ms)	**64.8 (196)**	**34.2 (150)**	42.5 (165)
Cocaine Stroop (ms)	**67.8 (152)**	**36.4 (165)**	42.7 (163)
Heroin IAT (ms)	208 (844)	79.8 (642)	107 (692)
Cocaine IAT (ms)	120 (832)	109 (594)	112 (664)
Heroin IAT (D score)	0.16 (0.61)	0.12 (0.57)	0.13 (0.58)
Cocaine IAT (D score)	0.11 (0.61)	0.16 (0.56)	0.14 (0.58)
Pharmacological Variables			
No. cigarettes smoked			
No cigarettes (%)	10.5	11.2	11.0
1 cigarette (%)	20.4	26.4	25.0
Many cigarettes (%)	69.1	62.4	64.0
Alcohol			
No alcohol (%)	97.7	98.6	98.4
Small amount (%)	1.7	1.2	1.3
Large amount (%)	0.6	0.3	0.3
Coffee			
No coffee (%)	31.7	37.2	35.9
Small amount (%)	52.7	49.3	50.1
Large amount (%)	15.6	13.5	14.0

Table 2. Continued

	TAs (n = 353)	RAs (n = 1129)	All Assessments (N = 1482)
Contextual Variables			
Social Context			
Alone (%)	54.7	46.1	48.1
With Others (%)	45.3	53.9	51.9
Location-1			
Living Room (%)	19.8	27.1	25.4
Dining Room (%)	22.4	21.8	21.9
Bedroom (%)	37.4	30.5	32.1
Medication room (%)	2.6	1.0	1.4
Somewhere else in clinic (%)	17.9	19.7	19.2
Location-2			
Outside (%)	**15.3**	**10.3**	11.5
Indoors (%)	**84.7**	**89.7**	88.5
Interruptions			
No Times (%)	48.5	50.5	50.0
One Time (%)	21.7	21.7	21.7
Two Times (%)	17.2	16.4	16.6
Three Times (%)	9.3	8.1	8.4
Four or more Times (%)	3.3	3.3	3.3

Note. Values are means (SD) unless otherwise indicated (N = 1482 assessments). Means and SDs are computed by aggregation across assessments. Mixed-model based estimates of the data, which account for the fact that participants differ in the number of observations they contribute, are available on request. Significant between-Assessment Type differences are bolded. Participants completed 381 heroin-Stroop and 404 cocaine-Stroop assessments, making 785 Stroop assessments in total (185 TAs, 600 RAs). Participants completed 342 heroin-IAT and 355 cocaine-IAT assessments, making 697 IAT assessments in total (168 TAs, 529 RAs). Explicit attitude ratings were assessed at IAT assessments.

RA = Random Assessment, TA = Temptation Assessment.

[a]State Anxiety is mean of six items, and Negative Affect is mean of seven items (see text).

Drug Stroop task

Participants were instructed that words written in different colors would be presented on the PDA screen one after the other and that the task was to indicate as rapidly and as accurately as possible which color the word was written in by pressing one of the three response buttons on the PDA using the stylus (see Fig. 1). Participants were instructed that they should ignore the meaning of the (target) word and to focus on the color. At each assessment, participants responded to a practice sequence of letter strings (e.g., MMMM; 33 trials), followed by two test blocks of 33 trials each, separated by a 5-s break. Each word was presented in capital letters and remained on the screen until either (1) the participant responded or (2) 3 s had elapsed. If the participant made an incorrect response or failed to

respond, there was a tone. Five-hundred milliseconds after a response (or 500 ms after the 3-s time window in case of a non-response), a new word was presented. During the inter-stimulus interval, the screen was blank.

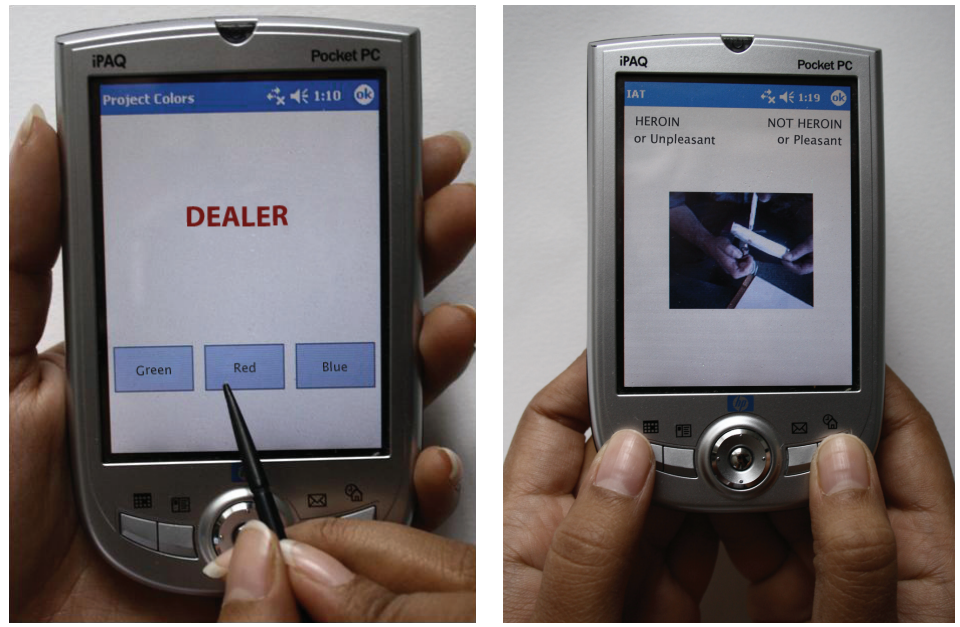

Figure 1. PDA versions of the modified Stroop task (left) and the IAT (right) (shown in English). In the Stroop task, the response buttons are boxes with color names within them (red, green, and blue). The positions of the response buttons on the screen varied across lists (e.g., on list 1 they were ordered [Blue] [Green] [Red]; on list 2 they were ordered as [Green] [Red] [Blue]). Participants make responses using the stylus. On the IAT, a picture or word is presented on each trial. There are labels on top of the screen to remind participants of the categories assigned to each key for the current task. Participants perform the categorization task by pressing either the left or the right key of the PDA. For the heroin-IAT, on two blocks of trials (Task 1), heroin is paired with pleasant, and not heroin is paired with unpleasant. On another two blocks (Task 2), heroin is paired with unpleasant, and not heroin is paired with pleasant (shown in Figure 1). The IAT effect is the difference in response times on the categorization task in these two tasks. Faster performance when heroin is paired with pleasant reflects a more positive implicit association with drug cues (see text for details).

Stimulus materials. At those assessments at which the Stroop task was administered, the participant completed either a heroin Stroop or a cocaine Stroop. The Stroop task was randomly selected (without replacement) from one of 24 sequences of words ("lists"), and therefore the selection of a heroin- or a cocaine-Stroop task was independent of the relative magnitude of reported heroin and cocaine craving. Twelve lists contained heroin words and matched neutral words (heroin Stroop), and the other 12 contained cocaine words and matched neutral words (cocaine Stroop). The order of presentation of neutral

and drug words was counterbalanced across lists. For each list, a random sequence was generated that determined the order of presentation of words for that list, under the constraint that the same color did not occur on two consecutive trials.

In the heroin version, each list contained 11 heroin-related words (Dutch equivalent of score, flash, smack, dope, dealer, junk, shot, ball, heroin, inhale, high) and 11 neutral words drawn from the category "transport" (Dutch equivalent of ticket, metro, tram, moped, bike path, scooter, zebra crossing, asphalt, gasoline, freeway, racing; see Franken et al. 2000). The heroin and neutral words were matched on word length (5.7 vs. 6.1 letters, respectively) and word frequency (3.3 vs. 5.0, respectively) using the CELEX database (Baayen et al. 1995). In the cocaine version, each list contained 11 cocaine words (Dutch equivalent of pipe, puff, crack, smoke, cocaine, blow, line, coke, snort, powder, base) and 11 neutral words drawn from the category "indoor features" (rug, blanket, sofa, oven, lamp, attic, cabinet, armchair, tap, couch, stove; word length 5.4 vs. 5.6, respectively; word frequency 11.2 vs. 12.9, respectively).

Scoring. Reaction times (RTs) from incorrect responses were discarded (3.5% of trials), as were RTs <100 ms (0.01% of trials). To reduce the influence of RT outliers caused by interruptions, we discarded RTs from assessments with interruptions as previously described (Waters and Li, 2008) (0.68% of trials). The drug Stroop effect was computed on each assessment by taking the difference score between mean RT on drug Stroop words and mean RT on linked neutral words. Using a split-half approach (odd and even trials), the estimated internal reliabilities of mean RT on neutral words (heroin lists), mean RT on heroin words, and the heroin Stroop effect were r=0.96, r=0.97, and r=0.72 respectively. The estimated internal reliabilities of mean RT on neutral words (cocaine lists), mean RT on cocaine words, and the cocaine Stroop effect were r=0.96, r=0.96, and r=0.68, respectively.

Implicit association test (IAT)

The IAT consists of two tasks. On task 1, participants are required to respond rapidly with a key press to items representing two concepts (e.g., heroin + pleasant) and with a different key press to items from two other concepts (e.g., not heroin + unpleasant). In task 2, the assignment of one concept is switched. For example, in the current case, not heroin + pleasant would share a response, and heroin + unpleasant would share the other response. The main idea is that it is easier to perform the key presses when the two concepts are strongly associated in memory than when the two concepts are unrelated. The IAT effect is an index of the relative strength of automatic associations. In the example above, it indicates whether associations are stronger between heroin and pleasant, and not heroin and unpleasant, than between not heroin and pleasant, and heroin and unpleasant. At those assessments at which the IAT was administered, the participant completed either a heroin IAT or a cocaine IAT. The PDA was programmed to present the heroin and cocaine IAT in an

alternating sequence; the selection of a heroin or a cocaine IAT was independent of the relative magnitude of reported heroin and cocaine craving. The heroin IAT consisted of four blocks: (1) first block of combined categorization task (task 1) (e.g., heroin + pleasant/not heroin + unpleasant), (2) second block for task 1, (3) first block of alternative combined categorization task (task 2) (e.g., not heroin + pleasant/heroin + unpleasant), and (4) second block for task 2. At each assessment, participants were randomly assigned to one of four IATs: (a) heroin + pleasant first, pleasant on left; (b) heroin + pleasant first, unpleasant on left; (c) heroin + unpleasant first, pleasant on left; and (d) heroin + unpleasant first, unpleasant on left. Analogous procedures were used for cocaine IAT. There were no practice blocks.

On each trial, a stimulus (picture or word) was presented in the center of the Pocket PC screen. On the top of the screen were labels to remind participants of the categories assigned to each key for the current task. Participants performed the categorization task by pressing either the left or the right key of the Pocket PC (Fig. 1). They were instructed to respond as quickly and as accurately as possible. The program randomly selected items such that the sequence of trials alternated between the presentation of a (heroin/not heroin or cocaine/not cocaine) picture and the presentation of a (pleasant/unpleasant) word. If the participant responded correctly, the program proceeded to the next trial. If the participant made an error, a red "X" appeared below the stimulus and remained there until the participant responded correctly. Participants were instructed to correct their errors as quickly as possible. The inter-trial interval was 150 ms.

IAT stimulus materials. We used 10 heroin and 10 neutral pictures in the heroin version of the IAT (see Franken et al. 2003) and 10 cocaine and 10 (different) neutral pictures in the cocaine version (van de Laar et al. 2004). We used 12 words to capture the pleasant concept (Dutch equivalent of nice, pleasant, cool, relaxing, soothing, restful, smooth, peaceful, positive, friendly, satisfying, calm) and 12 words to capture the unpleasant concept (nasty, unpleasant, dirty, foul, smelly, unhealthy, ugly, negative, antisocial, depressing, harmful, revolting).

Scoring. The error rate on the IAT was 13.0%. The scoring algorithm recommended by Greenwald and colleagues was used to derive the IAT effect (Greenwald et al. 2003). Data from all four blocks were used to compute the IAT effect. RTs>10,000 ms were eliminated (0.98% of RTs). The algorithm eliminates assessments on which a participant had RTs of less than 300 ms on more than 10% of the trials (30 assessments; 4.1% of completed assessments). The computed IAT effect, D, is similar to an effect-size measure (Greenwald et al. 2003). The untransformed IAT effect (in milliseconds) is also reported to assist in interpretation. (For the ms score, the difference score is not divided by pooled SD of RTs.) The estimated split-half internal reliability was 0.64 (ms score) and 0.72 (D score) for the heroin IAT and 0.72 (ms score) and 0.77 (D score) for the cocaine IAT.

PDA hardware and software

Study procedures were implemented on a HP iPAQ Pocket PC running the Microsoft Windows Pocket PC operating system. The iPAQ uses a pen-based, touch-screen system. Participants could prevent the PDA from presenting RAs for up to 2 h ("suspend" function). Participants could also delay RAs by 5 min (up to four times per RA). Because use of the suspend and delay functions may cause the data to become less representative of daily experience, participants were encouraged to use these functions as infrequently as possible.

Data reduction and analysis

Of the 68 participants, 64 participants contributed data to the study (353 TAs, 1129 RAs).[2] Linear mixed models (LMM) were used for the primary analyses involving continuous outcome variables using SAS proc mixed. LMM analyses take into account the dependence between observations due to clustering of the data by participants, and allow for different numbers of observations across participants. To select an appropriate working correlation structure, we first ran LMM analyses under two commonly used correlation structures (compound symmetry and first order autocorrelation) and compared the resulting Akaike/Schwartz information criteria (AIC/BIC). Based on the reported AIC/BIC (smaller is better), we selected the more appropriate working correlation structure for each dependent variable. To analyze dichotomous (e.g., Social Context) or categorical outcome variables (e.g., Location, see Table 2), we used proc glimmix in SAS (using maximum likelihood with adaptive quadrature estimation). This procedure permits the analysis of dichotomous and multinomial outcome variables, and also takes into account the clustering of the data by participants.

For analyses on the natural history of temptations over time, days (n=414) served as the unit of analysis. To assess the effect of Assessment Type (TAs vs. RAs), assessments (n=1482) were the unit of analysis. Assessment Type (TA vs. RA) was entered as a class (categorical) variable (reference category=RA). To control for the effect of time, day in study was entered as a continuous variable. Number of assessments within each day was entered as a continuous variable. For analyses on the drug Stroop effect or drug IAT, drug material type (heroin vs. cocaine Stroop; heroin vs. cocaine IAT) was entered as a class variable. Following the recommendations of Hedeker et al. (2009), if a significant effect of Assessment Type

[2] Data from two participants were lost due to PDA error, one participant dropped out of the study immediately following the training because he did not comprehend the procedures, and one participant dropped out of treatment prior to completing any assessments. Of the 64 participants, 10 relapsed (n=9) or dropped out of treatment (n=1) during the PDA study. Analyses on relapse are not reported in the present paper.

was observed, we added temptation rate [i.e., number of TAs divided by the total number of assessments (TAs + RAs)] as a subject-level covariate to the model. This allowed us to examine (1) whether subjects who reported more TAs exhibited higher scores (averaged over TAs and RAs) on the dependent variable and (2) the effect of Assessment Type controlling for temptation rate. A significant effect for the latter would bolster the conclusion that the effect of Assessment Type is a truly within-subject effect (Hedeker et al. 2009), that is, when subjects experience a TA they have higher scores on the dependent variable at TAs than at RAs.

If a significant between-assessment difference (TA vs. RA) was observed in the above analyses, we used LMM to examine whether mood and cognitions were elevated in RAs in the 1 h preceding a TA (1 h pre-TA, n=61; "proximal" RAs) compared to RAs occurring more than 3 h prior to a TA and more than 3 h after a TA (n=1232; "control RAs") (reference category = control RAs). In secondary analyses, we used LMM to examine whether mood and cognitions were elevated in RAs occurring 1 h to 3 h prior to a TA ("distal" RAs) compared to control RAs. As above, day in study and number of assessments within each day were entered as continuous variables in all analyses. For all analyses, alpha was set at 0.05. All tests were two-tailed.[3]

[3] The primary analyses were conducted on data from all available days (n=414) and assessments (n=1482). Secondary analyses were conducted on data derived from days (n=400) and assessments (n= 1437) that occurred before reported relapses. These analyses revealed very similar findings and are not reported here.

Results

On average, the 64 participants participated in the study for 6.47 days (SD=1.80). Participants completed 77.9% of presented RAs. They completed an average of 17.6 RAs (SD=7.3) and an average of 5.5 TAs (SD=6.1). Most participants (92.2%) completed at least one TA. The mean completion time was 5.7 min (SD=1.6) for assessments during which the Stroop task was administered and 8.2 min (SD=3.8) for assessments during which the IAT was administered.

Natural history of temptations

On average, there were 0.82 (SD=1.27) TAs recorded per day. The number of reported TAs per day declined over the course of the week [parameter estimate (PE)=−0.10, SE= 0.03, $p<0.01$; Fig. 2). In contrast, the number of completed RAs per day did not decline over time, e.g., from days 2 to 7 (whole study days) ($p>0.10$). The distribution of TAs and completed RAs over the day was similar: 20.0% of RAs and 24.7% of TAs occurred before 12:00 PM (midday), 29.1% (RAs) and 26.6% (TAs) occurred between 12:00 PM and 4:00 PM, 33.7% (RAs) and 31.4% (TAs) occurred between 4:00 PM and 8:00 PM, and 17.2% (RAs) and 17.3% (TAs) occurred after 8:00 PM. The mean time of day for TAs (3:28 PM; SD=4:05) was not significantly different (PE=0.43, SE=0.23, $p=0.06$) from the mean time of day for RAs (3:50 PM; SD=3:44).

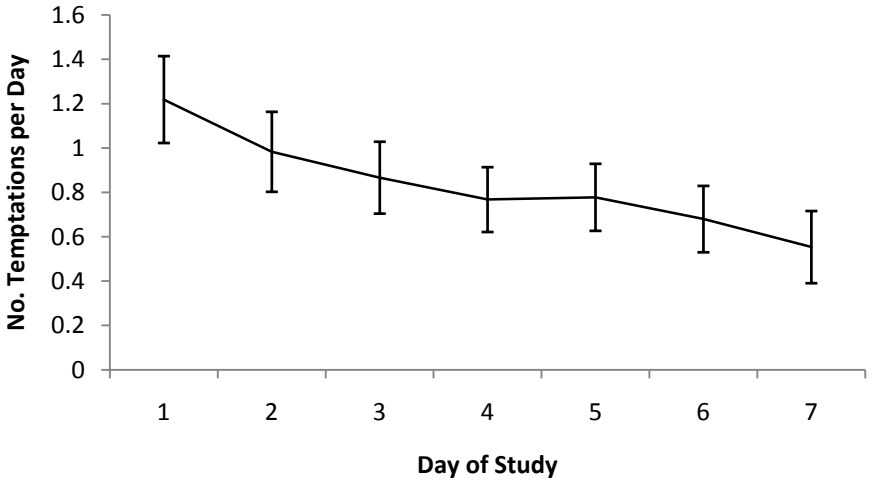

Figure 2. Mean no. of temptations reported per day (1 SE) by day in study.

Craving during temptations

Ratings for craving heroin (PE=0.86, SE=0.09, $p<0.01$) and cocaine (PE=1.02, SE=0.08, $p<0.01$) were both higher at TAs than RAs (Table 2). When temptation rate was added to the models, temptation rate was not associated with heroin craving ($p>0.1$) or with cocaine craving ($p>0.1$). Assessment type remained significant in these models ($ps<0.01$).

Participants' mean ratings (over all observations) for craving heroin and craving cocaine were strongly correlated (n=64, $r=0.67$, $p<0.01$). A within-subject correlation for craving heroin and craving cocaine could be computed for 53 participants; the within-subject correlations also suggested a strong association between heroin and cocaine craving (mean $r=0.69$, SE=0.36, $p<0.01$). There was evidence that ratings for craving heroin (PE=−0.049, SE= 0.024, $p<0.05$) and craving cocaine (PE=−0.035, SE= 0.020, $p=0.08$) declined over days in RAs. Ratings for craving heroin and craving cocaine did not decline over days in TAs ($ps>0.1$).

Subjective variables during temptations

Participants reported higher levels of negative affect (PE= 0.36, SE=0.06, $p<0.01$), anxiety (PE=0.42, SE=0.05, $p< 0.01$), and difficulty concentrating (PE=0.26, SE=0.09, $p< 0.01$) at TAs vs. RAs. When temptation rate was added to the models, temptation rate was associated with negative affect (PE=1.11, SE=0.47, $p<0.05$), state anxiety (PE= 1.24, SE=0.53, $p<0.05$), and difficulty concentrating (PE= 1.48, SE=0.74, $p<0.05$). Assessment type remained significant in these models ($ps<0.01$). Participants reported more positive explicit attitudes to heroin (PE=0.74, SE=0.13, $p< 0.01$) and cocaine (PE=0.94, SE=0.13, $p<0.01$) at TAs vs. RAs. When temptation rate was added to the models, temptation rate was not associated with explicit attitude to heroin ($p>0.1$) or with explicit attitude to cocaine ($p>0.1$). Assessment type remained significant in these models ($ps< 0.01$). There were no significant between-assessment differences for energy level or hunger (Table 2).

Implicit cognitions during temptations

Participants exhibited a robust drug Stroop effect (slower responses on drug words than neutral words, indicative of higher attentional bias) at both TAs (PE=67.7, SE=14.0, $p< 0.01$) and RAs (PE=35.6, SE=7.2, $p<0.01$). However, the drug Stroop effect was significantly elevated at TAs (PE= 31.7, SE=14.2, $p<0.05$) vs. RAs (Table 2). When temptation rate was added to this model, temptation rate was not associated with the drug Stroop effect ($p>0.1$). Assessment type remained significant in this model ($p<0.05$). There was no effect of Stroop type (heroin vs. cocaine Stroop) on the drug Stroop effect ($p>0.1$), and Stroop type did not

moderate the effect of assessment type on the drug Stroop effect (p> 0.1). As noted above, heroin craving and cocaine craving were higher at TAs vs. RAs. The drug Stroop effect was significantly elevated at TAs (PE=29.6, SE=14.9, p<0.05) vs. RAs when controlling for both heroin craving and cocaine craving. [4]

Participants tended to exhibit a positive IAT effect (faster performance when heroin/cocaine paired with pleasant compared to unpleasant, indicative of an automatic positive memory association) at both TAs (ms score–PE=185.8, SE=104.8, p=0.08; D score–PE=0.16, SE=0.08, p<0.05) and RAs (ms score–PE=97.7, SE=47.3, p<0.05; D score–PE=0.14, SE=0.05, p<0.01). However, no significant between-assessment (RAs vs. TAs) differences on the IAT effect (ms or D score) were observed. There was no effect of IAT type (heroin vs. cocaine IAT) on the IAT effect (p>0.1), and IAT type did not moderate the effect of assessment type on the drug IAT effect (p>0.1). [5]

Pharmacological and contextual variables

TAs were more likely to be reported when participants were outside the facility (in the garden; PE=–0.48, SE=0.21, p< 0.05). There were no other significant associations (Table 2).

Mood and cognition in the hours before temptations

Neither craving for heroin (p>0.1) nor craving for cocaine (p>0.1; Fig. 3 shows raw data) was significantly elevated in proximal RAs (RAs that occurred less than 1 h prior to TAs) vs. control RAs. Negative affect (p>0.1) (Fig. 3), anxiety (p>0.1), difficulty concentrating (p>0.1), and explicit attitudes to heroin (p>0.1) and cocaine (p>0.1) were also not significantly elevated in proximal RAs (vs. control RAs). However, the drug Stroop effect (PE=62.4, SE=29.5, p<0.05; Fig. 3) [but not the IAT effect (D score or ms score, ps>0.1)] was significantly elevated in proximal RAs (vs. control RAs; Fig. 3d). There were no significant differences when comparing distal RAs (RAs occurring 1 h to 3 h prior to a TA) and control RAs (all ps>0.1).

[4] The current paper focuses on between-assessment differences. A detailed analysis of the associations between craving ratings and implicit cognitions is beyond the scope of the current paper. However, when craving for heroin or cocaine is entered into the model (including day, number of assessments, and Stroop type, but excluding assessment type), the parameter estimates were non-significant (heroin: PE=2.41, SE=3.14, p>0.1; cocaine: PE=3.74, SE=3.01, p>0.1).

[5] One may question whether the drug-related pictures in the IAT could provoke temptations. Of the 529 RAs at which an IAT was administered, 30 (5.7%) were followed by a TA within an hour. For RAs in which a Stroop task was administered, 31 (5.2%) were followed by a TA within an hour. Therefore, most IAT RAs (94.3%) were not followed by a TA, and the post-assessment TA rate was not higher (PE=0.11, SE=0.26, p>0.66, using proc glimmix) following IAT vs. Stroop assessments (the Stroop task did not include pictures).

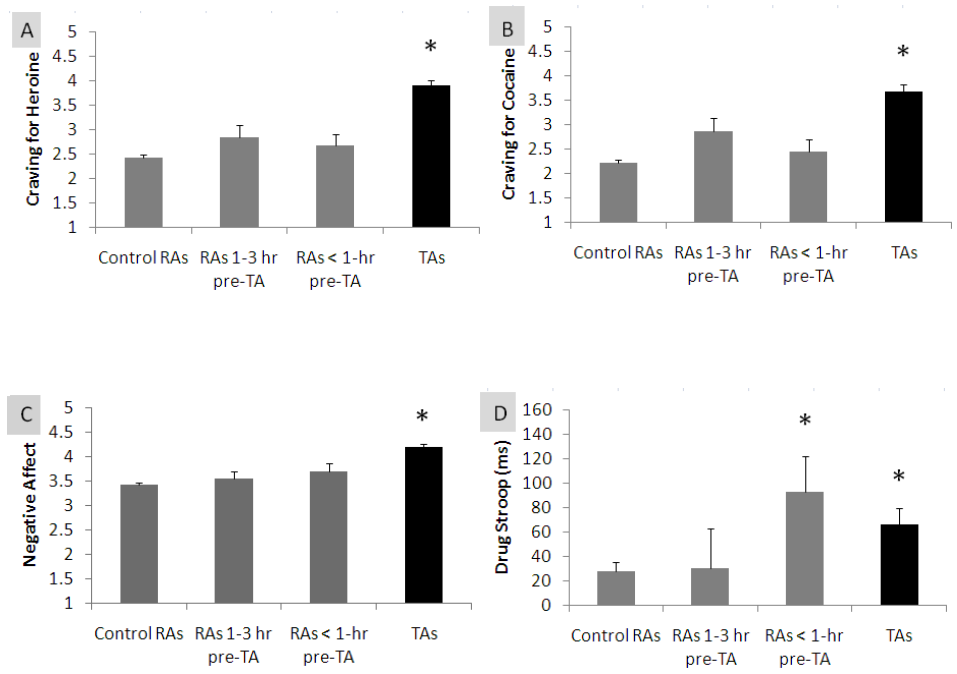

Figure. 3 Mean (1 SE) reported craving for heroin (A), reported craving for cocaine (B), reported negative affect (C), and drug Stroop effect (ms) (D) as a function of assessment type (RA vs TA) and time before TA (see text for details). Data shown are raw (uncorrected) means. RA = Random Assessment, TA = Temptation Assessment. *Significant difference vs. control RAs (p< .05).

Discussion

The main findings were as follows. First, participants reported on average around five and a half temptation episodes over the course of a week while in a clinical drug detoxification setting. Reports were maximal at the outset of the week. Second, negative affect was elevated when a participant reported a temptation episode. Explicit attitudes to heroin and cocaine were also elevated (more positive). Third, attentional bias to drug cues was elevated during temptation episodes, but implicit affective associations with drug cues were not more positive. Last, and perhaps of greatest interest, attentional bias – but not negative affect or explicit attitudes – was elevated in the 1 h prior to the report of a temptation episode. Thus, elevated attentional bias at random assessments may be a harbinger of temptation episodes.

The number of temptations declined during the week, suggesting improvement over time. However, participants may have become tired of completing study assessments over time,

meaning that the decline reflected study fatigue rather than a genuine change in drug use motivation. Note, however, that craving ratings tended to decline in random assessments over time, which suggests a genuine decline in drug use motivation. If real, the decline in reported temptations and heroin craving may reflect recovery from acute heroin withdrawal because methadone does not completely alleviate craving for heroin (Fareed et al., 2011). Speculatively, a decline in heroin craving may promote a reduction in cocaine craving due to cross-drug priming of craving (e.g., Epstein et al., 2010). These points notwithstanding, one should note that craving ratings and temptation rate might increase later in detoxification treatment when participants were withdrawn from methadone (Gossop et al., 1987; Glasper et al., 2008).

Overall, temptation episodes seem problematic for patients during detoxification treatment. The negative affect experienced during temptation episodes presumably impairs quality of life during drug detoxification and may increase the risk of relapse and/or treatment dropout. In addition, individuals who reported more temptations reported generally higher levels of negative affect and state anxiety (averaged across temptations and random assessments). These points notwithstanding, we do not know whether temptation episodes cause negative affect, whether negative affect causes temptation episodes, or whether a third variable underlies the association.

More importantly, the study revealed that attentional bias was elevated at temptation episodes. This finding is consistent with Franken's (2003) model. In this model, attentional bias results from incentive sensitization. Attentional bias to external or imaginal cues can cause increased craving and, presumably, temptations episodes (when craving is acutely elevated). Conversely, craving (and, presumably, temptations) can cause attentional bias. Either way, an association between assessment type and attentional bias should be and was observed.

Interestingly, however, the association between assessment type and attentional bias persisted when controlling for self-reported heroin and craving. Thus, the association between assessment type and attentional bias was not accounted for, or mediated by, craving. This finding suggests that there is another attribute of temptation episodes that is associated with elevated attentional bias. Berridge (2009) has noted that the attribution of incentive salience may occur to the mental representations of drug-related actions ("action salience") as well as the mental representations of drug-related stimuli. As Berridge (2009, p. 9) puts it, an addict "might urgently *want* to act". The attribution of incentive salience to stimuli and actions might occur in parallel, and the latter process may be subjectively detected in the absence of subjective craving. Speculatively, attentional bias may be more closely associated with the subjective correlate of action salience (wanting to act) than with the subjective correlate of incentive salience (craving).

We do not know whether the attentional bias causes the temptation episode or whether the temptation episode causes attentional bias (or whether a third factor underlies the association). However, attentional bias (but not negative affect or other mood measures) was elevated prior to the onset of a temptation episode. This is consistent with the idea that attentional bias can cause a temptation episode.

To definitively examine the causal relationship between attentional bias and temptation episodes, it is necessary to experimentally manipulate attentional bias. If attentional bias causes temptation episodes, then an attentional retraining intervention should influence the number of reported temptation episodes. The effect of attentional retraining on temptation episodes has not hitherto been examined. Laboratory studies have examined the effect of attentional retraining on self-reported craving. These studies have yielded mixed findings, with some studies reporting an effect (Field and Eastwood 2005; Attwood et al., 2008, males only), and others reporting no effect (Field et al., 2007; 2009a; Schoenmakers et al., 2007).

Whether or not the association between attentional bias and temptation episodes is causal, the study has implications for treatment. If elevated attentional bias is indeed a harbinger of temptation episodes, it may be possible to intervene (when attentional bias is elevated) to reduce the risk that a temptation episode is subseqzuently experienced. An ecological momentary intervention (EMI) could be delivered on a PDA, just in time, when the individual is most in need of that intervention (Shiffman et al., 2008). Interventions that reduce the risk of temptation episodes may improve quality of life during drug detoxification and, perhaps, reduce the risk of relapse. If the association between attentional bias and temptation episodes is shown to be causal, then an attentional retraining intervention, delivered on the PDA, would be warranted.

The study had a number of limitations. First, to avoid overburdening participants, we did not ask them to report when each temptation episode had concluded. Thus, we did not collect data on the duration of temptation episodes. In addition, it is likely that some of the RAs occurred during the temptation episode (e.g., those within 1 h of the temptation onset). Second, we did not directly assess whether each temptation was primarily directed toward heroin use or cocaine use (or both). Third, a relatively small number of RAs occurred within 1 h prior to a temptation episode. Thus, the null effects for negative affect and explicit attitudes (for the comparison between proximal and control RAs) should be treated with caution. Fourth, in common with other EMA studies, assessment type (RA vs. TA) is confounded with assessment initiation method (person-initiated vs. PDA-initiated). In future studies, it may be useful to collect data from person-initiated assessments when participants are not experiencing a temptation. Fifth, the generalizability of the findings to unmedicated users in outpatient or more naturalistic settings is not known. If the findings

generalized to other detoxification settings, this would be of significant clinical interest. Future research should investigate also the time course of temptations throughout the entire detoxification period. Last, as noted earlier, the direction of causality of the observed relationships remains uncertain.

The study also had strengths. We administered both subjective and cognitive assessments on the PDA. The data revealed that there were robust between-assessment differences on a number of subjective and cognitive measures. We were also able to examine the time course of mood and cognition prior to participants' entries of temptation episodes.

In sum, the data revealed that attentional bias – but not subjective measures – was elevated both prior to the entry of a temptation episode and during a temptation episode. Interventions that target cognitions prior to or during temptation episodes may reduce the probability or the duration of a temptation episode and, perhaps, reduce the risk of relapse.

Chapter 4

Individual differences in anterior cingulate activation associated with attentional bias predict cocaine use after treatment

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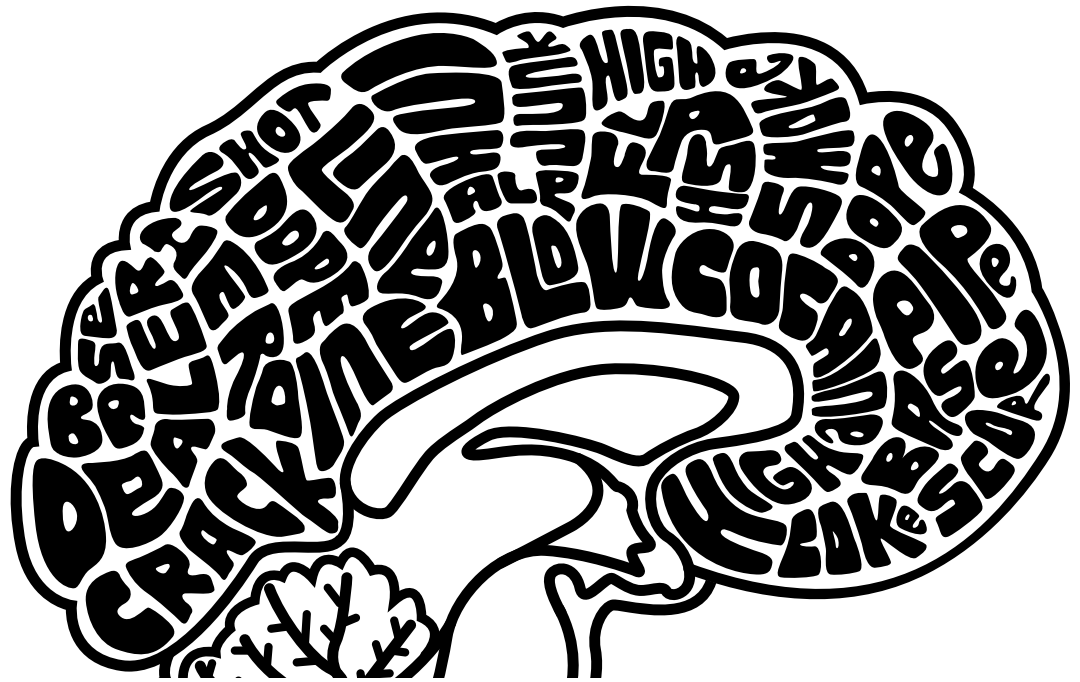

Neuropsychopharmacology, 2013, published online ahead of print Jan 30

Abstract

Drug-dependent patients often relapse into drug use after treatment. Behavioral studies show that enhanced attentional bias to drug cues is a precursor of relapse. The present functional magnetic resonance imaging (fMRI) study examined whether brain regions involved in attentional bias are predictive of cocaine use after treatment. Attentional bias-related brain activity was measured – with a cocaine Stroop task – in cocaine-dependent patients during their first week in detoxification treatment and was used to predict cocaine use at 3-month follow-up. The predictive value of attentional bias-related brain activity in a priori defined regions of interest, in addition to other measures such as self-reports of substance severity, craving and behavioral attentional bias were examined. The results show that craving in the week before treatment and individual variability in attentional bias-related activity in the dorsal anterior cingulate cortex (dACC) were significant predictors of days of cocaine use at 3-month follow-up and accounted for 45% in explained variance. Brain-activity in the dACC uniquely contributed 22% of explained variance to the prediction model. These findings suggest that hyperactive attentional bias-related brain activity in the dACC might be a biomarker of relapse vulnerability as early as in the first week of detoxification treatment. Ultimately, this may help to develop individually tailored treatment interventions to reduce relapse risk.

Introduction

The main goal of most substance dependence treatment is to prevent patients from relapsing into substance use. Despite the efforts to treat substance-dependent patients effectively, treatment dropout rates are generally more than 50% and most patients subsequently relapse (Miller, 1996; Franken and Hendriks, 1999; Hättenschwiler et al., 2000). The identification of predictors of substance use relapse have been of high interest in addiction research (e.g., Miller et al., 1996; Donovan, 1996; McKay, 1999). Particularly in cocaine addiction, a variety of predictors of relapse have been tested including demographic variables, substance use severity, and craving (for a review see Poling et al., 2007). These predictors are largely based on self-report measures. However, over the years the idea that addiction is a relapsing brain disorder (Leshner, 1997) has gained more interest. Support for this idea comes from recent studies suggesting that (neuro)cognitive measures might be better predictors of relapse than self-report measures (Marissen et al., 2006; Kosten et al., 2006). Currently, addiction research is focusing more on the role of cognitive predictors in relapse to substance use, and specifically the neural correlates of cognitive control (Garavan and Hester, 2007; Goldstein and Volkow, 2011).

Attentional bias is one of the most studied cognitive processes in addiction. Attentional bias in addiction refers to the automatically enhanced cognitive processing of drug-related (salient) stimuli compared with neutral (nonsalient) stimuli. Recent theories suggest that it is associated with craving and therefore has an important role in the maintenance and relapse of drug dependency (Franken, 2003; Field and Cox, 2008). A widely used task to measure attentional bias is the addiction Stroop task (Cox et al., 2006). Behavioral studies that have used the addiction Stroop paradigm in substance-dependent individuals have indeed found an attentional bias toward the substance of abuse (for a review see Cox et al., 2006). More importantly, several studies show that attentional bias to substance-related stimuli (on the behavioral level) is a predictor of treatment outcome and relapse in smoking (Waters et al., 2003a; Powell et al., 2010), alcohol (Cox, et al., 2002, 2007), heroin (Marissen et al., 2006) and cocaine use (Carpenter et al., 2006; Marhe et al., 2012). These results indicate a possible clinical relevance of attentional bias. In addition, more recent studies have taken an interest in studying the neural substrates of attentional bias in addiction.

Brain regions that have been found to be associated with attentional bias in addiction include (prefrontal) cortices such as the anterior cingulate cortex (ACC; Luijten et al., 2011a, 2012; Nestor et al., 2011; Vollstädt-Klein et al., 2012), dorsolateral prefrontal cortex (DLPFC; Hester and Garavan, 2009; Luijten et al., 2012; Vollstädt-Klein et al., 2012), insula (Luijten et al., 2011a; Vollstädt-Klein et al., 2012) and subcortical structures such as the nucleus accumbens (Nestor et al., 2011) and amygdala (Vollstädt-Klein et al., 2012; Janes et al., 2010a). Most pertinent to the present study is that attentional bias-related brain activity in

the insula and dorsal ACC (dACC) has been found to be predictive of smoking relapse (Janes et al., 2010b). Involvement of the ACC in response to cocaine cues has also been found in a study with cocaine users (using the addiction Stroop task; Goldstein et al., 2009). However, no study to date has examined whether brain regions involved in attentional bias to cocaine stimuli (as measured by a Stroop task) are predictive of cocaine relapse after treatment.

The goal of the present study therefore was to examine whether brain activity during a cocaine Stroop task measured in the first week of detoxification treatment would be associated with cocaine use measured at 3-month follow up. Based on aforementioned studies we hypothesized that brain regions involved in attentional bias (i.e., dACC, DLPFC, insula, nucleus accumbens and amygdala), would be associated with cocaine use at follow-up.

Materials and Methods

Participants

Participants were 34 cocaine-dependent inpatients recruited from an addiction treatment center (Bouman-GGZ) in Rotterdam, the Netherlands. Inclusion criteria were (1) age between 18 and 65 years; (2) DSM-IV diagnosis for cocaine dependence (assessed by both a physician and a research psychologist); and (3) the ability to speak, read, and write in Dutch at an eighth-grade literacy level. Exclusion criteria were (1) indications of severe psychopathology (i.e., psychosis, severe mood disorder, as assessed by a physician); (2) self-reported color blindness or (noncorrected) defective vision; (3) pregnancy or breast-feeding; and (4) functional magnetic resonance imaging (fMRI) contra-indications. We had to exclude the data of eight participants. Reasons for exclusion were: loss to follow-up (n=1); mismatch between self-reported days of cocaine use and urine results at follow-up (n=1); vision problems (n=2); an accuracy rate on the Stroop task of less than 60% (n=3; these participants also showed excessive head motion of > 3 mm); major anatomical abnormality observed on MRI (n=1). The final sample consisted of 26 cocaine-dependent patients (for demographics see Table 1).

Approval of the study was received from the Ethics Committee of the Erasmus MC - University Medical Center Rotterdam, Rotterdam, the Netherlands. All procedures were carried out with the adequate understanding and written informed consent of the participants. All participants received a financial compensation of 35 euros after completion of the fMRI measure and 25 euros after completion of the 3-month follow-up measure. The present study was part of a larger study that investigated relapse using other psychophysiological and cognitive measures (not reported in the present study).

Table 1. Demographic and Substance Use Variables[a]

Subject Variable	Final sample (n=26)
Demographic variables	
Age	38.7 (9.2)
Males (%)	85
Education (%)	
Primary education	4
Junior secondary education	54
Senior secondary education	31
Higher education	11
Substance use variables	
Total years of cocaine use	11.4 (6.3)
Number of days of cocaine use in 30 days before treatment entry	16.5 (11.9)
Cocaine administration route (%)	
Snorting	31
Smoking	65
Intravenous	4
Craving in the week before treatment	
OCDUS Desire and Control (1-5)	2.8 (1.1)

OCDUS, Obsessive Compulsive Drug Use Scale.

[a]Values are means (SD) unless otherwise indicated (%).

Stroop Task

A cocaine Stroop task was used to measure attentional bias for cocaine related stimuli. The task contained 10 cocaine words (Dutch equivalent of basepipe, crack, smoke, cocaine, blow, line, coke, snort, powder, base), 10 neutral words drawn from the category "indoor features" (Dutch equivalent of blanket, sofa, oven, lamp, attic, cabinet, armchair, tap, couch, stove), and 10 letter strings (e.g., MMMM; Waters et al., 2012). Letter strings were included to increase the number of conditions in the task which, in combination with a semi-random block order, reduced multicollinearity between parameter estimates for cocaine and neutral words (see Supplementary Information, Part I for more information on the order of task conditions). Words and letter strings were presented in the colors blue, yellow, green, or red. Participants were instructed that they should ignore the meaning of the word and only respond to the color that the word was presented in. They were instructed to indicate as rapidly and accurately as possible in which color the word was presented by pressing one of four response buttons with corresponding colors.

The task started with 32 practice trials consisting of only letter strings. Next, in the experimental phase, stimuli were presented in a blocked design with three categories (cocaine, neutral, and letter strings). Every category was presented six times, resulting in a total of 18 blocks. Each block contained 10 words. After each six blocks there was a 38 s resting period. Order of presentation of the task conditions was semi-random; block order was the same for each participant. Each experimental trial began with a 250 ms fixation cross, followed by stimulus presentation with a duration of 1750 ms. Response could be given within this timeframe. After response, the stimulus remained on screen. No feedback regarding performance accuracy was provided to the participants.

Procedure

Patients entered the treatment center for an inpatient detoxification treatment. A standard detoxification treatment in this setting has a duration of 3 weeks. The specific goal of this treatment is to reduce cocaine withdrawal symptoms by means of psychoeducation about the detox symptoms and individual therapy based on cognitive-behavioral techniques. Afterwards, the patients start a follow-up treatment at a different department within the same treatment center. This is usually a rehabilitation program with a variable duration between 1 month and 2 years, depending on the need for treatment.

Patients that met the study criteria were informed about the study on the second day of their detoxification treatment. They had 24 hours to decide whether to participate. Volunteers signed the informed consent on the third day of detoxification treatment. Cocaine use severity was assessed using the Addiction Severity Index (ASI; McLellan et al., 1980; Hendriks et al., 1989) and past week craving using the cocaine version of the Obsessive Compulsive Drug Use Scale (OCDUS; Franken et al., 2002). On the fourth day of treatment, participants were escorted to the Erasmus Medical Center where they performed the cocaine Stroop task in the scanner. After completion, participants were escorted back to the treatment center.

To ensure retention and compliance for the follow-up assessment the researcher first collected multiple contact information at the start of the study. For example, we collected phone numbers and e-mail addresses of the participant but also of their family, friends, social workers and other professionals involved with the patient. Second, the participant was informed that (s)he would receive a financial compensation of 25 euros for completion of the follow-up assessment. Third, participants were ensured that information on current use (both self-reports and urine screens) was used for research purposes only. Participants were contacted 3 months after study participation via telephone and/or e-mail to set up an appointment for a face-to-face follow-up interview. Follow-up tests were performed in the

treatment center. If a participant was out of treatment at this point, then he/she was asked to return once to the treatment center to complete the follow-up tests. If the participant was unable to travel to the main treatment center for the assessment, then the researcher would perform the assessment in the (for the participant) nearest Bouman-GGZ treatment facility. If that was also not possible, then we arranged transfer by taxi for the participant to the treatment center.

Outcome measure

The number of days of recent cocaine use was measured 3 months after study participation. At follow-up, participants were asked to report the number of days they had used cocaine in the last 30 days, which we labeled "recent cocaine use". Self-reports were biochemically verified by means of urine screens. All self-reports of 0 days of use in the last 30 days were confirmed by a negative urine screen, except for one participant who reported 0 days of use while the urine screen was positive. This participant was excluded from the analysis (see Participants section). In the final sample, 11 participants reported not to have used cocaine in the last month and 15 participants reported to have used cocaine 12.1 days on average (range 1-30, SD 10.6) in the last month.

fMRI data acquisition and processing

Imaging data were obtained with a 3T GE Healthcare MRI scanner. Blood oxygen level-dependent (BOLD) sensitive functional echo-planar imaging T2*-weighted images were acquired in 34 axial slices (thickness=2.6 mm, interslice gap=0.4 mm) covering the entire supratentorial brain with a repetition time (TR) of 2500 ms, echo time (TE) of 30 ms, field of view (FOV) of 220 mm, and matrix size of 64×64. A structural 3-dimensional inversion recovery (IR) fast spoiled gradient recalled echo (FSPGR) T1-weighted image was acquired in 192 axial slices (thickness=1.6 mm and 0.8 mm overlap, resulting in an effective slice thickness of 0.8 mm) with TR of 12.0 ms, TE of 3.7 ms, a rectangular FOV of 250×175 mm2, and matrix size of 416×256 mm. Due to an unexpected scanner-shutdown we were forced to continue the project on a different 3T scanner by the same vendor (GE Healthcare, Milwaukee, WI, USA) during the study. Data of n=8 were acquired on the Signa HDxt scanner and data of n=18 were acquired on the Discovery MR750 scanner. In the Supplementary Information (part VII) we describe additional analyses regarding the use of two scanners. There we report temporal signal to noise maps of both scanners and we conducted the main statistical analyses with scanner type included as covariate, showing that it is unlikely that the use of two scanners influenced the present findings.

Functional images were analyzed using SPM8 (Statistical Parametric Mapping; Wellcome Trust Centre for Neuroimaging, London, UK). Preprocessing of the functional data included

realignment and unwarping of all functional images. Next, the anatomical scan was co-registered to the mean T2*-weighted image and subsequently segmented into gray and white matter. Segmentation parameters were used for normalization using the SPM T1 MNI 512 template. Normalized images were spatially smoothed with an 8 mm full-width at half-maximum Gaussian filter. The three task conditions, cocaine words, neutral words and letters were modeled in the context of the general linear model, using delta functions convolved with a canonical hemodynamic response function (error rates were not associated with activation estimates, see Supplementary Information, Part IV for results). The contrast reflecting brain activation associated with attentional bias (cocaine words minus neutral words) was calculated for each individual. Subsequently, five a-priori regions of interest (ROIs) were selected based on their presumed role in attentional bias, including the: bilateral dACC, DLPFC, insula, nucleus accumbens and amygdala (Figure 1; see Introduction section for rationale). ROIs for the DLPFC, insula and amygdala were derived from the automatic anatomical labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002). Since the dACC and nucleus accumbens are not included in the AAL atlas, an 8 mm sphere around MNI coordinates ±8 30 32 was used as an ROI for the dACC (Mars et al., 2005) and an 8 mm sphere around MNI coordinates ±10 12 -2 was used for the nucleus accumbens (Knutson et al., 2008). To test the main attentional bias effect in the ROIs the cocaine minus neutral words contrast was entered in a random effects one-sample *t*-test. Results were thresholded at $p < .05$, Family Wise Error (FWE) corrected for multiple comparisons across the search volume (Small volume correction: Friston et al., 1996; Worsley et al., 1996). To do so, analyses were first thresholded at $p < .001$ uncorrected with 20 contingently activated voxels (160 mm3; see Supplementary Information, Part V), and then corrected using a small volume correction ($p < .05$ FWE corrected) in which the search volume was restricted by the a-priori defined ROIs.

Statistical Analyses

First, to demonstrate attentional bias on a behavioral level for cocaine words, behavioral data of the Stroop task were examined (means are displayed in Table 2). Differences in reaction times (RTs) and accuracy scores for the cocaine words and the neutral words were tested using a paired samples *t*-test. To use the Stroop effect as a predictor in regression models (described below) a single differential score was calculated for RT and for accuracy (by subtracting results on cocaine words from neutral words).

Second, linear regression analysis was used to examine the predictive value of multiple variables (i.e., addiction severity, craving, behavioral and brain related attentional bias) in the prediction of the outcome measure "recent cocaine use". Due to the relative large amount of predictor variables a stepwise regression analysis was performed (Field, 2009). The stepwise method tests, at each addition of a variable into the regression model, which

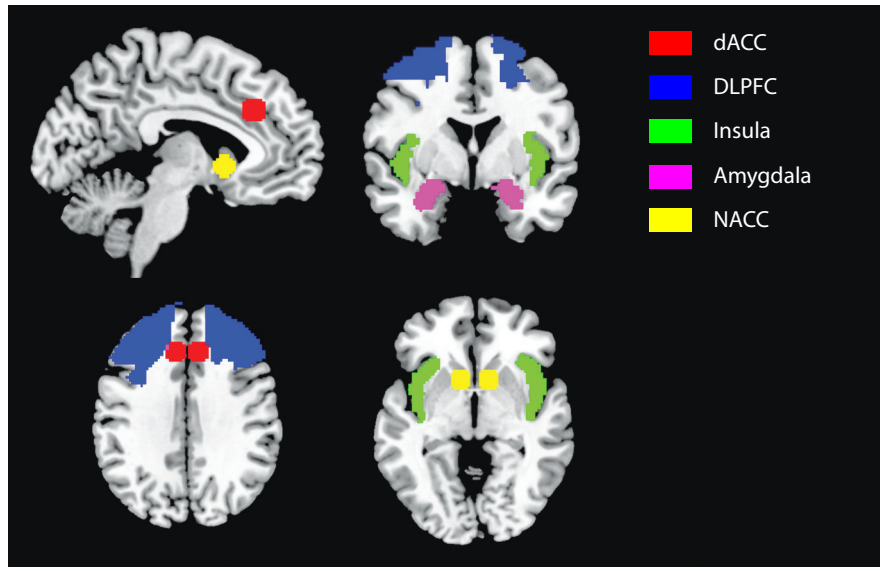

Figure 1. A-priori defined, literature-based regions of interest involved in attentional bias to substance cues. dACC, dorsal anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; NACC, nucleus accumbens.

variable contributes the least to the prediction of recent cocaine use and removes this variable from the model. By using this method all redundant predictors are filtered out of the model. Because we were interested in the unique contribution of three clusters of variables (i.e., self-reports, behavior, and imaging) we performed the regression analysis in three steps. Step 1 contained four self-report variables: total years of cocaine use, number of days of cocaine use in 30 days before treatment entry, and cocaine administration route (i.e., addiction severity) as well as craving in the week before treatment. Since cocaine administration route is a categorical variable with three levels, two dummy variables were created. Step 2 contained two variables of behavioral data: Stroop effect RT and Stroop effect accuracy. Step 3 contained the imaging variables (extracted contrast values for cocaine minus neutral words in the five bilateral ROIs: left and right dACC, left and right DLPFC, left and right insula, left and right nucleus accumbens, left and right amygdala). In each step, the selection criteria for inclusion and exclusion of predictors in the model were F_{enter}: $p \leq .05$ and F_{remove}: $p \geq .10$.

Third, we wanted to check the robustness of the individual predictors that were included in the model based on the results of the stepwise regression. To do so, bootstrapping was used with 2000 bootstrapped samples and a 95% confidence interval (CI; Efron and Tibshirani, 1993; Mooney and Duval, 1993). The bootstrap procedure can only be conducted when predictor variables are forcedly entered into the regression model (instead of stepwise). Therefore, predictors that met the inclusion criteria of the stepwise method were entered in a hierarchical regression analysis.

Finally, predictors were checked for multicollinearity by means of tolerance statistics. All statistical analysis were conducted with SPSS 18.0 (IBM Corporation, Armonk, NY).

Table 2. Mean Reaction Times (milliseconds) and Accuracy Scores (percentages) for the Stroop Task

	Mean	SD
RT cocaine words	972	137
RT neutral words	886	126
Accuracy cocaine words	91	8
Accuracy neutral words	93	8

RT, reaction time.

Results

Attentional bias

We found a significant difference between Stroop RTs on cocaine words and neutral words, (t[25]= 6.87, p < .001), with cocaine dependent patients responding slower to cocaine-related stimuli than to neutral stimuli. This indicates the presence of an attentional bias. No differences in accuracy between cocaine and neutral words were found, (t[25]= -1.84, *ns*).
For the imaging data, we did not find significant activation (p < .05 FWE small volume corrected) for the cocaine minus neutral words contrast in any of the ROIs within the patient sample.

Predictors of recent cocaine use

The stepwise regression yielded that two predictors – craving in the week before treatment and attentional bias related activity in the right dACC – met the selection criterion for inclusion in the model. Other self-report, behavioral and imaging variables were excluded based on the criterion (see Table 3a). Model statistics are displayed in Table 3b. The first step, including craving in the week before treatment, accounted for 23% of explained variance in recent cocaine use. Individual differences in brain activation for the attentional bias contrast in the right dACC added another 22% explained variance to the model. Thus, together both predictors accounted for 45% of explained variance in the prediction of recent cocaine use.

Bootstrapping confirmed that both individual predictors were robust predictors of treatment outcome (see Table 3c). The coefficients indicated a positive association between the predictors and the outcome measure. These findings showed that higher self-reported past-week craving and enhanced activation for cocaine words vs. neutral words in the right dACC (both measured during the first week of treatment) were associated with more days

of recent cocaine use (measured at 3-month follow-up). Direct associations between each significant predictor and recent cocaine use are displayed in Figure 2.

Finally, collinearity statistics indicated that the predictors were not associated with each other (tolerance = 0.98).

Table 3a. Statistics of Predictor Variables added in the Stepwise Regression Analysis

Predictor Variables	Standardized Coefficients (=β)	*t* statistic	*p*-value
Self-reports			
Total years of cocaine use	0.14	0.88	.387
Number of days of cocaine use in 30 days before treatment entry	0.04	0.22	.831
Cocaine administration route			
snorting vs. smoking	0.18	1.09	.287
snorting vs. intravenous	0.08	0.46	.647
Craving in the week before treatment	0.41	2.57	.017[a]
Behavior			
Stroop effect RT	-0.24	-1.51	.145
Stroop effect Accuracy	-0.11	-0.66	.519
Imaging[b]			
l-dACC	-0.53	-1.70	.104
r-dACC	0.47	3.00	.006[a]
l-DLPFC	-0.35	-1.39	.178
r-DLPFC	-0.27	-1.01	.322
l-insula	-0.36	-1.41	.174
r-insula	-0.06	0.21	.832
l-nucleus accumbens	-0.11	-0.40	.694
r-nucleus accumbens	-0.05	-0.17	.868
l-amygdala	-0.37	-1.53	.140
r-amygdala	0.04	0.15	.884

Table 3b. Model Statistics and Change Statistics of the Final Model Predicting Recent Cocaine Use

Predictor Variables	Model Statistics			Change Statistics		
	R^2	*F* Statistic	*p*-value	ΔR^2	ΔF Statistic	Δp-value
Step 1	0.23	7.15	.013			
Craving in the week before treatment						
Step 2	0.45	9.26	.001	0.22	9.00	.006
r-dACC[b]						

Table 3c. Bootstrap Results for Individual Predictors in the Final Model Predicting Recent Cocaine Use

Predictor Variables	Unstandardized Coefficients (=B)	Standard Error (=SE)	Bootstrapped 95% Confidence Interval
Craving in the week before treatment	3.82	1.48	1.48 – 7.36[c]
r-dACC[b]	15.62	5.35	4.61 – 25.14[c]

RT, reaction time; l, left; r, right; dACC, dorsal anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex.

[a]Meet selection criteria F_{enter}: $p \leq .05$ and F_{remove}: $p \geq .10$.

[b]Attentional bias contrast (cocaine minus neutral).

[c]Significant (value 0 is not in the confidence interval).

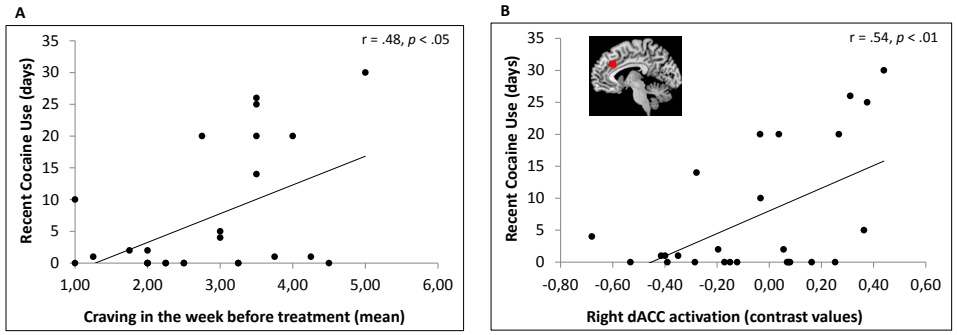

Figure 2. Correlation between (a) craving in the week before treatment and recent cocaine use and (b) attentional bias related activation in the right dACC and recent cocaine use. dACC, dorsal anterior cingulate cortex.

Discussion

The present study is the first to examine to what extent attentional bias-related brain activity predicts recent cocaine use after treatment, over and above other relevant predictors such as craving, substance use severity and behavioral measures of attentional bias. We found that both higher levels of self-reported craving in the week before treatment and enhanced attentional bias-related brain activity in the right dACC – measured in the first week of detoxification treatment – were associated with cocaine use at 3-month follow-up. Cocaine use severity, behavioral measures of attentional bias, and other brain regions that have previously been shown to be associated with attentional bias (i.e., DLPFC, insula, nucleus accumbens, and amygdala) were not significantly associated with cocaine use at 3-month follow-up. In addition, we found that when controlling for self-reported craving, individual differences in right dACC activity made a rather large and unique contribution to the prediction of recent cocaine use. These findings suggest that a neural correlate of attentional bias in the dACC might be a useful biomarker of cocaine use after treatment. Most importantly, as early as in the first week of treatment our findings provide information on an individual's risk to use cocaine again 3 months after treatment.

The dorsal part of the ACC has been implicated in cognitive processes such as salience detection (Seeley et al., 2007), conflict monitoring in general (Botvinick et al., 2004; Kerns et al., 2004; Egner et al., 2008) and in the presence of emotionally salient distractors (specifically the right dACC; Haas et al., 2006). Hyperactivity in the ACC associated with attentional bias to substance-related cues has previously been shown in smokers (Luijten et al., 2011a, 2012; Nestor et al., 2011; Janes et al., 2010b) and alcohol-dependent patients (Vollstädt-Klein et al., 2012), and is thought to reflect enhanced conflict when task performance is being interfered by the automatic detection of salient substance-related stimuli. However, the present design does not rule out alternative interpretations of the dACC involvement. For example, it might be possible that dACC activity is related to the greater requirement for cognitive control during the drug trials, rather than the content of the stimuli per se.

In relation to relapse, it is suggested that individual variations in the brain's ability to control cognitive conflict may account for differences in risk of relapse (Garavan and Hester, 2007). Our results support this idea by finding that when more top-down control is necessary (i.e., increased dACC activity) to focus on a cognitive task in the presence of distracting drug cues one is more vulnerable to use cocaine after treatment. Additionally, individuals who need less top-down control (as reflected by less to no attentional bias-related dACC activity) are less susceptible to return to daily use of cocaine. This is in line with findings of Janes et al. (2010b) who found that attentional bias-related dACC activity was predictive of relapse in smokers.

Concerning the self-report measures we examined in the current study, we found that self-reported craving in the week before treatment – but not substance use severity – was predictive of cocaine use at 3-month follow-up. Craving constitutes a central role in established theories of addiction (Robinson and Berridge, 1993). Indeed several studies have reported that subjective craving is associated with relapse and treatment outcome in cocaine-dependent patients (Weiss et al., 2003; Paliwal et al., 2008; Preston et al., 2009). More recent models of addiction propose a role for both craving and attentional bias in the maintenance of substance use and relapse (Franken, 2003; Field and Cox, 2008). Our results support this by finding that both self-reported craving in the week before treatment and individual variability in dACC activity related to attentional bias were associated with cocaine use at follow-up, suggesting a role for both processes in relapse. However, these models suggest that attentional bias predicts relapse via craving and not directly, whereas our results showed that dACC activity was a strong predictor, even when controlling for self-reported craving. This suggests that enhanced attentional bias-related brain activity might be independently associated with drug relapse.

Somewhat unexpected in the light of the recent discussion on the relation between craving and attentional bias (Field et al., 2009), no significant correlations between craving, attentional bias, and dACC activation were observed (see Supplementary Information, Part II for results). The meta-analysis by Field et al. (2009) showed that subjective craving is consistently (though weakly) correlated with behavioral and EEG indices of attentional bias. Concerning the behavioral measures, it is possible that the statistical power of the present study was too low to yield significant results given the fact that the correlations between craving and the Stroop task are known to be weak (r = .15). In addition, dACC activation was not found to be associated with craving nor behavioral attentional bias. This is somewhat unexpected since all measures could be regarded as measures of the same underlying processing: 'motivational salience'. Although exact interpretation is not straightforward (also given the relative small n), it seems at least to be an indication that the ACC does not necessarily be the neurobiological structure responsible for cocaine craving. Further, it should be kept in mind that craving was not measured during fMRI scanning but was an average measure (OCDUS) of the craving in the week before the fMRI measurement.

The present study indicates that cocaine use after treatment is better predicted by neuroimaging than behavioral measures of the addiction Stroop effect. Other fMRI studies examining neurocognitive predictors of substance relapse have reported similar results in methamphetamine relapse (Paulus et al., 2005) and cocaine relapse (Brewer et al., 2008; Jia et al., 2011). Although previous studies have reported an association between attentional bias on the behavioral level and drug relapse (Marissen et al., 2006; Carpenter et al., 2006) we could not find any significant associations between behavioral measures and cocaine use outcome (see Supplementary Information, Part III for results). It might be that functional

neuroimaging is a better predictor because it is a more sensitive measure of individual differences in biased attention to drug cues than behavioral measures.

Possible clinical implications of our results include the use of dopaminergic manipulation to reduce attentional bias-related brain activity (Ersche et al., 2010; Goldstein et al., 2010; Luijten et al., 2012) or attentional retraining (Schoenmakers et al., 2010). Patients who are vulnerable to relapse due to enhanced attentional bias for drug cues might benefit from such approaches, although these interventions need further investigation. Future intervention studies using either psychopharmacological interventions or cognitive training may obtain valuable information by identifying those patients with higher levels of dACC activity in response to drug cues.

The present study had limitations. First, we only measured days of cocaine use in the last month of the 3-month follow-up period. We could not rule out that patients who reported to have used 0 days in the last month did not use in the 2 months before follow-up and could therefore not term them as "nonrelapsers". Thus, with the present design it was not possible to predict relapse (yes vs. no) which makes it difficult to compare the present results with other fMRI studies on relapse prediction (e.g., Janes et al., 2010b; Paulus et al., 2005). However, it has been found that continuous and dichotomous drug use outcome measures are strongly related to each other (McKay et al., 2001), suggesting that the present outcome measure does provide some information on relapse risk. To examine associations between study variables and different drug use outcome measures, future studies should use multiple outcome measures (e.g., time to relapse, relapse vs. nonrelapse; see for a discussion also Miller et al., 1996). Second, while we found an association between enhanced attentional bias-related brain activity and cocaine use outcome in patients after treatment, we could not demonstrate an overall within-group attentional bias effect in the ROIs. The absence of an overall effect on the attentional bias contrast (cocaine minus neutral words) is not an unusual finding in cocaine Stroop fMRI research (Goldstein et al., 2007, 2009, 2010; Moeller et al., 2012) and may be due to the presence of individual differences in brain activity related to attentional bias (Hester and Garavan, 2009), as manifested by the fact that brain activity was predictive of relapse in a population of variable relapse risk. We would like to emphasize, however, that the task did activate regions that are typically expected to be activated for a Stroop task such as the dACC and the DLPFC for the neutral and cocaine condition separately (see Supplementary Figure 1 in the Supplementary Information, Part VI). Third, we did not assess other psychiatric disorders using a structured interview or questionnaire and therefore could not examine the influence of these disorders on cocaine use outcome. Finally, we had a large number of predictors and a relatively small sample which could have led to over-fitting of the prediction model. Therefore, we performed a stepwise regression analysis to remove all redundant predictors. To reduce the probability of type II errors, we included variables in

a hierarchical manner based upon previous literature (self-report measures first, behavior measures second, and neuroimaging measures third) so that the predictors are evaluated in each step separately.

In conclusion, the current study showed the clinical relevance of measuring attentional bias-related activity in the dACC in cocaine-dependent patients during the starting phase of treatment. Not only does this provide valuable information about the neurocognitive mechanisms of addiction and of addiction treatment processes, these measures may also help us identifying individuals who are at risk of relapse into cocaine use after detoxification treatment. Although direct clinical implications are not very easy to implement using fMRI methodology, ultimately findings like these may help to develop clinical profiles based on neurocognitive measures to design tailor-made follow-up treatment schedules. Future treatment intervention studies should investigate how this information might benefit relapse-vulnerable patients.

Supplementary Information

I. Order of task conditions in the Stroop task

The task conditions of the current Stroop task (i.e, cocaine words, neutral words and letters) were semi-randomly presented to the participants. All task conditions follow each other equally often. All participants performed the task with the same block order. More specifically, the order of the task conditions was: COCAINE – NEUTRAL – LETTERS – LETTERS – NEUTRAL – COCAINE – REST – COCAINE – LETTERS – NEUTRAL – NEUTRAL – LETTERS – COCAINE – REST – COCAINE – NEUTRAL – LETTERS – LETTERS – NEUTRAL – COCAINE. Previous work has shown that the order of stimuli may induce carry over effects (Waters et al., 2003a). That is, if a neutral condition is preceded by a more emotional condition, the effects of the emotional condition may persist and influence reaction times for the neutral condition, although this is particularly true for event-related designs. As all analyses in the main manuscript are focused on the difference between cocaine and neutral conditions, four different orders for the presentation of these two conditions can be identified within the current task, i.e., COCAINE – NEUTRAL, NEUTRAL – COCAINE, COCAINE – LETTERS – NEUTRAL, NEUTRAL – LETTERS – COCAINE. As there are no carry over effects expected when letters are in between the cocaine and neutral condition, an RM-ANOVA with Order as a two level factor (i.e., COCAINE-NEUTRAL versus NEUTRAL-COCAINE) was performed for reaction times representing the attentional bias effect, i.e., cocaine minus neutral reaction times. Results showed no significant effect of Order ($p = .30$) suggesting that no order or carry over effects are present in the current data. In addition, reaction times in both orders showed the expected attentional bias effect, $p < .05$.

II. Correlations between craving, behavioral attentional bias and r-dACC activity related to attentional bias

Craving was not significantly associated with behavioral measures of attentional bias – that is Stroop effect RT ($r = .09$, $p = .67$) and Stroop effect Accuracy ($r = .19$, $p = .37$) – nor with r-dACC activity for the attentional bias contrast ($r = .16$, $p = .44$). Also, there were no significant correlations between r-dACC activity for the attentional bias contrast and Stroop effect RT ($r = -.21$, $p = .31$) and Stroop effect Accuracy ($r = -.06$, $p = .79$).

III. Associations between behavioral attentional bias and recent cocaine use

To examine whether behavioral measures of the Stroop task were predictive of recent cocaine use - independent of the imaging measures - we repeated the linear regression

analysis reported in the main paper with only two steps: (1) self-report variables; and (2) behavioral measures. This revealed that only craving in the week before treatment was a significant predictor of recent cocaine use (see Table S1). Model statistics were identical to results reported in the main paper: $R^2 = 0.23$, $F(1,24) = 7.15$, $p = .01$, indicating that craving in the week before treatment explains 23% of the variance in recent cocaine use. All other predictor variables were statistically excluded from the regression model.

Exploratory, we also examined direct associations between behavioral attentional bias and recent cocaine use with Pearson's correlations. This revealed that neither Stroop effect RT ($r = -.28$, $p = .16$) nor Stroop effect Accuracy ($r = -.05$, $p = .80$) were directly associated with recent cocaine use.

IV. Error rate on the Stroop task and ROI-activity

The blocked fMRI analysis reported in the main paper included both correct and incorrect responses on the Stroop task. To examine whether incorrect responses on the Stroop task evoked different activation patterns we examined associations between the error rate on the Stroop task and ROI activity. The difference score in error rates on cocaine minus neutral words (Stroop effect Error) was not significantly associated with activity in the ROIs for the cocaine minus neutral words contrast (all $p > .20$), suggesting that activation estimates included in our main analysis are not associated with errors.

V. ROI results for the cocaine minus neutral words contrast thresholded at $p < .001$ uncorrected

In the main text, ROI analyses for the attentional bias contrast were thresholded at $p < .05$, Family Wise Error (FWE) using small volume correction. However, as the ROIs for the dACC and nucleus accumbens (NACC) are rather small (8mm spheres) we also examined the uncorrected data ($p < .001$) in these ROIs. Results showed no significant activation for the cocaine minus neutral words contrast in the dACC and NACC, which is similar to the results of the small volume corrected data.

VI. Task related brain activation

Figure S1 illustrates brain activation in regions related to the Stroop task for the cocaine and neutral condition separately.

VII. MRI scanner compatibility

Data for this study were collected using two 3.0 Tesla MRI GE scanners (n = 8 on the Signa HDxt and n = 18 on the Discovery MR750) due to the inability to continue data collection on the Signa HDxt after magnet failure. Identical 8-channel head coils were used for both scanners. Parameters for image acquisition as described in the main text were kept constant across scanners. Given that scanner vendor, field strength, head coil and scanner parameters were kept constant, differences between scanners were expected to be minimal.

Several approaches were adopted to assess and deal with inter-scanner reproducibility issues in cocaine-dependent patients (similar to the multicenter fMRI study in cannabis users performed by Jager et al., 2010). First, temporal Signal-to-Noise Ratio (tSNR) maps were created based on the preprocessed functional time series acquired during the Stroop task (i.e., the unwarped, co-registered and normalized time series). TSNR is a useful measure of image time course stability (Friedman and Glover, 2006) and is calculated by dividing the mean of a time series by its standard deviation. To remove low-frequency scanner drifts, tSNR maps were high pass filtered using a cut-off of 128 seconds (which is equivalent to the high pass filter used in the imaging analyses described in the main text). To ascertain the expected similarity, signal to noise maps from patients scanned on the Signa HDxt were quantitatively compared to those from patients scanned on the Discovery MR750 using a nonparametric two sample *t*-test. As tSNR cannot be assumed to be normally distributed (both thermal and physiological noise contribute, which have different distributions), nonparametric statistics were applied, using the SnPM5b toolbox in SPM5 developed by Andrew Holmes and Tom Nichols (see also *http://www2.warwick.ac.uk/fac/sci/statistics/staff/academic-research/nichols/software/snpm/*). An approximate test of 1000 permutations was used and a FamilyWiseError (FWE) corrected *p*-value of .05 was applied. The analysis showed increased tSNR in the Signa HDxt compared to the Discovery MR750 in 7 small clusters (ranging from 1-3 voxels), all located outside the brain. Increased tSNR on the Discovery MR750 relative to the Signa HDxt was found in a single voxel in the cerebellum (MNI coordinates -4 -48 -14, $t = 6.04$, $p < .05$ FWE corrected). To increase statistical power, we also calculated mean tSNR values for the regions of interest (ROIs) described in the main text (i.e., bilateral dACC, DLPFC, insula, amygdala, and NACC) and compared the extracted tSNR values per ROI between scanners using a Mann-Whitney U test implemented in SPSS. No significant differences in mean tSNR values were found in any of the ROIs for time series acquired at the Signa HDxt compared to time series acquired at the Discovery MR750 (all *p*s >.05). See Figure S2 for average tSNR values in patients in all ROIs for both scanners separately.

Second, possible differences between scanners in activation estimates in ROIs (i.e., contrast values for cocaine minus neutral words that were used in the regression analyses described

in the main text, as well as activation estimates for brain activation associated with cocaine words per se) were investigated using two sample *t*-tests. No significant differences in activation estimates were found in any of the ROIs for time series acquired at the Signa HDxt compared to time series acquired at the Discovery MR750 (all *p*s > .05).

Third, for data analysis in studies involving data from multiple scanners it is important to sufficiently smooth the images (Friedman et al., 2006). Therefore preprocessing of the data described in the main text included a smoothing step of 8mm full-width at half-maximum Gaussian filter (i.e., more than two-times the voxel size). This is not uncommon in fMRI analyses because of the assumptions of Gaussian Random Field Theory needed for some algorithms, but important in the context of scanner differences is that smoothness equalization (the procedure of smoothing image data from different scanners with scanner-related variability in 'raw' smoothness to a constant FWHM) markedly reduces any possible activation effect size differences between scanners (Friedman et al., 2006).

Finally, we conducted the stepwise regression analyses in the same manner as reported in the main text, while including scanner type as a covariate. Scanner type was coded dichotomously. Specifically, the model was built up as follows: step 1 contained the variable scanner type; step 2 contained the four self-report variables (total years of cocaine use, number of days of cocaine use in 30 days before treatment entry, and cocaine administration route, and craving in the week before treatment); step 3 contained two behavioral variables (Stroop effect RT and Stroop effect accuracy); and step 4 contained ten imaging variables (bilateral dACC, DLPFC, insula, NACC, amygdala). In each step, the selection criteria for inclusion and exclusion of predictors in the model were F_{enter}: $p \leq .05$ and F_{remove}: $p \geq .10$. Results revealed that scanner type was not a significant predictor of recent cocaine use ($\beta = -0.13$, $t = -0.67$, $p = .51$). All other predictor statistics remained the same (see Table 3a in main text). Additionally, to ensure that scanner type did not influence the final model (including craving in the week before treatment and right dACC activity), it was entered in a second hierarchical step to test whether its addition would yield a significant change to the prediction model. Model statistics are displayed in Table S2. The addition of scanner type yielded no significant change to the model, indicating that scanner type did not influence outcome prediction. Furthermore, statistics of the individual predictors again revealed that scanner type was not a significant predictor of recent cocaine use, which was confirmed by the bootstrap procedure (see Table S3). In addition, collinearity statistics indicated that the predictors were not associated with each other (all tolerance ≥ 0.70).

Pilot participants

Ideally, inter-scanner reproducibility is assessed using the same participants for both scanners. Therefore, four healthy pilot participants who were scanned on the Signa HDxt before the start of the current study also performed the Stroop task during image acquisition on

the Discovery MR750. TSNR and activation estimates in the ROIs were compared between the two scan occasions for the pilot participants using Wilcoxon nonparametric and regular paired-samples *t*-tests, respectively, implemented in SPSS. None of the ROIs showed significant differences between the two-scanners for either mean tSNR values or activation estimates (all *p*s > .05). See Figure S3 for average tSNR values in pilot participants in all ROIs for both scanners separately.

In conclusion, tSNR and estimation estimates did not significantly differ between the two scanners both in patients and pilot participants, and main results were not changed when including scanner in the regression analysis. Therefore, we are confident that results of the study described in the main text are unlikely to be influenced by the data acquisition on two scanners.

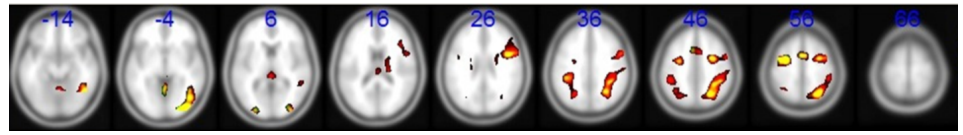

Figure S1. Activation patterns in the final sample (n=26). Red colors indicate unique activation for cocaine words, whereas yellow colors indicate overlap between cocaine and neutral words during performance on the cocaine Stroop task.

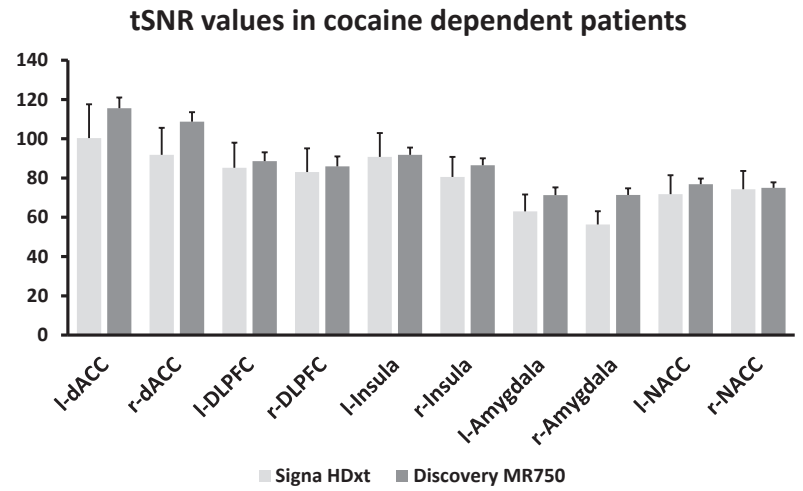

Figure S2. Mean tSNR values and standard errors in the regions of interest in cocaine dependent patients. tSNR, temporal Signal-to-Noise Ratio; l, left; r, right; dACC, dorsal anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; NACC, nucleus accumbens.

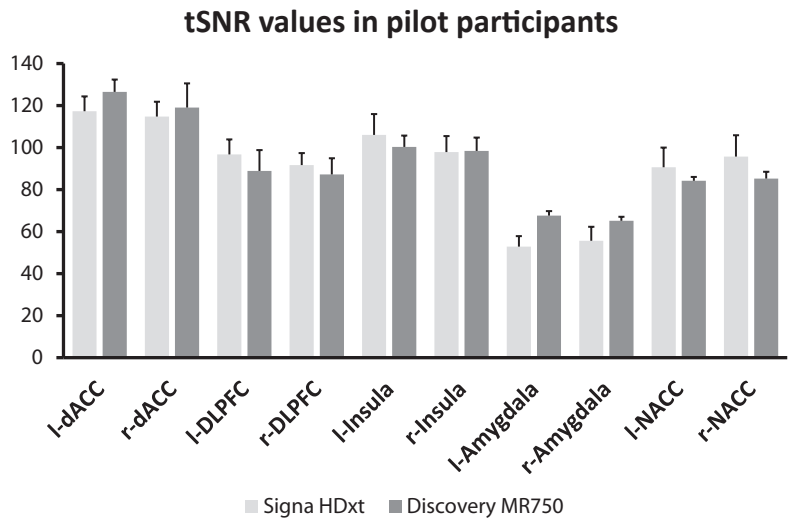

Figure S3. Mean tSNR values and standard errors in the regions of interest in pilot participants. tSNR, temporal Signal-to-Noise Ratio; l, left; r, right; dACC, dorsal anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; NACC, nucleus accumbens.

Table S1. Statistics of Self-report and Behavioral Variables Predicting Recent Cocaine Use

Predictor Variables	Standardized Coefficients (=β)	*t* statistic	*p*-value
Self-reports			
Total years of cocaine use	0.25	1.41	.172
Number of days of cocaine use in 30 days before treatment entry	-0.01	-0.04	.966
Cocaine administration route			
snorting vs. smoking	0.12	0.63	.538
snorting vs. intravenous	0.17	0.90	.379
Craving in the week before treatment	0.48	2.67	.013
Behavior			
Stroop effect RT	-0.33	-1.92	.067
Stroop effect Accuracy	-0.15	-0.79	.436

Table S2. Model Statistics and Change Statistics of the Final Model Predicting Recent Cocaine Use Including Scanner Type

	Model Statistics			Change Statistics		
Predictor Variables	R^2	*F* Statistic	*p*-value	ΔR^2	ΔF	Δp-value
Step 1	0.45	9.26	.001			
Craving in the week before treatment						
r-dACC[a]						
Step 2	0.46	6.18	.003	0.01	0.45	.509
Scanner type						

Table S3. Bootstrap Results for Individual Predictors in the Final Model Predicting Recent Cocaine Use Including Scanner Type

Predictor Variables	Unstandardized Coefficients (=B)	Standard Error (=SE)	Bootstrapped 95% Confidence Interval
Craving in the week before treatment	3.15	2.10	0.06 – 8.65[b]
r-dACC[a]	15.49	5.81	2.53 – 25.57[b]
Scanner type	-2.70	4.77	-11.69 – 7.18

r, right; dACC, dorsal anterior cingulate cortex.

[a]Attentional bias contrast (cocaine minus neutral).

[b]Significant (value 0 is not in the confidence interval).

Chapter 5

Error-related brain activity predicts cocaine use after treatment at 3-month follow-up

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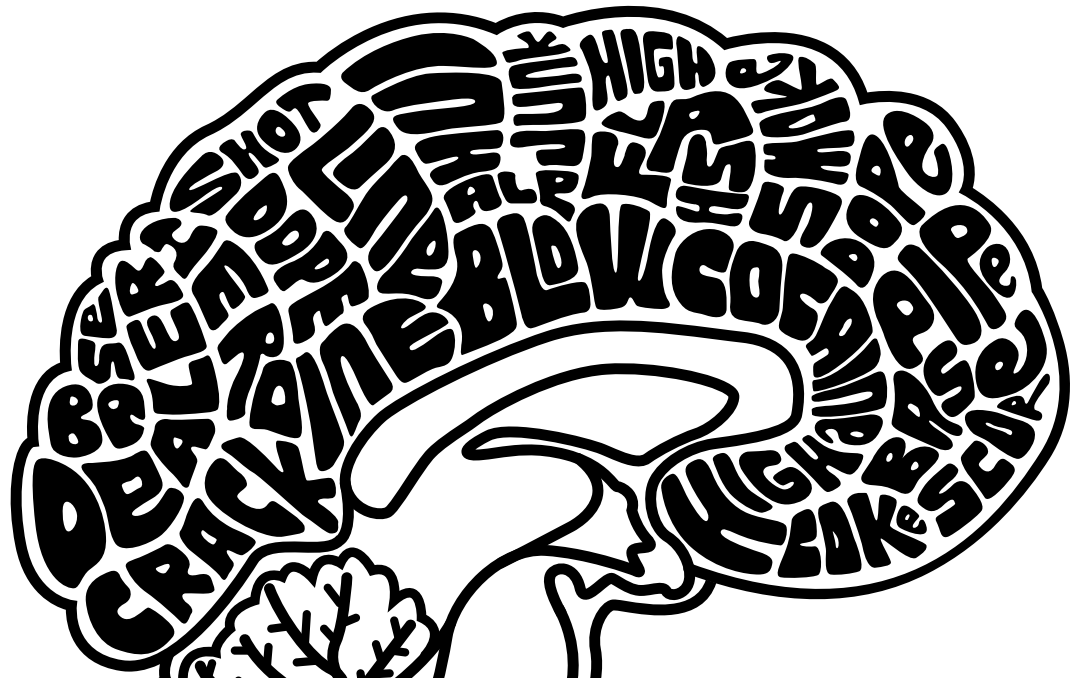


Biological Psychiatry, 2013, published online ahead of print Jan 29

Abstract

Background
Relapse after treatment is one of the most important problems in drug dependency. Several studies suggest that lack of cognitive control is one of the causes of relapse. In this study, a relative new electrophysiological index of cognitive control, the error-related negativity, is investigated to examine its suitability as predictor of relapse.

Methods
The error-related negativity was measured in 57 cocaine-dependent patients during their first week in detoxification treatment. Data from 49 participants were used to predict cocaine use at 3-month follow-up. Cocaine use at follow-up was measured by means of self-reported days of cocaine use in the last month verified by urine screening.

Results
A multiple hierarchical regression model was used to examine the predictive value of the error-related negativity while controlling for addiction severity and self-reported craving in the week before treatment. The error-related negativity was the only significant predictor in the model and added 7,4% of explained variance to the control variables, resulting in a total of 33,4% explained variance in the prediction of days of cocaine use at follow-up.

Conclusions
A reduced error-related negativity measured during the first week of treatment was associated with more days of cocaine use at 3-month follow-up. Moreover, the error-related negativity was a stronger predictor of recent cocaine use than addiction severity and craving. These results suggest that underactive error-related brain activity might help to identify patients who are at risk of relapse as early as in the first week of detoxification treatment.

Introduction

One of the major challenges in addiction treatment is to prevent relapse after detoxification and other treatment. Typically, 50% of drug-dependent patients drop out of treatment and consequently relapse into drug use (Gossop et al., 1987; Franken and Hendriks, 1999; Hättenschwiler et al., 2000). Currently, there is insufficient knowledge about the factors influencing treatment outcome and relapse. Although there are indications that drug use severity and self-reported measures such as craving can predict relapse to a certain extent (Carroll et al., 1993; Reiber et al., 2002; Weiss et al., 2003), new developments in cognitive neuroscience provide an opportunity to investigate additional predictors of relapse that go beyond self-report.

One of the essential features of substance dependence is the loss of control over compulsive drug-seeking behavior, which manifests in two characteristics of substance dependence: not being able to stop drug use and relapse after a period of abstinence and the continuation of substance use despite the negative consequences (APA, 1994; Goldstein and Volkow, 2002; Garavan and Hester, 2007). An important index of cognitive control is error processing (Gehring et al., 1993; Botvinick et al., 2001), which refers to the ability to adequately process adverse consequences and thereby pursue goal-directed behavior. Neuroimaging studies have found that activity in the anterior cingulate cortex (ACC) – a consistently observed neural correlate of error detection (e.g., Ridderinkhof et al., 2004; Carter and Van Veen, 2007) – is diminished in cocaine-dependents during response inhibition and error processing (Kaufman et al., 2003; Hester and Garavan, 2004; Goldstein and Volkow, 2011).

Strongly related to ACC activity is the error related negativity (ERN), an electrophysiological index of error processing (Mathalon et al., 2003; Miltner et al., 2003; Van Veen and Carter, 2002). The ERN is a negative deflection in the event-related potential (ERP) that occurs approximately 25-100 ms after an erroneous response is made and is thought to reflect the automatic processing of an error (Gehring et al., 1995; Bernstein et al., 1995). Some theories suggest that the amplitude of the ERN reflects the ability to monitor ongoing behavior and is used to correct or improve subsequent behavior (Holroyd and Coles, 2002; Yeung et al., 2004). Another theory suggests that the relative strength of the ERN alludes to the motivational significance of an error for an individual (Gehring et al., 1993; Hajcak et al., 2005; Olvet and Hajcak, 2008), which accounts more for individual differences in the strength of the ERN. For example, when errors are more salient to an individual this elicits a larger ERN compared with someone who experiences an error as less meaningful. In concordance, abnormalities in the ERN have been found to be associated with several psychiatric disorders, such as anxiety, depression, and substance abuse (for a review see Olvet and Hajcak, 2008). Because research has shown that the ERN is a stable measure with good psychomet-

ric properties, it is suggested that it represents a trait that might serve as a neurobiological marker of psychopathology (Olvet and Hajcak, 2008; Hajcak, 2012).

Importantly, it has also been shown that cocaine-dependent patients have a reduced ERN (Franken et al., 2007; Sokhadze et al., 2008). Additionally, a reduced ERN has also been found in other addictive behaviors, such as smoking (Luijten et al., 2011b). It has been suggested that this inadequate response to errors may underlie one of the hallmark characteristics of addiction - that is, the persistence of drug taking despite adverse consequences. Different results (i.e., increased ERN) have been found in alcohol-dependent individuals (Padilla et al., 2011; Schellekens et al., 2010), but this is arguably related to the comorbid anxiety symptoms in that population (Schellekens et al., 2010).

More clinically relevant is the plausibility that deficits in the ERN contribute to the maintenance of substance dependence and relapse to substance use. A few studies that have successfully associated reduced activity in neural correlates of cognitive control to relapse support the clinical relevance of neurological data (Bauer, 1997; Paulus et al., 2005; Brewer et al., 2008). However, no study to date has investigated whether the reduced ERN found in substance-dependent subjects may be a predictor of relapse.

The main goal of this study was to examine whether an electrophysiological index of cognitive control, the ERN, is predictive of cocaine use in cocaine-dependent patients 3 months after the start of detoxification treatment. Specifically, we hypothesized that a reduced ERN, as measured in cocaine-dependent patients during their first week of detoxification treatment, would be associated with cocaine use after 3 months.

Methods and Materials

Participants

Fifty-seven cocaine-dependent patients were recruited from an addiction treatment center (Bouman GGZ) in Rotterdam, The Netherlands. Inclusion criteria were (1) age between 18 and 65 years; (2) presence of the DSM-IV diagnosis for cocaine dependence(assessed by both a physician and a research psychologist); and (3) the ability to speak, read, and write in Dutch at an eighthgrade literacy level. Exclusion criteria were (1) indications of severe psychopathology (i.e., psychosis, severe mood disorder, as assessed by a physician); (2) self-reported color blindness or (uncorrected) defective vision; and (3) pregnant or breastfeeding. Of all 57 participants data from n=8 were not included for the following reasons: (1) two participants were lost to follow-up; (2) one participant did not understand the flanker task (regarded first letter instead of central letter as the target); (3) one participant made

too few errors (<5) to obtain a reliable ERN (see Olvet and Hajcak, 2009); (4) in four participants >50% of ERN segments contained artifacts. Table 1 shows all demographic variables and substance-use variables for the final sample (n=49).

Additionally, we also tested 25 healthy control subjects, without a history of substance or alcohol dependence. A previous study by our lab showed that cocaine-dependent patients have diminished error processing compared with healthy control subjects (Franken et al., 2007). To confirm these results we compared the patient sample of the current study with a control group. Data of two control subjects were excluded from analysis because they either made too few errors or had too many artifacts in the ERN segments. Demographics of the final sample of controls (n=23) are displayed in Table 1. The patient and control group did not significantly differ in age, sex, or education (Table 1).

The study was approved by the Ethics Committee of the Erasmus Medical Center, Rotterdam, The Netherlands. All procedures were carried out with the adequate understanding and written informed consent of the participants. They received a financial compensation of 20 euros after completion of the electroencephalography (EEG) measure and 25 euros after completion of the 3-month follow-up measure (patients only).

Task

The Eriksen Flanker task was used to measure error processing (Eriksen and Eriksen, 1974), and ERPs were recorded. The stimuli consisted of four letter strings (HHHHH, SSSSS, HHSHH, SSHSS). Participants were instructed to respond to the central letter. On a response box, they had to press H with their right index finger when the central letter was an H and S with their left index finger when the central letter was an S. Each experimental trial started with a fixation cue for 150 ms where the central (target) letter would appear. The letter string was shown for 52 ms followed by a blank screen for 648 ms. Participants had 700 ms from stimulus onset to respond. After the end of the response period, a feedback symbol appeared for 500 ms indicating whether the given response was correct (+), incorrect (-), or too late (!). An intertrial interval was used of 100 ms.

Table 1. Demographic and Substance Use Variables of Cocaine Dependent Participants and Control subjects

Subject Variable	Patients (n = 49)	Controls (n = 23)	Test Value	*p*-value
Demographic variables				
Age	39.6 (8.4)	39.9 (9.4)	t = -0.18	.86
Males (%)	89	74	χ^2 = 2.16	.14
Education (%)				
Primary education	8	0	χ^2 = 6.27	.18
Junior secondary education	59	43		
Senior secondary education	23	35		
Higher education	10	22		
Addiction severity variables				
Total years of cocaine use	12.2 (6.8)	na		
Cocaine use in 30 days before treatment entry	17.6 (11.5)	na		
Main administration route (%)				
Intranasal	27	na		
Smoking	65	na		
Intravenous	8	na		
Craving in the week before treatment entry				
OCDUS Desire and Control (1-5)	3.0 (1.1)	na		

Values are means (SD) unless otherwise indicated (%).

na, not applicable; OCDUS, Obsessive Compulsive Drug Use Scale.

Procedure

Patients entered the treatment center for an inpatient detoxification treatment and were informed about the study on the second day of their treatment. They had 24 hours to decide whether to participate. Volunteers signed the informed consent form on the third day of detoxification treatment. First, we assessed addiction severity using the Addiction Severity Index (McLellan et al., 1980; Hendriks et al., 1989) and past week craving using the Obsessive Compulsive Drug Use Scale (Franken et al., 2002). Second, participants were taken to the EEG lab of Erasmus University Rotterdam. Upon arrival, participants

were seated in a sound-attenuated room with dimmed lights. The Eriksen flanker task was explained to them. After a practice phase consisting of eight letter strings, participants started the test phase, which consisted of 400 letter strings, divided in 5 blocks. In between blocks, participants could rest as long as needed.

After the Flanker task, a series of other tasks were administered but are not reported in this article. The order of the tasks was not counterbalanced. After completion of all tasks, the participant was taken back to the treatment center.

Treatment

A typical detoxification treatment in this setting has a duration of 3 weeks and the specific goal is to reduce withdrawal symptoms. Treatment interventions in the detoxification phase include psycho-education about the detox symptoms and individual therapy based on cognitive-behavioral techniques. After detoxification treatment, the patients start follow-up treatment in a different department within the same treatment center. This is usually a rehabilitation program with a variable duration between 1 month and 2 years, depending on the need for treatment.

Outcome measure

Recent cocaine use was measured at follow-up, 3 months after study participation. Several procedures were performed to ensure compliance with follow-up: 1) we collected as much contact information as possible (e.g., phone numbers, e-mail addresses) of the participant and other contacts such as family, friends, social workers and other professionals involved with the patient; 2) participants received a financial compensation of 25 euros for completion of the follow-up test; 3) participants were ensured that information on current use (self-reports and urine screens) was used for research purposes only.

Participants were contacted via telephone and/or e-mail to set up an appointment for the follow-up interview. Follow-up tests were assessed in the treatment center. If a participant was out of treatment at this point, he or she was asked to return once to the main treatment center to complete the follow-up test. If the participant was unable to travel to this location, the researcher would perform the assessment at the nearest treatment facility to the participant or arranged taxi transfer to the treatment center for the participant.

At follow-up, participants were asked to report the number of days they had used cocaine in the past 30 days, which we labeled "recent cocaine use". Self-reports were biochemically verified by means of urine screens. All participants who reported that they had not used

in the last 30 days also had a negative urine screen at follow-up. Of the final sample, n=18 reported to have used 0 days in the past 30 days and n=31 reported to have used 11.55 days on average (SD 10.28, range 1-30).

EEG recording and processing

Brain activity was recorded with EEG using a Biosemi ActiveTwo System amplifier from 32 scalp sites and one additional scalp site (FCz). Silver chloride active (Ag/AgCl) electrodes were placed upon the scalp according to the 10-20 International System. Four external electrodes were used to measure vertical electro-oculogram (VEOG) and horizontal electro-oculogram (HEOG) and were placed above and below the left eye (VEOG) and at the outer canthi of both eyes (HEOG). Two external electrodes were used for recording reference activity. These were placed on the left and right mastoids. All signals were digitized with a sampling rate of 512 Hz and 24-bit analogue-to-digital conversion, and were filtered offline. During offline processing, no more than two bad channels per subject were removed from the EEG signal and new values per channel where calculated using topographic interpolation. The computed average of the mastoids were used as reference. The data were filtered using a low cutoff of 0.15 Hz and high cutoff of 30 Hz (24 dB/octave slope). Data were segmented in epochs from 100 ms pre-response to 600 ms post-response. HEOG and VEOG artifacts were corrected using the Gratton and Coles algorithm (Gratton and Coles, 1983). The mean 100 ms pre-stimulus period served as baseline. Artifact rejection was done automatically. Minimum and maximum allowed amplitude -100 to +100 μV was used. ERPs were averaged according to response condition (correct and incorrect). The ERN was quantified by mean amplitude measure in the 25 to 100 ms time window. A cluster of electrode sites Fz, FCz and Cz were used for the analysis of the ERN. These electrode sites are typically used in ERN research (Franken et al., 2007; Ridderinkhof et al., 2002; Hajcak et al., 2005; Hajcak and Foti, 2008) because the ERN is maximal at the frontocentral midline of the scalp (see also Figure 1). Difference waves were calculated (incorrect minus correct) to obtain a single relative measure of error processing (Weinberg et al., 2012). All waveforms are displayed in Figure 1.The magnitude of the ERN is negative. Therefore, a negative difference wave amplitude indicates that relative to the correct response, the amplitude on the incorrect response is larger. Thus, a more negative value indicates a larger ERN (i.e., increased error-related brain processing).

Data Analysis

We first conducted an analysis of variance to compare the ERN of patients vs. controls, to confirm that patients in this sample had a reduced ERN. Second, we examined the direct associations (using Pearson's correlation) between recent cocaine use and all predictor variables, to show the effect size for each measure independently. Third, a hierarchical

regression analyses was conducted to predict recent cocaine use. In Step 1, addiction severity variables (total years of cocaine use, cocaine use in 30 days before treatment entry, and cocaine administration route) and craving in the week before treatment were entered as control variables. Because administration route was a categorical variable with three categories, two dummy variables were created, both coded as 0 vs. 1: intranasal vs. smoking; and intranasal vs. intravenous. In Step 2, the ERN was entered into the equation, to examine its unique contribution to the model. To check robustness of the individual predictors, bootstrapping was used with 2000 bootstrapped samples and a 95% confidence interval (CI; Efron and Tibshirani, 1993; Mooney and Duval, 1993). Finally, predictors were checked for multicollinearity by means of tolerance statistics.

Results

First, we confirmed that the cocaine-dependent patients in the current sample have a reduced ERN compared with nondependent control subjects (F[1,70] = 10.03, p< .01; see Figure 1), which is similar to the results of Franken and colleagues (2007). Results on the behavioral measures of the flanker task are reported in the Supplement.

Second, recent cocaine use was directly associated with total years of cocaine use, cocaine use in the 30 days before treatment, craving in the week before treatment and the ERN (Table 2).

Third, and most important, are the results of the hierarchical regression to predict recent cocaine use (Table 3). In Step 1 of the model, the addiction severity variables and craving in the past week before treatment entry were entered. Together, these variables explained 26% of the variance in the number of days of cocaine use in the past month (F[5,43] = 3.03, p< .05). Individually, only administration route intranasal vs. smoking was significant, indicating that smoking was associated with more days of cocaine use at follow-up. In step 2, the ERN was entered. This model, including addiction severity variables, craving and the ERN explained an additional 7,4% (medium to small effect; Cohen, 1988) of the variance in the number of days of cocaine use in the last month (F_{change}[1,42] = 4.62, p< .05). Thus, the second model explained a total of 33,4% of the variance F[6,42] = 3.51, p< .01). The added predictive value of the ERN (R^2_{change}=0.074) was a medium to small effect (Cohen, 1988) and the ERN was the only significant individual predictor in this model. The results showed that a reduced ERN (measured during the first week of treatment) was associated with more days of recent cocaine use (measured at 3-month follow-up). Figure 2 displays the direct association between the ERN and recent cocaine use. Finally, collinearity statistics indicated that the predictors were not associated with each other (all tolerance ≥ 0.50).

Although it was not our main interest, we also examined associations between behavioral measures of error processing and recent cocainez use. Pearson's correlations showed that behavioral measures were not significantly associated with recent cocaine use (all *ps* > .15).

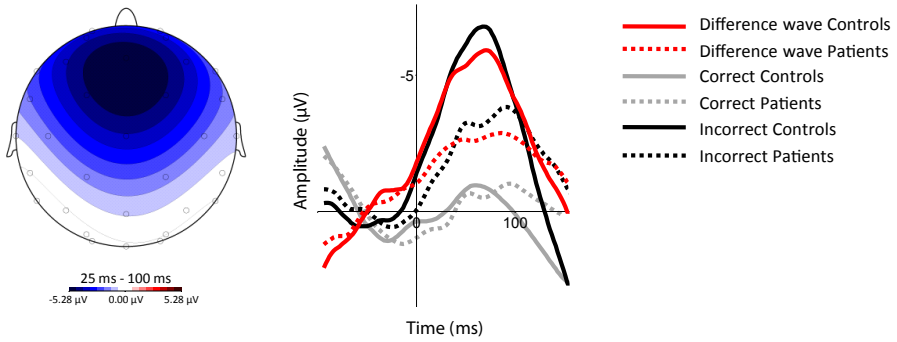


Figure 1. Scalp topography (left) and response-locked correct, incorrect and difference waves at FCz (right) of cocaine dependent patients and control subjects. Responses occurred at 0 ms. µV, mean amplitude; ms, milliseconds.

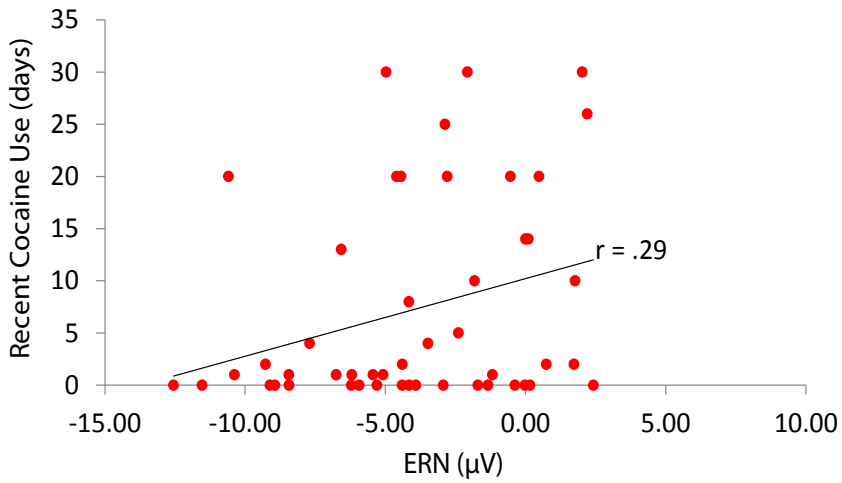


Figure 2. Direct association between the ERN and recent cocaine use at 3-month follow-up. ERN, Error-Related Negativity; µV, mean amplitude.

Table 2. Correlations between Outcome Measure "Recent Cocaine Use" and all Predictor Variables

	Total years of cocaine use	Cocaine use in 30 days before treatment	Administration route intranasal vs. smoking	Admininistration route intranasal vs. intravenous	Craving in the week before treatment	Error-Related Negativity (ERN)
Recent cocaine use	.28[a]	.34[a]	.23	.25	.30[a]	.29[a]
Total years of cocaine use		.17	.30[a]	.13	-.09	.26
Cocaine use in 30 days before treatment			.12	.32[a]	.59[b]	.07
Administration route intranasal vs. smoking				-.41[b]	-.09	.17
Administration route intranasal vs. intravenous					.40[b]	.01
Craving in the week before treatment						-.27

[a]*p*< .05; [b]*p*< .01.

Table 3. Results of Hierarchical Regression Analysis with Bootstrap procedure

Predictor Variable	R^2	Standardized Coefficients (=β)	Unstandardized Coefficients (=B)	Bootstrapped 95% Confidence Interval
Step 1	0.26[a]			
Total years of cocaine use		0.17	0.25	-0.29–0.78
Cocaine use in 30 days before		0.10	0.08	-0.28–0.39
treatment entry				
Administration route				
intranasal vs. smoking		0.28[a]	5.75[a]	1.01–10.56[a]
intranasal vs. intravenous		0.24	8.47	-3.68–17.02
Craving in the week before treatment		0.19	1.64	-1.68–5.61
Step 2	0.33[b]			
Error-Related Negativity (ERN)		0.30[a]	0.77[a]	0.11–1.50[a]

[a]*p*< .05; [b]*p*<.01.

Discussion

The current study is one of the few studies to link basic neurocognitive control processes directly with clinical outcome. It is the first to examine error-related brain activity as a predictor of cocaine use after treatment. In line with our hypothesis, the results showed that a reduced ERN in cocaine-dependent patients in treatment is associated with later cocaine use. The ERN seems a robust predictor of cocaine use after treatment, even when controlling for other predictors such as addiction severity and craving. This finding suggests that cocaine-dependent individuals with strongly diminished error-related brain activity are more at risk of relapse. Moreover, it shows that error-related brain processes measured in the first week of detoxification treatment are associated with 3-month later cocaine use, which suggests that neurocognitive control measures such as the ERN can provide useful information on relapse risk as early as in the first week of treatment.

Several studies, including the current study, have shown that error processing is diminished in drug-dependent individuals, as indicated by a reduced ERN (Franken et al., 2007; Sokhadze et al., 2008).These studies, together with other neuroimaging studies showing diminished error-related ACC activity in drug-dependents (Kaufman et al., 2003; Hester and Garavan, 2004; Goldstein and Volkow, 2011), support the theory that reduced cognitive control is one of the main characteristics of drug dependency (Goldstein and Volkow, 2002). Poor performance monitoring influences performance on a higher level of self-control such as impulse control and decision-making (Kerns et al., 2004). Hence, it might be that deficits in the ERN and ACC functioning - reflecting poor error monitoring - represent the fundamental process underlying dysfunctional decision making that is frequently observed in drug-dependent patients (Bechara et al., 2006). Most pertinent to this study is that individual variations in these neurophysiological correlates of cognitive control have been proposed to account for differences in relapse risk (Garavan and Hester, 2007; Paulus et al., 2005; Brewer et al., 2008). Our results indeed suggest that variations in the ERN amplitude are associated with cocaine use at follow-up. More specifically, patients with reduced ERN are more at risk of subsequent relapse than patients with larger ERN.

The identification of multiple predictors of treatment outcome and relapse have been a priority in drug addiction research, and it has been discussed that models of substance use relapse should be multifactorial (Donovan, 1996; Poling et al., 2007). For example, Donovan (1996) proposed that theoretically relevant variables should always be implemented in prediction models and Poling and colleagues (Poling et al., 2007) argued that in prediction research, baseline drug use severity variables should be taken into account because addiction populations generally vary in severity. Nonetheless, many prediction studies have merely looked at direct associations between the independent variable of interest and the outcome measure. For example, several studies have investigated the predictive utility of

craving, a phenomenon that plays a central role in influential theories of addiction (Robinson and Berridge, 1993; Tiffany, 1990). Some studies did report direct associations between craving and subsequent cocaine use (Weiss et al., 2003; Preston et al., 2009), but other studies found that self-reported craving at the start of treatment was not predictive of cocaine use at follow-up (Weiss et al., 1995; Bordnick and Schmitz, 1998). This suggests that other factors might influence relapse and drug use. In line with this idea are substance relapse studies showing that (neuro)cognitive measures are better predictors of subsequent relapse than self-reported craving, such as attentional bias for drug cues (Marissen et al., 2006; Marhe et al., 2012) and increased brain activity after exposure to cocaine stimuli in areas such as the posterior cingulate cortex (Kosten et al., 2006).Correspondingly, our data have provided robust evidence that a neurophysiological measure of cognitive control, the ERN, is a stronger predictor of cocaine use at follow-up than addiction severity and craving.

The present results yield new insight in the clinical relevance of cognitive control in cocaine dependence treatment and have important implications for clinical practice. There is growing interest in the use of the ERN as a screening tool for treatment outcome or diagnostic instrument in several psychiatric disorders showing abnormalities in the ERN (Olvet and Hajcak, 2008; Hoffmann and Falkenstein, 2012). The advantage of using EEG to assess neurophysiological components of cognitive control is that it is noninvasive, less expensive and more accessible than other neuroimaging techniques such as functional magnetic resonance imaging. With respect to cocaine dependence treatment, it might be helpful to use EEG to assess the ERN as a routine screening tool at the start of detoxification treatment. The relative strength of the ERN amplitude can provide more insight in a patient's responsiveness to treatment. Additionally, treatment programs could be adjusted to the individual patient to improve outcomes and ultimately prevent relapse.

Limitations of the study should be noted. First, we only measured days of cocaine use in the past month of the 3-month follow-up period. Second, we did not examine the influence of comorbid psychiatric disorders on cocaine use outcome. Future research should address these limitations by measuring cocaine use during the whole 3-month period to examine time to relapse, and using a larger sample size to test more predictors in a multiple regression model, such as comorbidity.

Overall, our findings have provided evidence for the role that neurophysiological measures of cognitive control can play in identifying cocaine-dependent individuals who are at risk of relapse, as early as in their first week of detoxification treatment. Identification of these cognitive processes and neural correlates as possible predictors of drug relapse, on top of other wellestablished predictors, have important implications for the clinical practice. Ultimately, electrophysiological screening tools may be implemented in treatment programs to identify patients who are more susceptible to relapse.

Supplementary Information

Differences in behavioral measures between controls and patients

The behavioral measures of the Eriksen Flanker task were: overall reaction time (RT), RT on correct trials, RT on incorrect trials and percentage of errors. Means of both groups and test results are displayed in Table S1. Results indicate that patients and controls did not significantly differ in the overall RT, RT on correct trials and RT on incorrect trials. However, patients made significantly more errors than controls.

Table S1. Behavioral Measures of the Eriksen flanker task

	Patients (n = 49)	**Controls (n = 23)**	***t* Value**	***df***	***p*-value**
RT overall	469 (68)	474 (49)	0.37	70	.71
RT correct trials	475 (67)	479 (45)	0.29	70	.77
RT incorrect trials	432 (66)	441 (63)	0.54	70	.59
Percentage errors (%)	16 (12)	9 (7)	-3.06	65.9	<.01

RT, reaction time.

Note. Values are group means (SD). RT expressed in milliseconds.

Associations between behavioral measures and the ERN

The results of Pearson's correlations are displayed in Table S2. The results show that the ERN was significantly associated with the percentage errors, indicating that the less errors were made the more negative the ERN amplitude was (i.e., increased error processing). Furthermore, there was a marginal significant association between RT on incorrect trials and the ERN. Thus, it might be that the slower the RT on incorrect trials the more negative the ERN is.

Table S2. Correlations Between Behavioral Measures and the ERN

	ERN amplitude	***p*-value**
RT overall	-.16	.19
RT correct trials	-.13	.30
RT incorrect trials	-.21	.08
Percentage errors (%)	.56	<.01

Note. ERN difference wave amplitude

Chapter 6

Summary and Discussion

The general aim of this thesis was to examine the neurocognitive mechanisms of drug addiction and associations with temptations and relapse during and/or after detoxification treatment. Earlier substance relapse prediction studies have primarily focused on self-report measures such as craving levels. More recently, addiction theories and research have underlined the role of cognitive motivational and control processes, which has resulted in a current focus on neurocognitive measures as predictors of treatment outcome and relapse. It is suggested that these automatic, implicit processes might be additional measures, or even better measures of drug relapse than self-report measures, possibly by bypassing (sub)conscious processes such as social desirability or misrepresentations of one's thoughts and feelings. The present thesis revealed new information on the role of drug-related motivational processes (e.g., attentional bias) and cognitive control processes (e.g., attentional control, error processing) of heroin and/or cocaine-dependent patients during detoxification treatment and in association with relapse risk. These processes were measured using cognitive paradigms (i.e., Stroop task, Implicit Association task, Flanker task) implemented in relatively new methodologies such as ecological momentary assessment (EMA), electroencephalography (EEG) and functional magnetic resonance imaging (fMRI). Above all, we tested the predictive value of these (neuro)cognitive measures in addition to self-report measures such as substance use severity and craving. The main results and conclusions of the previous chapters will be discussed next. Finally, treatment implications, study limitations and suggestions for future research are described.

Real-time measures of explicit and implicit drug-related cognitions during treatment: precipitants of temptations and relapse

There is ample empirical support for the role of explicit cognitions such as craving and implicit cognitions such as attentional bias in addiction. Addiction models suggest a role for both processes in the maintenance of drug use behaviors and drug relapse (e.g., Franken, 2003; Field and Cox, 2008). Several laboratory studies have indeed reported an association between drug relapse and self-reported craving levels (e.g., Weiss et al., 2003) or attentional bias measured with a reaction time task such as the modified Stroop task (e.g., Marissen et al., 2006). However, since drug-related motivational processes are prone to changes over time and context dependent a more sensitive method to investigate this is EMA. Addiction studies have used EMA to study self-reported precipitants of drug use (e.g., Epstein et al., 2009; Preston et al., 2009). Yet, there are no previous EMA studies in clinical populations using reaction time tasks to examine automatic cognitive processes and their relation with relapse. Chapters 2 and 3 of the present thesis describe the first EMA study examining both explicit and implicit

drug-related cognitions daily among heroin, and mostly also cocaine, dependent inpatients during their first week of detoxification treatment in an addiction treatment center.

The main goal of **chapter 2** was to examine whether real-time measures of drug-related implicit cognitions (i.e., attentional bias and implicit memory associations with drugs) and explicit cognitions (i.e., self-reported craving and explicit attitude to drugs) were associated with drug relapse during the first week of detoxification treatment (EMA study week; early relapse) and during the rest of the detoxification treatment (2-3 weeks after the EMA study week; late relapse). In addition, the longitudinal structure of the data allowed us to examine the pattern of implicit and explicit drug-related cognitions in the assessments preceding the relapse day. Self-report items on craving/explicit attitude and reaction time tasks to measure attentional bias (drug Stroop task) and implicit associations (Implicit Association Test; IAT) were implemented on hand-held computers (PDAs) and after training participants carried around the PDA for 1-week. They completed up to 4 random assessments per day (announced by a beep) and were instructed to also complete an assessment when they experienced a temptation to use drugs (i.e., an acute rise in urge to use heroin or cocaine or when a person feels (s)he is on the brink of acquiring and using heroin or cocaine).

As expected, results on the explicit measures showed that early relapsers (i.e., those who relapsed during study) reported higher drug craving levels than non-EMA relapsers (i.e., those who did not relapse during study) at temptation versus random assessments, which is consistent with previous EMA research in the field of addiction research (e.g., Shiffman et al., 1997). Reports of more positive explicit attitude to drugs was associated with both early and late (those who relapsed after study) relapse during temptation episodes versus random prompts. These findings suggest that self-report measures of craving and explicit attitude assessed with EMA during treatment provide information on relapse risk, respectively during the first week and during the entire detoxification treatment process.

Most interestingly, results on the implicit measures revealed that early relapsers exhibited elevated levels of attentional bias and more positive implicit associations with drugs than non-EMA relapsers, but only during temptation episodes. These results persisted when controlling for self-reported craving and explicit attitude, thus suggesting an independent role for implicit automatic processes in relation to relapse. Contrary to our expectations, an association between implicit measures and late relapse was not observed, probably because of the longer lag between EMA assessments and late relapse. Consistent with this suggestion is that attentional bias was elevated in the temptation assessments most proximal to the relapse day. This indicates that attentional bias provides information about the timing of relapse. In other words, when a patient in treatment experiences elevated attentional bias during a temptation episode, (s)he might be at risk of relapse in the short

term. In sum, these findings emphasize the clinical relevance of implicit cognitive measures and, most innovatively, the relevance and feasibility of measuring attentional bias during temptations in a treatment setting using EMA methodology. Implicit cognitions assessed during EMA may help to identify individuals at risk of subsequent relapse.

Although relapse was not associated with number of reported temptations, the finding that drug-related cognitions were elevated in relapsers typically during temptation episodes implies that temptations during treatment are problematic. Since temptation episodes share commonalities with relapse episodes, we further examined the course and precipitants of temptations during detoxification treatment.

In **chapter 3** real-time data of heroin-dependent patients during their first week of treatment was used to examine mood and cognitions during random versus temptation assessments. First, the number of reported temptations declined during the study week, possibly due to improvement during treatment, methadone maintenance or maybe due to study fatigue. Despite this decline, data revealed that throughout the study week patients exhibited higher levels of negative affect during temptation assessments compared to random assessments. This indicates that temptation episodes during the first week of detoxification treatment are experienced as problematic events for patients. Concerning the drug-related measures, the data revealed that patients exhibited elevated levels of craving, positive explicit attitudes to drugs and attentional bias (but not implicit associations) during temptation episodes compared to random events. Again, the association between attentional bias and temptation episodes persisted when controlling for subjective craving. Most interestingly, results regarding changes over time yielded that only attentional bias was elevated in random assessments in the hour preceding a temptation episode. This suggests that attentional bias is a harbinger of temptation episodes.

In general, the findings of chapters 2 and 3 revealed more detailed, real-time information on the association between attentional bias and drug relapse compared to previous laboratory studies (see General Introduction for an overview of these studies). The current findings suggest an important role for attentional bias in the timing of temptations and relapse during treatment. Implicit associations however did not provide information on the timing of temptation episodes and relapse, but did show that individuals exhibiting a highly positive implicit attitude during temptations throughout the first week of detoxification were generally more vulnerable to relapse. Most interestingly, the present results showed that implicit cognitive measures provide information on temptations and relapse risk beyond that gained from self-reported craving and explicit attitudes.

Neurophysiological measures of attentional bias and error processing: associations with cocaine use after treatment

Chapters 2 and 3 have showed that - on the behavioral level - the enhanced attentional processing of drug cues relative to neutral cues is a precipitant of relapse and temptations during the first week of treatment. In addition, we investigated whether attentional bias on the neural level was also a predictor of relapse. Previous neuroimaging studies have showed that brain regions involved in attentional bias to substance-related stimuli include the anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), insula, nucleus accumbens and amygdala (Hester and Garavan, 2009; Janes et al., 2010a; Janes et al., 2010b; Luijten et al., 2011a; Luijten et al., 2012; Nestor et al., 2011; Vollstädt-Klein et al., 2012).

In **chapter 4** an fMRI study was conducted among cocaine-dependent inpatients during their first week of detoxification treatment. A cocaine Stroop task (same as used in chapters 2 and 3) was assessed to measure attentional bias during scanning. The main goal of this chapter was to examine whether attentional bias-related brain activity in above mentioned brain regions was associated with cocaine use outcome 3 months after the start of treatment. Moreover, it was tested whether brain activity (in response to drug-related stimuli versus neutral stimuli) was a better predictor of cocaine relapse than self-reported craving before treatment, substance-use severity measures, and behavioral attentional bias. Cocaine use outcome was defined as reported number of cocaine use days in the last month (urine verified) and was measured 3 months after the start of the detoxification treatment.

Results demonstrated that enhanced attentional bias-related activity in the right dorsal ACC (r-dACC) and self-reported craving in the week before treatment were associated with cocaine use at 3-month follow-up. Furthermore, r-dACC activity related to attentional bias made a large unique contribution to the prediction of cocaine use outcome, even when controlling for self-reported craving before treatment. Since the dACC has found to be involved in salience detection and conflict monitoring, it has been suggested that hyperactivity in the dACC reflects enhanced conflict in the presence of emotionally salient distracters, in this case drug-related stimuli. Regarding the present results, the increased dACC activity in response to drug cues versus neutral cues might reflect that patients at risk of relapse need more top-down resources to focus on cognitive tasks when drug-related cues are present as distractors (thus biasing attention) during the task. Similar findings have been reported in smokers (Janes et al., 2010b). This implies that relapse-vulnerable individuals have reduced or lack the ability

to control their substance-related cognitions, regulated by the dACC, and thereby might experience more difficulties in controlling their substance-use behavior.

The findings of chapter 4 further showed that measures of substance use severity and behavioral performance on the Stroop task were not associated with cocaine use outcome, suggesting that these measures are not as sensitive as dACC activity and craving in the prediction of relapse vulnerability in the 3 months after treatment. A possible explanation is that the association between attentional bias on the behavioral level and relapse diminishes when there is a long lag between the behavioral assessment and the outcome measure (Powell et al., 2010). Supposedly, functional neuroimaging is a more robust measure of attentional bias that is less interfered by a long lag between assessment time and relapse and thus a better predictor of relapse on the long term than behavior. This interpretation is further supported by the findings of chapter 2, which yielded that behavioral assessment of attentional bias is associated with relapse on the short term (i.e., first week of detoxification treatment) but not on the long term (after detoxification treatment).

Besides the prominent role of attentional bias in addiction, it has also been suggested that at the same time the ability to control (drug-related) cognitions and drug use behaviors is reduced in drug-dependent individuals. That is, both drug-related motivational processes as well as dysfunctions in cognitive control contribute to compulsive drug use behavior (Goldstein and Volkow, 2002; Garavan and Hester, 2007). In addition, theory and supporting empirical research state that the inability to exert cognitive control has a neural basis in regions of the prefrontal cortex in substance-dependent people (Goldstein and Volkow, 2011). Yet, not many studies have examined whether these dysfunctions in brain areas associated with cognitive control are predictive of drug relapse (Brewer et al., 2008; Paulus et al., 2005). Chapter 5 reported an EEG study that investigated whether individual differences in brain activity related to error processing (an index of basic cognitive control) was associated with cocaine relapse.

Drug users are characterized by their continuation of substance use despite the negative consequences. The ability to adequately monitor negative consequences in behavior, referred to as error processing, is necessary for optimal behavioral performance to guide our behavior towards our long-term goals (e.g., maintain abstinence from substance use). Error processing has been measured using speeded reaction time tasks where it is inevitable to make an error, such as the Go-Nogo task or the Eriksen flanker task. It has been previously reported that substance-dependent individuals show a decreased sensitivity to errors and this has been attributed to reduced activation in the dACC (Kaufman et al., 2003). Likewise, electrophysiological research has showed

that the error-related negativity (ERN) - which is the brain's fast, automatic response reflecting initial detection of an error - is reduced in cocaine users compared to healthy controls (Franken et al., 2007; Sokhadze et al., 2008).

In **chapter 5** it was examined whether individual differences in the ERN amplitude are associated with cocaine use outcome after treatment. To measure the brain's error processing we measured event-related potentials in response to an Eriksen flanker task in cocaine-dependent patients during their first week of detoxification treatment. To replicate results of Franken et al. (2007) we also tested differences in the ERN amplitude between cocaine-dependent patients and non-substance-dependent controls. The Eriksen flanker task was used to measure event-related potentials (ERPs) in response to errors. We tested to what extent the ERN predicts cocaine use after treatment, in addition to other relevant predictors such as substance use severity and subjective craving (before treatment).

Results confirmed, as expected, that the ERN amplitude was reduced in cocaine-dependent patients compared to non-dependent controls, replicating the results of Franken et al. (2007). In other words, the patient sample of the present study also displayed reduced brain activation in the automatic detection of an error. Most interestingly, ERN amplitude predicted cocaine use outcome, over and above substance use severity and craving. Specifically, the ERN was the only significant individual predictor in the model and uniquely accounted for 7,4% of explained variance in cocaine use outcome (together with substance use severity and craving the prediction model explained a total of 33,4% of the variance). This indicates that patients exhibiting underactive error-related brain activity are more at risk of relapse. Moreover, an electrophysiological measure - the ERN - might help to identify relapse vulnerable patients as early as in the first week of detoxification treatment.

Chapters 4 and 5 have showed that individual differences in brain activation involved in respectively attentional bias and cognitive control, are associated with cocaine use 3 months after treatment. In other words, it suggests that both enhanced dACC activity related to attentional bias for drug cues and underactive error-related brain activity are related to relapse on the later term, which is conform theories suggesting that both processes contribute to the continuation of drug use (Goldstein and Volkow, 2002; Garavan and Hester, 2007). Additionally, disruptions of the prefrontal cortex may reflect potentiated relapse vulnerability (Goldstein and Volkow, 2011). Most interestingly is that all chapters have showed that neurocognitive measures are adequate predictors of drug relapse, over and above self-report measures such as craving.

Beyond craving: Are neurocognitive measures better predictors of relapse?

Craving constitutes a central role in theories of addiction, including recent ones (Berridge and Robinson, 2003; Franken, 2003; Field and Cox, 2008). Despite the emphasis on craving in addiction models, the exact role of craving in addiction has not been clearly researched due to conceptual and measurement issues (Sayette et al., 2000; Collin Drummond et al., 2000). The use of ecological momentary assessment (EMA) has facilitated the measurement of acute and fluctuating processes involved in addiction, including subjective craving. Indeed, some studies have showed that elevated levels of self-reported craving are precipitants of drug use, the most recent one being an EMA study showing an increase in the pattern of cocaine craving a few hours before cocaine use in an outpatient sample (Preston et al., 2009). Using the same craving measure (i.e., patients responded on a Likert scale whether they crave heroin or cocaine "at this moment") the EMA studies described in chapters 2 and 3 found that elevated levels of self-reported craving during temptation episodes where associated with early relapse in an inpatient sample. However contrary to Preston's results, we did not find a specific increase in craving levels in the hours before temptation episodes or in the days before relapse. Thus, craving did not provide information on the timing of temptations and relapse. Conversely, attentional bias did provide this information.

According to the most recent addiction models craving is associated with the automatic process of attentional bias (Franken, 2003; Field and Cox, 2008). More specifically, they propose that attentional bias is the cognitive process behind the classically conditioned relationship between drug cues and craving (Robinson and Berridge, 1993). Consequently, attentional bias causes increased craving and in turn craving further stimulates attentional bias, which ultimately can result in the continuation of drug use or relapse (Franken, 2003). However, studies examining the association between attentional bias, craving and relapse have reported divergent results. For example, Waters et al. (2003a) and Marissen et al. (2006) found an association between attentional bias and (respectively smoking and heroin) relapse even after controlling for subjective craving. In contrast, a recent study showed that attentional bias was not associated with treatment outcome in alcohol-dependent patients, while self-reported craving was (Field et al., 2012). Similar to the results of Waters et al. (2003a) and Marissen et al. (2006), the results of chapters 2 and 4 have showed that when controlling for self-reported craving the associations between attentional bias and relapse persisted, indicating that in our studies this relationship is not accounted for or mediated by craving. Thus, although Franken (2003) has proposed that craving and attentional bias have a mutual excitatory relationship that can result in relapse via craving, the present thesis suggests that attentional bias (both behavior and brain-activity) might be associated

with drug relapse independently from craving. The fact that attentional bias and craving are not two sides of the same coin is also observed in a meta-analysis of Field et al. (2009) who showed that although there is a significant correlation between attentional bias and craving, this correlation is rather small ($r = .19$).

Note that the craving measure we used in chapter 4 is different from the measure used in chapters 2 and 3. In chapter 4 we used the Obsessive Compulsive Drug Use Scale (OCDUS; Franken et al., 2002) to assess levels of subjective craving experienced in the week before entering the detoxification treatment, while in the EMA studies described in chapters 2 and 3 we measured craving "at this moment". It has been previously reported that acute craving and attentional bias-related brain activity in the insula and putamen are associated with each other in a sample of smokers (Luijten et al., 2011a). As we did not measure craving "at this moment" in chapter 4, we could not examine the association between attentional bias-related brain activity and acute craving.

In chapters 2 and 3 we did find an association between attentional bias and temptations, that is, attentional bias for drugs was elevated in the hour before a reported temptation episode and was also elevated in the temptation assessments most proximal to the relapse day. While craving and temptations share commonalities the results persisted when controlling for subjective craving, indicating that possibly another attribute of temptation is associated with attentional bias. Consider the definition we used for temptation, which has two parts, namely 1) an acute rise in the urge to use drugs; and 2) feeling of being at the brink of acquiring and using drugs. While the first part seems more related to craving the second part seems more closely related to an action, or "wanting" the drug. In concordance with this idea, Berridge (2009) has suggested that the attribution of incentive salience to drug cues may – besides the mental representations of drug-related stimuli – also correspondingly arise from the mental representations of drug-related actions ("action salience"). Furthermore, an addict "might urgently *want* to act" (Berridge, 2009, p. 391) without subjectively experiencing craving. Thus, pertaining to the present results, attentional bias may be more closely associated with action salience (wanting to act) than with incentive salience (craving).

Finally, concerning neurophysiological measures, a previous fMRI study among cocaine-dependent patients reported that increased brain-activity after exposure to cocaine stimuli in areas such as the posterior cingulate cortex, but not self-reported craving, was associated with relapse (Kosten et al., 2006). However, chapter 4 showed that both craving in the week before treatment and dACC-activity related to attentional bias contributed to the prediction of cocaine use after treatment. Conversely, chapter 5 showed that the ERN was the only significant predictor of cocaine use after treatment in a model including self-reported addiction severity and craving in the week before treatment. This indicates that

a neurophysiological measure of basic cognitive control is a better predictor than self-reported craving.

In sum, the present thesis has showed that neurocognitive measures provide information on relapse risk over and above subjective craving. It is not suggested that craving is unimportant in addiction; rather it seems that neurocognitive measures yield more detailed information, for example about the timing of relapse, and may be of larger contribution to the prediction of relapse than self-reported craving. Furthermore, despite improvements in the measurement of subjective craving, the disadvantage remains that it is based on self-report, which might be biased due to limited insight in one's motivations, thoughts and feelings or due to a social desirable answering pattern (for example, someone who is in a detoxification treatment clinic does not want to admit (s)he is experiencing craving; Hammersley, 1994; Marissen et al., 2005). Neurocognitive measures are probably less susceptible to these biased (sub)conscious processes.

Treatment implications

Currently, the main goal of detoxification treatment programs is to reduce withdrawal symptoms and increase the physical stability of the patient (e.g., with medication). There is not much focus on risk taxation regarding relapse during detoxification treatment while typically 50% of the patients dropout during this phase (e.g., Gossop et al., 2002; Day and Strang, 2011). The present thesis has shown that patients who are at risk of relapse might be identified as early as in the first week of treatment using neurocognitive measures. However, neuroimaging techniques are less feasible to directly implement into treatment, specifically fMRI. The information gained by using this technique is of great interest for future studies investigating pharmacological and neurocognitive interventions. For example, relapse vulnerable patients with enhanced dACC activity related to attentional bias might benefit from cognitive interventions such as attentional retraining (Schoenmakers et al., 2010) or psychopharmacological interventions, such as dopaminergic manipulation to reduce attentional bias-related brain activity (Ersche et al., 2010; Goldstein et al., 2010; Luijten et al., 2012). As the effects of these interventions are still rather ambiguous they need further investigation.

Although obtaining more information of how brain responses are related to clinical outcomes is important to improve treatment programs, acquiring an MRI scanner within the treatment facility would probably not be very cost-effective. In contrast, EEG would be a more cost-effective neuroimaging tool that could be implemented in treatment programs. EEG is non-invasive, less expensive and more accessible than fMRI scanning. In addition, the idea to use EEG as a diagnostic instrument has gained interest specifically for ERP components that have excellent psychometric properties and can be measured in the individual with single-trials, such as the ERN (Hajcak, 2012; Hoffmann and Falkenstein, 2012). Regarding the results of the present thesis, it might be helpful to use EEG to routinely assess the ERN amplitude in cocaine-dependent patients at the start of detoxification treatment. The relative strength of the ERN amplitude might help to identify patients that are vulnerable for relapsing into drug use after treatment. Additionally, treatment programs could be tailored to the patient's need to improve outcomes. However, to be able to use the ERN as an individual screening tool for treatment planning, future studies should reconfirm the association between the ERN and drug relapse and further examine the sensitivity and specificity of the ERN as a predictor of relapse.

Arguably, the most feasible option would be to implement PDAs into the detoxification treatment program. The main advantage of PDAs is that they are even more cost-effective than EEG and easy to use. They could be used not only for risk taxation of relapse but also to gain more information on temptation episodes during treatment. The present thesis has showed that temptation episodes during the first week of detoxification treatment are problematic and that elevated attentional bias can be a harbinger of a temptation episode and also relapse on the short term. However, currently there is no specific care for a patient's acute temptation episode, possibly because patients find it difficult to report an acute temptation to the treatment staff. Our study has showed that it is feasible to have patients report their temptations on a PDA and subsequently measure explicit and implicit cognitions during this episode. More research is needed regarding the causal relationship between attentional bias and temptations/relapse. If elevated attentional bias indeed causes temptations during treatment and subsequent relapse, a possible clinical implication would be to have an attentional retraining program (Schoenmakers et al., 2010) delivered on the PDA (i.e., ecological momentary intervention) just before the occurrence of a temptation episode. Interventions that reduce the risk of temptation episodes may improve quality of life during drug detoxification and might also reduce the risk of relapse. If the association between attentional bias and temptations/relapse is not causal, the EMA data may still reveal which individuals are at risk of experiencing a temptation or relapse and perhaps when they are at risk of relapse. In addition, EMA data could facilitate drug detoxification treatment. For example, more therapy time or instant intervention at a critical temptation period might be allocated to those individuals at greater risk of relapse.

Limitations of the present thesis and suggestions for future research

First, the causality of the observed relationships described in the present thesis remains uncertain. For example, it is unknown whether neurocognitive dysfunctions in drug-dependent individuals directly cause relapse or whether a third variable is re-

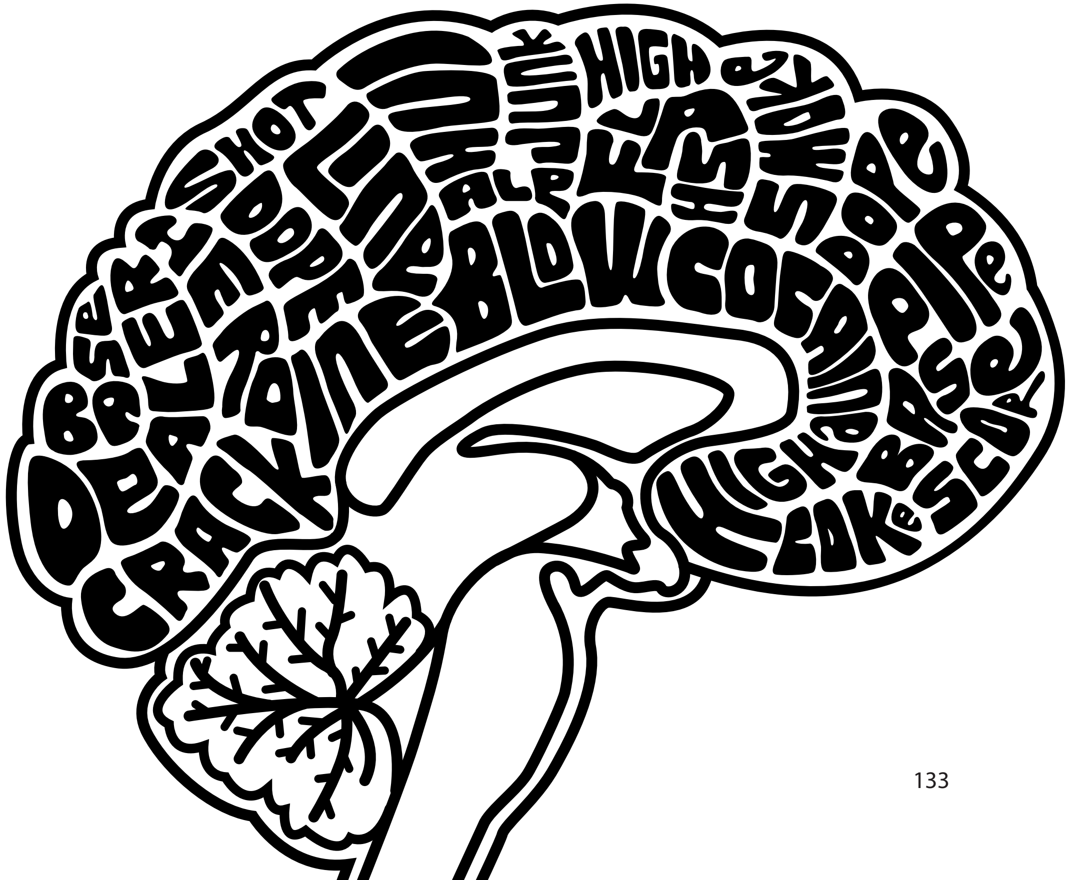
sponsible for this relationship, such as comorbid psychiatric disorders. Furthermore, the present thesis does not answer whether these dysfunctions are inherent in drug-dependent patients or whether this is a consequence of excessive drug use. However, regarding error processing it has been found that the ERN is reduced in a high-risk adolescent population suggesting that the ERN is an endophenotype of substance use disorder (Euser et al., 2012). Second, since we used different measures of relapse it is difficult to compare the present results. In chapter 2 both short-term (first week) and long-term (3 weeks) outcome was studied, while the studies described in chapters 4 and 5 only examined long-term outcome (3 months). Therefore, we cannot discard that the neurophysiological measures we used in the final chapters might also be associated with short-term outcome. However, evidently EMA methodology is more feasible to examine short-term outcome because EMA can assess cognitive processes that are state-dependent, i.e. fluctuating processes which occur more proximal to a relapse. On the other hand, neurophysiological measures might be better at identifying more distal predictors of relapse that are usually thought of as more trait-dependent factors (McKay et al., 2006), such as the ERN (Olvet and Hajcak, 2008). Another limitation regarding the outcome measures is that short-term relapse in chapter 2 was measured with self-reports only and not verified by urine screening. Furthermore, chapters 4 and 5 did not examine acute craving; rather only craving in the week before treatment was assessed. Finally, the present thesis has not addressed the role of response inhibition which is another important index of cognitive control.

Future studies should address these limitations by using longitudinal research designs and examine multiple relapse measures such as time to relapse, preferably verified by weekly or even daily urine screening. In addition, because of the pronounced theoretical role of craving in addiction, studies should always include measures of subjective craving at the time of testing. Furthermore, it would be interesting to investigate the predictive value and underlying associations of several cognitive processes such as attentional bias, implicit associations, error processing and response inhibition in one model, to examine to what extent these processes are associated with relapse. For example, it might be that the overall inability to pursue cognitive control over behavior influences the level of attentional bias and craving (Field and Cox, 2008) and consequently increases the risk of relapse. Finally, it is of theoretical as well as clinical importance that studies investigating cognitive and neurobiological processes of addiction include demographic, substance use and other self-report measures in prediction models to test the additional value of these relatively "new" measures. Ideally, relapse prediction models should be multifactorial and should include (socio)demographic, psychological, physiological and cognitive variables. Of course, very large sample sizes are needed to accomplish such goals.

Main conclusion

This thesis has yielded important information on neurocognitive mechanisms of drug dependence in relation to treatment processes and outcome. It revealed that neurocognitive processes provide information on relapse vulnerability above and beyond the information gained from self-report measures such as craving. Neurocognitive measures – assessed early in treatment – may help to identify those individuals who are at risk for subsequent relapse and perhaps, by using EMA, when they are at risk of relapse.

References



Aharonovich, E., Hasin, D. S., Brooks, A. C., Liu, X., Bisaga, A., & Nunes, E. V. (2006). Cognitive deficits predict low treatment retention in cocaine dependent patients. *Drug and Alcohol Dependence, 81*(3), 313-322.

American Psychiatric Association (1994). *Diagnostic and Statistical Manual of Mental Disorders,* 4th ed. Washington, DC: American Psychiatric Press.

Ames, S. L., Grenard, J. L., Thush, C., Sussman, S., Wiers, R. W., & Stacy, A. W. (2007). Comparison of indirect assessments of association as predictors of marijuana use among at-risk adolescents. *Experimental and Clinical Psychopharmacology, 15,* 204–218.

Attwood, A. S., O'Sullivan, H., Leonards, U., Mackintosh, B., & Munafo, M.R. (2008). Attentional bias training and cue reactivity in cigarette smokers. *Addiction, 103,* 1875–1882.

Baayen, R. H., Piepenbrock, R., & Gulikers, L. (1995). *The CELEX Lexical Database* (Release 2). Philadelphia: Linguistic Data Consortium, University of Pennsylvania.

Baker, T. B., Piper, M. E., McCarthy, D. E., Majeskie, M. R., & Fiore, M. C. (2004). Addiction motivation reformulated: An affective processing model of negative reinforcement. *Psychological Review, 111,* 33–51.

Bauer, L. O. (1997). Frontal P300 decrements, childhood conduct disorder, family history, and the prediction of relapse among abstinent cocaine abusers. *Drug and Alcohol Dependence, 44,* 1-10.

Bechara, A., Noël, X., & Crone, E. A. (2006). Loss of willpower: Abnormal neural mechanisms of impulse control and decision making in addiction. In: R.W. Wiers, & A.W. Stacy (Eds.), *Handbook of implicit cognition and addiction*. Thousand Oaks, CA: Sage.

Beck, A., Wüstenberg, T., Genauck, A., Wrase, J., Schlagenhauf, F., Smolka, M. N., … Heinz, A. (2012). Effect of brain structure, brain function, and brain connectivity on relapse in alcohol-dependent patients. *Archives of General Psychiatry,* 69(8), 842-853.

Bernstein, P. S., Scheffers, M. K., & Coles, M. G. H. (1995). "Where Did I Go Wrong?" A Psychophysiological Analysis of Error Detection. *Journal of Experimental Psychology: Human Perception and Performance, 21,* 1312-1322.

Berridge, K. C. (2009) Wanting and liking: observations from the neuroscience and psychology laboratory. *Inquiry, 52*, 378–398.

Berridge, K. C., & Robinson, T. E. (2003). Parsing reward. *Trends in Neurosciences, 26*(9), 507-513.

Bordnick, P. S., & Schmitz, J. M. (1998). Cocaine craving: an evaluation across treatment phases. *Journal of Substance Abuse, 10,* 9-17.

Botvinick, M. M., Carter, C. S., Braver, T. S., Barch, D. M., & Cohen, J. D. (2001). Conflict monitoring and cognitive control. *Psychological Review, 108,* 624-652.

Botvinick, M. M., Cohen, J. D., & Carter, C. S. (2004). Conflict monitoring and anterior cingulate cortex: an update. *Trends in Cognitive Sciences, 8*(12), 539-546.

Brewer, J. A., Worhunsky, P. D., Carroll, K. M., Rounsaville, B. J., & Potenza, M. N. (2008). Pretreatment brain activation during Stroop task is associated with outcomes in cocaine-dependent patients. *Biological Psychiatry, 64,* 998-1004.

Burden, J. L., & Maisto, S. A. (2000). Expectancies, evaluations and attitudes: Prediction of college student drinking behavior. *Journal of Studies on Alcohol, 61,* 323–331.

Carpenter, K. M., Schreiber, E., Church, S., & McDowell, D. (2006). Drug Stroop performance: Relationships with primary substance of use and treatment outcome in a drug-dependent outpatient sample. *Addictive Behaviors, 31,* 174–181.

Carroll, K. M., Power, M.-E. D., Bryant, K., & Rounsaville, B. J. (1993). One-year follow-up status of treatment-seeking cocaine abusers: Psychopathology and dependence severity as predictors of outcome. *Journal of Nervous and Mental Disease, 181,* 71-79.

Carter, C. S., & Van Veen, V. (2007). Anterior cingulate cortex and conflict detection: An update of theory and data. *Cognitive, Affective and Behavioral Neuroscience, 7,* 367-379.

Chassin, L., Presson, C. C., Sherman, S. J., Seo, D.-C., & Macy, J. T. (2010). Implicit and explicit attitudes predict smoking cessation: Moderating effects of experienced failure to control smoking and plans to quit. *Psychology of Addictive Behaviors, 24,* 670–679.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences*. Hillsdale, NJ: Erlbaum.

Colin Drummond, D., Litten, R. Z., Lowman, C., & Hunt, W. A. (2000). Craving research: Future directions. *Addiction, 95*(8), S247-S255.

Constantinou, N., Morgan, C. J. A., Battistella, S., O'Ryan, D., Davis, P., & Curran, H. V. (2010). Attentional bias, inhibitory control and acute stress in current and former opiate addicts. *Drug and Alcohol Dependence, 109,* 220–225.

Cooney, N. L., Litt, M. D., Cooney, J. L., Pilkey, D. T., Steinberg, H. R., & Oncken, C. A. (2007). Alcohol and tobacco cessation in alcohol-dependent smokers: Analysis of real-time reports. *Psychology of Addictive Behaviors, 21,* 277–286.

Cox, W. M., Fadardi, J. S., & Pothos, E. M. (2006). The Addiction-Stroop test: Theoretical considerations and procedural recommendations. *Psychological Bulletin, 132,* 443–476.

Cox, W. M., Hogan, L. M., Kristian, M. R., & Race, J. H. (2002). Alcohol attentional bias as a predictor of alcohol abusers' treatment outcome. *Drug and Alcohol Dependence, 68,* 237–243.

Cox, W. M., Pothos, E. M., & Hosier, S. G. (2007). Cognitive-motivational predictors of excessive drinkers' success in changing. *Psychopharmacology, 192,* 499–510.

Cunningham, W. A., Preacher, K. J., & Banaji, M. R. (2001). Implicit attitude measures: Consistency, stability, and convergent validity. *Psychological Science, 12*(2), 163-170.

Day, E., & Strang, J. (2011). Outpatient versus inpatient opioid detoxification: A randomized controlled trial. *Journal of Substance Abuse Treatment, 40,* 56–66.

De Houwer, J. (2002). The implicit association test as a tool for studying dysfunctional associations in psychopathology: Strengths and limitations. *Journal of Behavior Therapy and Experimental Psychiatry, 33*(2), 115-133.

De Leeuw, R. N. H., Engels, R. C., Vermulst, A. A., & Scholte, R. H. J. (2008). Do smoking attitudes predict behavior: A longitudinal study on the bi-directional relations between adolescents' smoking attitudes and behaviors. *Addiction, 103,* 1713–1721.

De Ruiter, M. B., Oosterlaan, J., Veltman, D. J., Van Den Brink, W., & Goudriaan, A. E. (2012). Similar hyporesponsiveness of the dorsomedial prefrontal cortex in problem gamblers and heavy smokers during an inhibitory control task. *Drug and Alcohol Dependence, 121,* 81-89.

Donovan, D. M. (1996). Assessment issues and domains in the prediction of relapse. *Addiction, 91,* S29-S36.

Efron, B., Tibshirani, R. J. (1993). *An Introduction to the Bootstrap.* New York, NY: Chapman & Hall.

Egner, T., Etkin, A., Gale, S., & Hirsch, J. (2008). Dissociable neural systems resolve conflict from emotional versus nonemotional distracters. *Cerebral Cortex, 18,* 1475-1484.

Epstein, D. H., Marrone, G. F., Heishman, S. J., Schmittner, J., & Preston, K. L. (2010). Tobacco, cocaine, and heroin: craving and use during daily life. *Addictive Behaviors, 35,* 318–324.

Epstein, D. H., Willner-Reid, J., Vahabzadeh, M., Mezghanni, M., Lin, J., & Preston, K. L. (2009). Real-time electronic diary reports of cue exposure and mood in the hours before cocaine and heroin craving and use. *Archives of General Psychiatry, 66,* 88–94.

Eriksen, B. A., & Eriksen, C. W. (1974). Effects of noise letters upon the identification of a target letter in a nonsearch task. *Perception and Psychophysics, 16,* 143–149.

Ersche, K. D., Bullmore, E. T., Craig, K. J., Shabbir, S. S., Abbott, S., Müller, U., … Robbins, T. W. (2010). Influence of compulsivity of drug abuse on dopaminergic modulation of attentional bias in stimulant dependence. *Archives of General Psychiatry, 67*(6), 632-644.

Euser, A. S., Evans, B. E., Greaves-Lord, K., Huizink, A. C., & Franken, I. H. A. (2012). Diminished error-related brain activity as a promising endophenotype for substance-use disorders: evidence from high-risk offspring. *Addiction Biology,* published online first. doi: 10.1111/adb.12002.

Falkenstein, M., Hohnsbein, J., Hoormann, J., & Blanke, L. (1991). Effects of crossmodal divided attention on late ERP components. II. error processing in choice reaction tasks. *Electroencephalography and Clinical Neurophysiology, 78*(6), 447-455.

Fareed, A., Vayalapalli, S., Stout, S., Casarella, J., Drexler, K., & Bailey, S.P. (2011). Effect of methadone maintenance treatment on heroin craving, a literature review. *Journal of Addictive Diseases, 30,* 27–38.

Fazio, R. H., & Olson, M. A. (2003). Implicit measures in social cognition: Their meaning and uses. *Annual Review of Psychology, 54*, 297–327.

Field, A. (2009). *Discovering statistics using SPSS,* 3rd ed. London, UK: Sage.

Field, M. & Cox, W. M. (2008). Attentional bias in addictive behaviors: A review of its development, causes, and consequences. *Drug and Alcohol Dependence, 97,* 1-20.

Field, M., Duka, T., Eastwood, B., Child, R., Santarcangelo, M., & Gayton, M. (2007). Experimental manipulation of attentional biases in heavy drinkers: do the effects generalise? *Psychopharmacology, 192,* 593–608.

Field, M., Duka, T., Tyler, E., &n Schoenmakers, T. (2009a). Experimental attentional bias modification in tobacco smokers. *Nicotine and Tobacco Research, 11*, 812–822.

Field, M., & Eastwood,B. (2005). Experimental manipulation of attentional bias increases the motivation to drink alcohol. *Psychopharmacology, 183,* 350–357.

Field, M., Mogg, K., Mann, B., Bennett, G. A., & Bradley, B. P. (2013). Attentional biases in abstinent alcoholics and their association with craving. *Psychology of Addictive Behaviors,* in press.

Field, M., Munafo, M. R., & Franken, I. H. A. (2009b). A meta-analytic investigation of the relationship between attentional bias and subjective craving in substance abuse. *Psychological Bulletin, 135,* 589–607.

Forman, S. D., Dougherty, G. G., Casey, B. J., Siegle, G. J., Braver, T. S., Barch, D. M., … Lorensen, E. (2004). Opiate addicts lack error-dependent activation of rostral anterior cingulate. *Biological Psychiatry, 55*(5), 531-537.

Franken, I. H. A. (2003). Drug craving and addiction: Integrating psychological and neuropsychopharmacological approaches. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 27,* 563–579.

Franken, I. H. A., & Hendriks, V. M. (1999). Predicting outcome of inpatient detoxification of substance abusers. *Psychiatric Services, 50,* 813–817.

Franken, I. H. A., Hendriks, V. M., & Van den Brink, W. (2002). Initial validation of two opiate craving questionnaires: The Obsessive Compulsive Drug Use Scale and the Desires for Drug Questionnaire. *Addictive Behaviors, 27,* 675-685.

Franken, I. H. A., Kroon, L. Y., Wiers, R. W., & Jansen, A. (2000). Selective cognitive processing of drug cues in heroin dependence. *Journal of Psychopharmacology, 14,* 395– 400.

Franken, I. H. A., Stam, C. J., Hendriks, V. M., & Van den Brink, W. (2003). Neurophysiological evidence for abnormal cognitive processing of drug cues in heroine dependence. *Psychopharmacology, 170,* 205–212.

Franken, I. H. A., Van Strien, J. W., Franzek, E. J., & Van de Wetering, B. J. M. (2007): Error-processing deficits in patients with cocaine dependence. *Biological Psychology, 75,* 45-51.

Freedman, M. J., Lester, K. M., McNamara, C., Milby, J. B., & Schumacher, J. E. (2006). Cell phones for ecological momentary assessment with cocaine-addicted homeless patients in treatment. *Journal of Substance Abuse Treatment, 30,* 105–111.

Friston, K. J., Holmes, A., Poline, J. B., Price, C. J., & Frith, C. D. (1996). Detecting activations in PET and fMRI: Levels of inference and power. *Neuroimage, 4,* 223-235.

Garavan, H., & Weierstall, K. (2012). The neurobiology of reward and cognitive control systems and their role in incentivizing health behavior. *Preventive Medicine, 55*(SUPPL.), S17-S23.

Garavan, H. & Hester, R. (2007). The role of cognitive control in cocaine dependence. *Neuropsychology Review, 17,* 337-345.

Gehring, W. J., Coles, M. G., Meyer, D. E., & Donchin, E. (1995). A brain potential manifestation of error-related processing. *Electroencephalography and Clinical Neurophysiology, S44,* 261-272.

Gehring, W. J., Goss, B., Coles, M. G. H., Meyer, D. E., & Donchin, E. (1993). A neural system for error detection and compensation. *Psychological Science, 4,* 385-390.

Glasper, A., Gossop, M., de Wet, C., Reed, L., & Bearn, J. (2008). Influence of the dose on the severity of opiate withdrawal symptoms during methadone detoxification. *Pharmacology, 81,* 92–96.

Goldstein, R. Z., Alia-Klein, N., Tomasi, D., Carrillo, J. H., Maloney, T., Woicik, P. A., … Volkow, N. D. (2009). Anterior cingulate cortex hypoactivations to an emotionally salient task in cocaine addiction. *Proceedings of the National Academy of Sciences of the United States of America, 106*(23), 9453-9458.

Goldstein, R. Z., Tomasi, D., Rajaram, S., Cottone, L. A., Zhang, L., Maloney, T., … Volkow, N. D. (2007). Role of the anterior cingulate and medial orbitofrontal cortex in processing drug cues in cocaine addiction. *Neuroscience, 144,* 1153-1159.

Goldstein, R. Z. & Volkow, N. D. (2011). Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. *Nature Reviews Neuroscience, 12*, 652-669.

Goldstein, R. Z., & Volkow, N. D. (2002). Drug addiction and its underlying neurobiological basis: Neuroimaging evidence for the involvement of the frontal cortex. *American Journal of Psychiatry, 159,* 1642-1652.

Goldstein, R. Z., Woicik, P. A., Maloney, T., Tomasi, D., Alia-Klein, N., Shan, J. … Volkow, N. D. (2010). Oral methylphenidate normalizes cingulate activity in cocaine addiction during a salient cognitive task. *Proceedings of the National Academy of Sciences of the United States of America, 107,* 16667-16672.

Gossop, M., Bradley, B., & Phillips, G. T. (1987). An investigation of withdrawal symptoms shown by opiate addicts during and subsequent to a 21-day in-patient methadone detoxification procedure. *Addictive Behaviors, 12,* 1–6.

Gossop, M., Green, L., Phillips, G., & Bradley, B. (1987). What happens to opiate addicts immediately after treatment: A prospective follow up study. *British Medical Journal, 294,* 1377–1380.

Gossop, M., Stewart, D., Browne, N., & Marsden, J. (2002). Factors associated with abstinence, lapse or relapse to heroin use after residential treatment: Protective effect of coping responses. *Addiction, 97,* 1259–1267.

Gratton, G., Coles, M. G., & Donchin, E. (1983). A new method for off-line removal of ocular artifact. *Electroencephalography and Clinical Neurophysiology, 55,* 468–484.

Greenwald, A. G., Nosek, B. A., & Banaji, M. R. (2003). Understanding and using the Implicit Association Test: I. An improved scoring algorithm. *Journal of Personality and Social Psychology, 85,* 197–216.

Haas, B. W., Omura, K., Constable, R. T., & Canli, T. (2006). Interference produced by emotional conflict associated with anterior cingulate activation. *Cognitive Affective & Behavioral Neuroscience, 6,* 152-156.

Hajcak, G. (2012). What we've learned from our mistakes: Insights from error-related brain activity. *Current Directions in Psychological Science, 21,* 101-106.

Hajcak, G. & Foti, D. (2008). Errors are aversive: Defensive motivation and the error-related negativity: Research report. *Psychological Science, 19,* 103-108.

Hajcak, G., Moser, J. S., Yeung, N., & Simons, R. F. (2005). On the ERN and the significance of errors. *Psychophysiology, 42,* 151–160.

Hammersley, R. (1994). A digest of memory phenomena for addiction research. *Addiction, 89,* 283–293.

Hättenschwiler, J., Rüesch, P., & Hell, D. (2000). Effectiveness of inpatient drug detoxification: Links between process and outcome variables. *European Addiction Research, 6,* 123–131.

Hedeker, D., Mermelstein, R. J., Berbaum, M. L., & Campbell, R. T. (2009). Modeling mood variation associated with smoking: an application of a heterogeneous mixed-effects model for analysis of ecological momentary assessment (EMA) data. *Addiction, 104,* 297–307.

Hendriks, V. M., Kaplan, C. D., Van Limbeek, J., & Geerlings, P. (1989). The Addiction Severity Index: reliability and validity in a Dutch addict population. *Journal of Substance Abuse Treatment, 6,* 133–141.

Hester, R. & Garavan, H. (2009). Neural mechanisms underlying drug-related cue distraction in active cocaine users. *Pharmacology Biochemistry and Behavior, 93,* 270-277.

Hester, R. & Garavan, H. (2004). Executive dysfunction in cocaine addiction. Evidence for discordant frontal, cingulate, and cerebellar activity. *Journal of Neuroscience, 24,* 11017-11022.

Hester, R., Nestor, L., & Garavan, H. (2009). Impaired error awareness and anterior cingulate cortex hypoactivity in chronic cannabis users. *Neuropsychopharmacology, 34*(11), 2450-2458.

Hester, R., Dixon, V., & Garavan, H. (2006). A consistent attentional bias for drug-related material in active cocaine users across word and picture versions of the emotional Stroop task. *Drug and Alcohol Dependence, 81,* 251–257.

Hester, R., Simões-Franklin, C., & Garavan, H. (2007). Post-error behavior in active cocaine users: Poor awareness of errors in the presence of intact performance adjustments. *Neuropsychopharmacology, 32*(9), 1974-1984.

Hoffmann, S., & Falkenstein, M. (2012). Predictive information processing in the brain: Errors and response monitoring. *International Journal of Psychophysiology, 83*(2), 208-212.

Holroyd, C. B., & Coles, M. G. H. (2002). The neural basis of human error processing: Reinforcement learning, dopamine, and the Error-Related Negativity. *Psychological Review, 109,* 679–709.

Janes, A. C., Pizzagalli, D. A., Richardt, S., Frederick, B. deB., Holmes, A. J., Sousa, J., … Kaufman, M. J. (2010a). Neural Substrates of Attentional Bias for Smoking-Related Cues: An fMRI Study. *Neuropsychopharmacology, 35,* 2339-2345.

Janes, A. C., Pizzagalli, D. A., Richardt, S., Frederick, B. deB., Chuzi, S., Pachas, G., … Kaufman, M. J. (2010b). Brain reactivity to smoking cues prior to smoking cessation predicts ability to maintain tobacco abstinence. *Biological Psychiatry, 67,* 722–729.

Jia, Z., Worhunsky, P. D., Carroll, K. M., Rounsaville, B. J., Stevens, M. C., Pearlson, G. D., & Potenza, M. N. (2011). An initial study of neural responses to monetary incentives as related to treatment outcome in cocaine dependence. *Biological Psychiatry, 70*(6), 553-560.

Kaufman, J. N., Ross, T. J., Stein, E. A., & Garavan, H. (2003). Cingulate hypoactivity in cocaine users during a GO-NOGO task as revealed by event-related functional magnetic resonance imaging. *Journal of Neuroscience, 23,* 7839-7843.

Kerns, J. G., Cohen, J. D., MacDonald III, A. W., Cho, R. Y., Stenger, V. A, & Carter, C. S (2004). Anterior cingulate conflict monitoring and adjustments in control. *Science, 303,* 1023-1026.

Knutson, B., Wimmer, G. E., Rick, S., Hollon, N. G., Prelec, D., & Loewenstein, G. (2008). Neural antecedents of the endowment effect. *Neuron, 58,* 814-822.

Kosten, T. R., Scanley, B. E., Tucker, K. A., Oliveto, A., Prince, C., Sinha, R., … Wexler, B. E. (2006). Cue-induced brain activity changes and relapse in cocaine-dependent patients. *Neuropsychopharmacology, 31*, 644-650.

Leshner, A. I. (1997). Addiction is a brain disease, and it matters. *Science, 278,* 45-47.

Liu, S., Moeller, F. G., Lane, S. D., Schmitz, J. M., Waters, A. J., & Cunningham, K.A. (2010). Relationship between attentional bias to cocainerelated stimuli and impulsivity in cocaine-dependent subjects. *American Journal of Drug and Alcohol Abuse, 37,* 117–122.

Ludwig, A. M., Wikler, A., & Stark, L. H. (1974). The first drink: Psychobiological aspects of craving. *Archives of General Psychiatry, 30,* 539–547.

Luijten, M., Van Meel, C. S., & Franken, I. H. A. (2011b). Diminished error processing in smokers during smoking cue exposure. *Pharmacology Biochemistry and Behavior , 97,* 514-520.

Luijten, M., Veltman, D. J., Hester, R., Smits, M., Pepplinkhuizen, L., & Franken, I. H. A. (2012). Brain activation associated with attentional bias in smokers is modulated by a dopamine antagonist. *Neuropsychopharmacology, 37*(13), 2772-2779.

Luijten, M., Veltman, D. J., den Brink, W. V., Hester, R., Field, M., Smits, M., & Franken, I. H. A. (2011a). Neurobiological substrate of smoking-related attentional bias. *Neuroimage, 54,* 2374-2381.

Marhe, R., Waters, A. J., Van de Wetering, B. J. M., & Franken, I. H. A. (2013). Implicit and explicit drug-related cognitions during detoxification treatment are associated with drug relapse: An ecological momentary assessment study. *Journal of Consulting and Clinical Psychology, 81*(1), 1-12.

Marissen, M. A. E., Franken, I. H. A., Blanken, P., van den Brink, W., & Hendriks, V. M. (2005). The relation between social desirability and different measures of heroin craving. *Journal of Addictive Diseases, 24,* 91–103.

Marissen, M. A. E., Franken, I. H. A., Waters, A. J., Blanken, P., van den Brink, W., & Hendriks, V. M. (2006). Attentional bias predicts heroin relapse following treatment. *Addiction, 101,* 1306–1312.

Mars, R. B., Coles, M. G. H., Grol, M. J., Holroyd, C. B., Nieuwenhuis, S., Hulstijn, W., & Toni, I. (2005). Neural dynamics of error processing in medial frontal cortex. *Neuroimage, 28,* 1007-1013.

Mathalon, D. H., Whitfield, S. L., & Ford, J. M. (2003). Anatomy of an error: ERP and fMRI. *Biological Psychology, 64,* 119–141.

McCarthy, D. M., & Thompsen, D. M. (2006). Implicit and explicit measures of alcohol and smoking cognitions. *Psychology of Addictive Behaviors, 20,* 436–444.

McKay, J. R., Alterman, A. I., Koppenhaver, J., Mulvaney, F., Bovasso, G., & Ward, K. (2001). Continuous, categorical, and time to event cocaine use outcome variables: Degree of intercorrelation and sensitivity to treatment group differences. *Drug and Alcohol Dependence, 62,* 19-30.

McKay, J. R. (1999). Studies of factors in relapse to alcohol, drug and nicotine use: A critical review of methodologies and findings. *Journal of Studies on Alcohol, 60,* 566–576.

McKay, J. R., Franklin, T. R., Patapis, N., & Lynch, K. G. (2006). Conceptual, methodological, and analytical issues in the study of relapse. *Clinical Psychology Review, 26,* 109–127.

McLellan, A. T., Lewis, D. C., O'Brien, C. P., & Kleber, H. D. (2000). Drug dependence, a chronic medical illness: implications for treatment, insurance, and outcomes evaluation. *Journal of the American Medical Association, 284*(13), 1689-1695.

McLellan, A. T., Luborski, L., Woody, G. E., & O'Brien, C. P. (1980). An improved diagnostic evaluation instrument for substance abuse patients: The Addiction Severity Index. *Journal of Nervous and Mental Disease, 168,* 26-33.

Miller, W. R. (1996). What is a relapse? Fifty ways to leave the wagon. *Addiction, 91,* S15-S27.

Miller, W. R., Westerberg, V. S., Harris, R. J., & Tonigan, J. S. (1996). What predicts relapse? Prospective testing of antecedent models. *Addiction, 91,* S155-S172.

Miltner, W. H. R., Lemke, U., Weiss, T., Holroyd, C., Scheffers, M. K., & Coles, M. G. H. (2003). Implementation of error-processing in the human anterior cingulate cortex: a source analysis of the magnetic equivalent of the error-related negativity. *Biological Psychology, 64,* 157–166.

Moeller, S. J., Tomasi, D., Woicik, P. A., Maloney, T., Alia-Klein, N., Honorio, J., … Goldstein, R. Z. (2012). Enhanced midbrain response at 6-month follow-up in cocaine addiction, association with reduced drug-related choice. *Addiction Biology, 17*(6), 1013-1025.

Mooney, C. Z., & Duval, R. D. (1993). *Bootstrapping: A nonparametric approach to statistical inference.* Newbury Park, CA: Sage.

Nestor, L., McCabe, E., Jones, J., Clancy, L., & Garavan, H. (2011). Differences in "bottom-up" and "top-down" neural activity in current and former cigarette smokers: Evidence for neural substrates which may promote nicotine abstinence through increased cognitive control. *Neuroimage, 56,* 2258-2275.

Olvet, D. M., & Hajcak, G. (2008). The error-related negativity (ERN) and psychopathology: Toward an endophenotype. *Clinical Psychology Review, 28,* 1343-1354.

Olvet, D. M., & Hajcak, G. (2009). The stability of error-related brain activity with increasing trials. *Psychophysiology, 46,* 957-961.

Padilla, M. L., Colrain, I. M., Sullivan, E. V., Mayer, B. Z., Turlington, S. R., Hoffman, L. R., … Pfefferbaum, A. (2011). Electrophysiological evidence of enhanced performance monitoring in recently abstinent alcoholic men. *Psychopharmacology, 213,* 81-91.

Paliwal, P., Hyman, S. M., & Sinha, R. (2008). Craving predicts time to cocaine relapse: Further validation of the Now and Brief versions of the cocaine craving questionnaire. *Drug and Alcohol Dependence, 93,* 252-259.

Passetti, F., Clark, L., Davis, P., Mehta, M. A., White, S., Checinski, K., … Abou-Saleh, M. (2011). Risky decision-making predicts short-term outcome of community but not residential treatment for opiate addiction. implications for case management. *Drug and Alcohol Dependence, 118*(1), 12-18.

Paulus, M. P., Tapert, S. F., & Schuckit, M. A. (2005). Neural activation patterns of methamphetamine-dependent subjects during decision making predict relapse. *Archives of General Psychiatry, 62,* 761-768.

Poling, J., Kosten, T. R., & Sofuoglu, M. (2007). Treatment outcome predictors for cocaine dependence. *American Journal of Drug and Alcohol Abuse, 33,* 191-206.

Powell, J., Dawkins, L., West, R., Powell, J., & Pickering, A. (2010). Relapse to smoking during unaided cessation: clinical, cognitive and motivational predictors. *Psychopharmacology, 12,* 537-549.

Preston, K. L., Vahabzadeh, M., Schmittner, J., Lin, J., Gorelick, D. A., & Epstein, D. H. (2009). Cocaine craving and use during daily life. *Psychopharmacology, 207,* 291–301.

Reiber, C., Ramirez, A., Parent, D., & Rawson, R. A. (2002). Predicting treatment success at multiple time points in diverse patient populations of cocaine-dependent individuals. *Drug and Alcohol Dependence, 68,* 35-48.

Ridderinkhof, K. R., De Vlugt, Y., Bramlage, A., Spaan, M., Elton, M., Snel, J., & Band, G. P. H. (2002). Alcohol consumption impairs detection of performance errors in mediofrontal cortex. *Science, 298,* 2209-2211.

Ridderinkhof, K. R., Ullsperger, M., Crone, E. A., Nieuwenhuis, S. (2004). The role of the medial frontal cortex in cognitive control. *Science, 306,* 443-447.

Robbins, S. J., & Ehrman, R. N. (2004). The role of attentional bias in substance abuse. *Behavioral and Cognitive Neuroscience Reviews, 3*(4), 243-260.

Robinson, T. E., & Berridge, K. C. (1993). The neural basis of drug craving: An incentive-sensitization theory of addiction. *Brain Research Reviews, 18,* 247-291.

Roefs, A., Huijding, J., Smulders, F. T. Y., Macleod, C. M., de Jong, P. J., Wiers, R. W., & Jansen, A. T. M. (2011). Implicit measures of association in psychopathology research. *Psychological Bulletin, 137,* 149–193.

Rooke, S. E., Hine, D. W., & Thorsteinsson, E. B. (2008) Implicit cognition and substance use: a meta-analysis. *Addictive Behaviors, 33,* 1314–1328.

Rosenberg, H. (2009). Clinical and laboratory assessment of the subjective experience of drug craving. *Clinical Psychology Review, 29,* 519–534.

Sayette, M. A., Martin, C. S., Perrott, M. A., Wertz, J. M., & Hufford, M. R. (2001). A test of the appraisal-disruption model of alcohol and stress. *Journal of Studies on Alcohol, 62,* 247–256.

Sayette, M. A., Shiffman, S., Tiffany, S. T., Niaura, R. S., Martin, C. S., & Shadel, W. G. (2000). The measurement of drug craving. *Addiction, 95,* 189–210.

Schellekens, A. F., De Bruijn, E. R., Van Lankveld, C. A., Hulstijn, W., Buitelaar, J. K., De Jong, C. A., & Verkes, R. J. (2010). Alcohol dependence and anxiety increase error-related brain activity. *Addiction, 105,* 1928-1934.

Schneider, W., & Shiffrin, R. M. (1977). Controlled and automatic human information processing: 1. Detection, search, and attention. *Psychological Review, 84,* 1–66.

Schoenmakers, T. M., de Bruin, M., Lux, I. F. M., Goertz, A. G., Van Kerkhof, D. H. A.T., & Wiers, R. W. (2010). Clinical effectiveness of attentional bias modification training in abstinent alcoholic patients. *Drug and Alcohol Dependence, 109,* 30-36.

Schoenmakers, T. M., Wiers, R. W., Jones, B. T., Bruce, G., & Jansen, A. T. M. (2007). Attentional retraining decreases attentional bias in heavy drinkers without generalization. *Addiction, 102,* 399–405.

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., … Greicius, M.D. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *Journal of Neuroscience, 27,* 2349-2356.

Shiffman, S. (2000). Comments on craving. *Addiction, 95*(Suppl. 2), S171–S175.

Shiffman, S. (2009). Ecological momentary assessment (EMA) in studies of substance use. *Psychological Assessment, 21,* 486–497.

Shiffman, S., Engberg, J. B., Paty, J. A., Perz, W. G., Gnys, M., Kassel, J. D., & Hickcox, M. (1997). A day at a time: Predicting smoking lapse from daily urge. *Journal of Abnormal Psychology, 106,* 104–116.

Shiffman, S., Paty, J. A., Gnys, M., Kassel, J. A., & Hickcox, M. (1996). First lapses to smoking: Within-subjects analysis of real-time reports. *Journal of Consulting and Clinical Psychology, 64,* 366–379.

Shiffman, S., Stone, A. A., & Hufford, M. R. (2008) Ecological momentary assessment. *Annual Review of Clinical Psychology, 4,* 1–32.

Shiffman, S., & Waters, A. J. (2004). Negative affect and smoking lapses: A prospective analysis. *Journal of Consulting and Clinical Psychology,72,* 192–201.

Sofuoglu, M., Devito, E. E., Waters, A. J., & Carroll, K. M. (2013). Cognitive enhancement as a treatment for drug addictions. *Neuropharmacology, 64,* 453-463.

Sokhadze, E., Stewart, C., Hollifield, M., & Tasman, A. (2008). Event-related potential study of executive dysfunctions in a speeded reaction task in cocaine addiction. *Journal of Neurotherapy, 12,* 185–204.

Stacy, A. W., Wiers, R. A. (2010). Implicit cognition and addiction: a tool for explaining paradoxical behavior. *Annual Review of Clinical Psychology, 6,* 551–575.

Stark, M. J. (1992). Dropping out of substance abuse treatment: a clinically oriented review. Clinical *Psychology Review, 12,* 93–116.

Stevens, L., Verdejo-García, A., Goudriaan, A. E., Roeyers, H., Dom, G., & Vanderplasschen, W. Impulsivity as a vulnerability factor for poor addiction treatment outcomes: A review of findings among individuals with substance use disorders. Under revision.

Stone, A. A., Shiffman, S., Atienza, A., & Nebeling, L. (Eds.). (2007). *The science of real time data capture: Self-reports in health research.* New York, NY: Oxford University Press.

Streeter, C. C., Terhune, D. B., Whitfield, T. H., Gruber, S., Sarid-Segal, O., Silveri, M. M., … Yurgelun-Todd, D. A. (2008). Performance on the stroop predicts treatment compliance in cocaine-dependent individuals. *Neuropsychopharmacology, 33*(4), 827-836.

Tiffany, S. T. (1990). A cognitive model of drug urges and drug-use behavior: Role of automatic and nonautomatic processes. *Psychological Review, 97,* 147-168.

Tiplady, B., Oshinowo, B., Thomson, J., & Drummond, G. (2009). Alcohol and cognitive function: Assessment in everyday life and laboratory settings using mobile phones. Alcoholism: *Clinical and Experimental Research, 33,* 2094–2102.

Turner, T. H., LaRowe, S., Horner, M. D., Herron, J., & Malcolm, R. (2009). Measures of cognitive functioning as predictors of treatment outcome for cocaine dependence. *Journal of Substance Abuse Treatment, 37*(4), 328-334.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., … Joliot, M. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage, 15,* 273-289.

UNODC (2012). *World Drug Report 2012.* New York, NY: United Nations publication.

Van de Laar, M. C., Licht, R., Franken, I. H. A., & Hendriks, V. M. (2004). Event related potentials indicate motivational relevance of cocaine cues in abstinent cocaine addicts. *Psychopharmacology, 177,* 121–129.

Van Veen, V., & Carter, C. S. (2002). The anterior cingulate as a conflict monitor: fMRI and ERP studies. *Physiology and Behavior, 77,* 477–482.

Volkow, N. D., Fowler, J. S., & Wang, G. -J. (2004). The addicted human brain viewed in the light of imaging studies: Brain circuits and treatment strategies. *Neuropharmacology, 47*(SUPPL. 1), 3-13.

Vollstädt-Klein, S., Loeber, S., Richter, A., Kirsch, M., Bach, P., von der Goltz, C., … Kiefer, F. (2012). Validating incentive salience with functional magnetic resonance imaging: association between mesolimbic cue reactivity and attentional bias in alcohol-dependent patients. *Addiction Biology, 17,* 807-816.

Waters, A. J., & Li, Y. (2008). Evaluating the utility of administering a reaction time task in an ecological momentary assessment study. *Psychopharmacology, 197,* 25–35.

Waters, A. J., Marhe, R., & Franken, I. H. A. (2012). Attentional bias to drug cues is elevated before and during temptations to use heroin and cocaine. *Psychopharmacology, 219,* 909–921.

Waters, A. J., Shiffman, S., Bradley, B. P., & Mogg, K. (2003b). Attentional shifts to smoking cues in smokers. *Addiction, 98*(10), 1409-1417.

Waters, A. J., Shiffman, S., Sayette, M. A., Paty, J. A., Gwaltney, C. G., & Balabanis, M. H. (2003a). Attentional bias predicts outcome in smoking cessation. *Health Psychology, 22,* 378–387.

Watson, D. (2000). *Mood and temperament.* New York, NY: Guilford.

Weinberg, A., Klein, D. N., & Hajcak, G. (2012). Increased error-related brain activity distinguishes generalized anxiety disorder with and without comorbid major depressive disorder. *Journal of Abnormal Psychology, 121,* 885-896.

Weiss, R. D., Griffin, M. L., & Hufford, C. (1995). Craving in hospitalized cocaine abusers as a predictor of outcome. *American Journal of Drug and Alcohol Abuse, 21,* 289-301.

Weiss, R. D., Griffin, M. L., Mazurick, C., Berkman, B., Gastfriend, D. R., Frank, A., … Moras, K. (2003). The relationship between cocaine craving, psychosocial treatment, and subsequent use. *American Journal of Psychiatry, 160,* 1320–1325.

Wiers, R. W., & Stacy, A. W. (Eds) (2006) *Handbook of implicit cognition and addiction*. Thousand Oaks, CA: Sage.

Wiers, R. W., & Stacy, A. W. (2006). Implicit cognition and addiction. *Current Directions in Psychological Science, 15,* 292–296.

Wiers, R. W., Van Woerden, N., Smulders, F. T. Y., & de Jong, P. J. (2002). Implicit and explicit alcohol-related cognitions in heavy and light drinkers. *Journal of Abnormal Psychology, 111,* 648–658.

Wilkinson, L., & the APA Task Force on Statistical Inference. (1999). Statistical methods in psychology journals: Guidelines and explanations. *American Psychologist, 54,* 594–604.

Wise, R. A. (1988). The neurobiology of craving: Implications for the understanding and treatment of addiction. *Journal of Abnormal Psychology, 97,* 118–132.

Worsley, K. J., Marrett, S., Neelin, P., Vandal, A. C., Friston, K. J., & Evans, A. C. (1996). A unified statistical approach for determining significant signals in images of cerebral activation. *Human Brain Mapping, 4,* 58-73.

Yeung, N., Botvinick, M. M., & Cohen, J. D. (2004). The neural basis of error detection: Conflict monitoring and the Error-Related Negativity. *Psychological Review, 111,* 931–959.

Samenvatting (Summary in Dutch)

Achtergrond

Wereldwijd gebruiken ongeveer 35 miljoen mensen heroïne en/of cocaïne; dat is 0.8% van de volwassen wereldpopulatie. Circa 10-13% van deze druggebruikers zijn of worden afhankelijk van de drug, ofwel verslaafd[1] (UNODC, World Drug Report, 2012). Personen met een middelenafhankelijkheid vallen vaak terug, ondanks hun inzet om abstinent te blijven (APA, 1994). Middelenafhankelijkheid wordt daarom ook wel gekenmerkt als een chronische stoornis van terugval. Hierdoor is het voornaamste doel van behandelcentra om behandeluitval en daaropvolgend terugval te voorkomen. Helaas vallen gemiddeld 50% van de heroïne en cocaïne afhankelijke patiënten vaak al tijdens de eerste fase van klinische behandeling uit, namelijk in de detoxificatie of ontwenningsfase. Uitval uit behandeling hangt samen met hoge terugvalpercentages (Gossop et al., 1987, 2002). Om deze percentages terug te dringen en behandelingen voor drugafhankelijkheid te verbeteren moeten we eerst weten welke factoren voorspellend zijn voor terugval.

Eerder onderzoek heeft de relatie bestudeerd tussen terugval en persoonlijke en sociale kenmerken. Voorbeelden hiervan zijn demografische factoren (geslacht, leeftijd, educatieniveau, etniciteit) en andere factoren zoals de ernst van de drugverslaving, medische problemen en psychopathologie (Stark, 1992; Poling et al., 2007). Andere factoren die voorspellend zijn voor terugval zijn emotionele staat, zoals een negatieve emotionele staat (Shiffman en Waters, 2000) en druggerelateerde gevoelens, zoals de houding tegenover het druggebruik (Burden en Maisto, 2000) of hunkering (*craving*) naar het middel (Weiss et al., 2003; Preston et al., 2009). Een belangrijk kenmerk dat deze factoren delen is dat ze vaak zelf-gerapporteerd zijn. Het gaat hier dan ook om bewuste, gecontroleerde processen, ook wel "expliciete processen" genoemd. Zelf-rapportage heeft echter zijn beperkingen. Mensen – en vooral drugverslaafden – hebben vaak weinig inzicht in hun eigen motivaties en kunnen daarom hun gedachten en gevoelens niet goed uitdrukken. Daarnaast is het ook mogelijk dat men sociaal wenselijke antwoorden geeft.

Bij (neuro)cognitief onderzoek is er minder snel sprake van dit probleem omdat snelle, automatische cognitieve processen worden gemeten die vaak onmogelijk bewust waar te nemen zijn, maar die wel invloed hebben op ons gedrag. Dit soort onderzoek richt zich op processen zoals aandacht, controle, inhibitie en het monitoren van gedrag, ook wel "impliciete processen" genoemd. Ze kunnen gemeten worden met behulp van taken waar iemands reactietijd opgenomen wordt. De breinprocessen die hierbij een rol spelen kunnen in kaart gebracht worden met *neuroimaging* technieken zoals functionele MRI (fMRI) en electroencefalografie (EEG).

[1]De termen verslaving en middelenafhankelijkheid verwijzen naar dezelfde stoornis. Middelenafhankelijkheid is de klinische term zoals gehanteerd in de DSM-IV (APA, 1994).

In verslavingsonderzoek is er steeds meer interesse voor de rol van deze automatische, impliciete processen. Theorieën stellen dat er bij verslaving sprake is van een overactief motivationeel systeem, dat ontstaat door herhaaldelijk gebruik van drugs waardoor het beloningssysteem in het brein (het dopamine-systeem) zodanig overgevoelig raakt dat niet alleen het gebruik van drugs maar slechts het zien van drugs of druggerelateerde stimuli een belonende, motivationele waarde krijgt toegekend (Robinson en Berridge, 1993). Hierdoor wordt ook de aandacht automatisch getrokken richting druggerelateerde stimuli. Dit wordt aandachts*bias* genoemd (Franken, 2003).

Aandachtsbias voor drugs wordt vaak gemeten met behulp van een druggerelateerde versie van de Stroop taak. In deze taak worden neutrale en druggerelateerde woorden één voor één aangeboden in een bepaalde kleur en de opdracht is om de kleur van het woord zo snel mogelijk te benoemen terwijl de inhoud van het woord genegeerd wordt. Het idee achter deze taak is dat drugafhankelijke personen afgeleid raken van de opdracht wanneer hun aandacht automatisch (en dus te snel voor bewuste waarneming) getrokken wordt naar de druggerelateerde inhoud van het woord, waardoor de reactietijd langzamer is dan wanneer er een neutraal woord wordt getoond. Veel studies hebben met behulp van deze taak aangetoond dat verslaafde personen een aandachtsbias voor drugs hebben (voor een overzicht zie Cox et al., 2006).

Een ander automatisch proces dat een rol speelt bij verslaving is impliciete geheugenassociaties. Drugafhankelijke patiënten slaan bepaalde associaties met het gebruiken van drugs op in het geheugen (bijv. de positieve belonende effecten of de negatieve ontwenningsverschijnselen). Als gevolg hiervan worden deze (positieve of negatieve) associaties in het geheugen automatisch geactiveerd wanneer men drugs of druggerelateerde stimuli ziet (Stacy en Wiers, 2010). Onderzoek heeft aangetoond dat over het algemeen alcohol afhankelijken en rokers negatieve impliciete associaties hebben met het middel waaraan zij verslaafd zijn, terwijl cocaïne afhankelijken meer positieve en opgewonden associaties hebben met drugs (Roefs et al., 2011).

Aandachtsbias voor drugs en impliciete geheugenassociaties kunnen beide bijdragen aan de motivatie om door te gaan met druggebruik. Verslavingstheorieën suggereren dat naast het overactieve motivationele systeem er tegelijkertijd sprake is van een minder actief vermogen om gedrag te controleren, ook wel cognitieve controle genoemd (Goldstein en Volkow, 2002). Het breinsysteem dat cognitieve controle uitoefent op het gedrag, zoals inhibitie of het vermogen om je gedrag te monitoren, is voornamelijk gelokaliseerd in het voorste gedeelte van het brein, ook wel de prefrontale cortex genoemd (Goldstein et al., 2011). Een goed functionerend controlesysteem is van belang om doelgericht te handelen. Neem het voorbeeld van een persoon die een bar binnen loopt op een zomerse dag. Zijn

of haar aandacht wordt meteen getrokken naar een biertje op de tafel (aandachtsbias) en diegene weet uit eerdere ervaringen dat een biertje een lekkere dorstlesser is (geheugenassociatie). Echter, de persoon realiseert zich dat hij/zij niet teveel biertjes kan drinken omdat er morgen een belangrijke vergadering is en hij/zij altijd hoofdpijn krijgt na het drinken van teveel biertjes. Vervolgens zal de persoon niet meer dan één biertje drinken en controleert zijn/haar drang om meer te drinken (cognitieve controle). Bij een verslaafd persoon is de balans tussen het motivationele systeem en het cognitieve controlesysteem verstoord (Volkow et al., 2004). Anders gezegd: er is een verstoorde balans in de hersenen tussen "het gaspedaal" en "de rem". Dit zou kunnen verklaren waarom drugafhankelijke personen hun gebruik niet kunnen beheersen en vaak terugvallen na een periode van abstinentie (Garavan en Hester, 2007).

Een basisonderdeel van cognitieve controle is foutenverwerking, een manier om ons gedrag te monitoren. Het verwijst naar het vermogen om foutief gedrag op een juiste manier te verwerken zodat we ons gedrag doelgericht kunnen aanpassen en toekomstige fouten kunnen voorkomen. Een van de meest kenmerkende eigenschappen van verslaving is dat men vaak doorgaat met druggebruik ondanks de negatieve gevolgen zoals sociale, interpersoonlijke en fysieke problemen (APA, 1994). Eerder onderzoek laat zien dat drugafhankelijke patiënten een minder sterke of zelfs zwakke foutenverwerking hebben, zowel op gedragsniveau als in de hersenen (Franken et al., 2007). Dit zou ten grondslag kunnen liggen aan het onvermogen van verslaafden om te stoppen met druggebruik ondanks de negatieve consequenties.

Het is klinisch relevant om te onderzoeken in hoeverre impliciete cognities zoals aandachtsbias en cognitieve controle samenhangen met terugval in druggebruik. Eerdere studies hebben aangetoond dat een verhoogde aandachtsbias voorspellend is voor terugval in nicotine, alcohol, heroïne en cocaïne afhankelijkheid (voor een overzicht zie hoofdstuk 1, tabel 1). Sommige studies laten zien dat aandachtsbias zelfs een betere voorspeller is van terugval dan zelf-gerapporteerde craving (Marissen et al., 2006). Ook een verhoogde aandachtsbias-gerelateerde hersenactiviteit in gebieden zoals de insula en de dorsale anterior cingulate cortex (dACC) is voorspellend voor terugval in nicotine afhankelijkheid (Janes et al., 2010b). Studies die de relatie tussen cognitieve functies en terugval hebben bestudeerd hebben over het algemeen gevonden dat een verminderd cognitief vermogen, zowel gedragsmatig als in het brein, geassocieerd is met een hogere kans op terugval (zie hoofdstuk 1, tabel 1).

Deze studies suggereren dat neurocognitieve methoden kunnen helpen om te identificeren wie vatbaar is voor terugval in druggebruik. Het doel van dit proefschrift was om meer inzicht te krijgen in de toegevoegde waarde van neurocognitieve methoden in de voorspelling van terugval, bovenop zelf-gerapporteerde maten zoals craving. Er is

onderzocht of de volgende processen adequate voorspellers zijn: 1) dagelijkse metingen van impliciete cognitieve processen in de klinische omgeving van een drugafhankelijke patiënt, zowel op willekeurige tijden als op momenten van verleiding; 2) hersenactiviteit die geassocieerd is met aandachtsbias voor drugs; 3) hersenactiviteit die geassocieerd is met foutenverwerking, een indicator van cognitieve controle.

Samenvatting onderzoeksbevindingen

Dagelijkse metingen van expliciete en impliciete druggerelateerde cognities tijdens behandeling: voorspellers van verleiding en terugval

De hierboven beschreven studies die aandachtsbias als voorspeller van terugval hebben bestudeerd, hebben dat eenmalig in een laboratorium gemeten. De middelenafhankelijke personen moesten dus buiten hun eigen omgeving een aandachtsbias-taak uitvoeren, wat slechts een momentopname oplevert. Aandachtsbias kan – net als craving – veranderen over de tijd en is context-afhankelijk. Het is daarom erg interessant en nuttig om dit herhaaldelijk op verschillende momenten te meten. Ecological momentary assessment (EMA) is een methode waarbij in de eigen omgeving van een persoon gemeten kan worden (vandaar "ecological") op elk moment gedurende de dag (vandaar "momentary"). "Assessment" staat voor de test die herhaaldelijk, gedurende de dag in de omgeving van een persoon afgenomen kan worden. Deze tests kunnen geprogrammeerd worden op kleine handcomputers, ook wel PDA's genoemd, zodat de proefpersoon het bij zich kan dragen.

Verslavingsstudies hebben EMA gebruikt om zelf-gerapporteerde voorspellers van druggebruik te meten, zoals craving (Epstein et al., 2009; Preston et al., 2009). Er zijn echter geen eerdere EMA studies die bij klinische populaties reactietijdtaken hebben gebruikt om impliciete cognitieve processen te meten. Hoofdstuk 2 en 3 van dit proefschrift beschrijven de eerste EMA studie dat zowel expliciete als impliciete druggerelateerde cognities heeft bestudeerd op een dagelijks niveau in heroïne en cocaïne afhankelijke patiënten tijdens hun eerste week van een klinische opname op de detoxificatie afdeling van een behandelcentrum.

Het doel van **hoofdstuk 2** was om te onderzoeken of herhaaldelijke metingen van impliciete cognities (aandachtsbias en impliciete geheugenassociaties met drugs) en expliciete cognities (zelf-gerapporteerde craving en houding tegenover drugs) geassocieerd waren met terugval in druggebruik tijdens de eerste week van detoxificatie behandeling (EMA studieweek; vroege terugval) en tijdens de rest van de detoxificatie

behandeling (2-3 weken na de EMA studieweek; late terugval). Deelnemers maakten een test op 4 willekeurige momenten per dag en op momenten dat ze in de verleiding waren om drugs te gebruiken (d.w.z. een acute stijging in de drang om heroïne of cocaïne te gebruiken of wanneer een persoon voelt dat hij/zij op het punt staat om heroïne of cocaïne te gaan gebruiken). De resultaten lieten zien dat patiënten die vroeg teruggevallen waren (tijdens de EMA studieweek) – in vergelijking met patiënten die niet teruggevallen waren – hogere niveaus van zelf-gerapporteerde craving hadden en een meer positieve houding tegenover drugs rapporteerden. De resultaten van de impliciete metingen waren als volgt: vroege terugvallers toonden verhoogde niveaus van aandachtsbias en meer positieve impliciete associaties met drugs dan niet-terugvallers, maar alleen tijdens momenten van verleiding. Bij late terugval werd er alleen een verband gevonden met zelf-gerapporteerde houding tegenover drugs, maar niet met craving en de impliciete cognities. De meest interessante bevinding was dat aandachtsbias verhoogd was in de verleidingsmomenten die het dichts tegen de terugval-dag lagen. Met andere woorden, wanneer een patiënt in behandeling verhoogde aandachtsbias ervaart tijdens een verleidingsmoment, dan zou hij/zij het risico kunnen lopen om op de korte termijn terug te vallen.

De bevindingen van hoofdstuk 2 duiden aan dat momenten van verleiding tijdens de behandeling problematisch zijn. Omdat verleiding overeenkomsten heeft met terugval hebben we bekeken hoe het verloop van verleidingsmomenten eruit ziet tijdens detoxificatie behandeling en wat eraan vooraf gaat.

In **hoofdstuk 3** is er gekeken naar het verschil tussen de stemming en cognities van patiënten tijdens willekeurige momenten en tijdens verleidingsmomenten. Ondanks dat het aantal gerapporteerde verleidingsmomenten afnam tijdens de EMA studieweek (wellicht door herstel van ontwenning, of studievermoeidheid) lieten de data zien dat patiënten hogere niveaus van negatieve emoties rapporteerden tijdens een moment van verleiding dan tijdens willekeurige momenten. Dit suggereert dat verleidingsmomenten als problematisch ervaren worden door drugafhankelijke patiënten tijdens hun eerste week van behandeling. Verder liet de data zien dat craving, een positieve houding tegenover drugs en aandachtsbias (maar niet impliciete associaties) hoger waren tijdens verleidingsmomenten dan tijdens willekeurige momenten. Ook hier was de meest interessante bevinding dat aandachtsbias verhoogd was in de willekeurige momenten die een uur voor een verleidingsmoment plaatsvonden. Dit suggereert dat aandachtsbias een verleidingsmoment zou kunnen aankondigen.

Over het algemeen geven de resultaten van hoofdstuk 2 en 3 meer gedetailleerde informatie over de samenhang tussen aandachtsbias, verleiding en terugval in druggebruik dan de eerder besproken studies die zijn uitgevoerd in een laboratorium. De huidige bevindingen suggereren dat er een belangrijke rol is van aandachtsbias in de timing van verleiding en

terugval tijdens detoxificatie behandeling. Bovendien bleven de resultaten overeind zelfs als er gecontroleerd werd voor zelf-gerapporteerde craving en houding tegenover drugs.

Neurofysiologische metingen van aandachtsbias en foutenverwerking: associaties met cocaïnegebruik na behandeling

In **hoofdstuk 4** is er met behulp van fMRI onderzocht of aandachtsbias-gerelateerde activiteit in de hersenen ook een voorspeller is van terugval in druggebruik. Dit onderzoek werd uitgevoerd bij cocaïne afhankelijke patiënten tijdens hun eerste week van de detoxificatie behandeling. Eerdere fMRI studies hebben aangetoond dat de volgende hersengebieden een rol spelen bij aandachtsbias voor middelen-gerelateerde stimuli: de anterior cingulate cortex (ACC), dorsolaterale prefrontale cortex (DLPFC), insula, nucleus accumbens en amygdala (Hester en Garavan, 2009; Janes et al., 2010a, 2010b; Luijten et al., 2011a, 2012; Nestor et al., 2011; Vollstädt-Klein et al., 2012). In hoofdstuk 4 is gekeken welke van deze hersengebieden tijdens het uitvoeren van een drugversie van de Stroop taak (zelfde als in hoofdstuk 2 en 3) samenhangen met cocaïnegebruik 3 maanden na de behandeling. De resultaten demonstreerden dat een hogere aandachtsbias-gerelateerde activiteit in de rechter dACC (r-dACC) en zelf-gerapporteerde craving in de week voor de behandeling, voorspellend waren voor cocaïnegebruik 3 maanden na behandeling. Aandachtsbias-gerelateerde r-dACC activiteit bleef een sterke voorspeller van terugval, zelfs nadat er gecontroleerd werd voor zelf-gerapporteerde craving. Omdat de dACC betrokken is bij het detecteren van opvallende informatie en bij het monitoren van conflicterende informatie wordt er gedacht dat de activatie in de dACC hier aangeeft dat er een verhoogd conflict is tijdens de taakuitvoering wanneer er afleidende informatie aanwezig is die van emotioneel belang is, in dit geval cocaïne-gerelateerde stimuli. Met andere woorden, wanneer een drugverslaafde de kleur moet benoemen van een cocaïne-gerelateerd woord zal hij/zij meer hersenactiviteit nodig hebben om zich te richten op de taak dan bij een neutraal woord, omdat hij/zij afgeleid wordt door de inhoud van het drugwoord. De huidige resultaten suggereren dat patiënten die gevoelig zijn voor terugval een verminderd vermogen hebben om hun druggerelateerde cognities te onderdrukken (aangestuurd door de dACC) en daardoor meer moeite hebben met het controleren van hun druggebruik.

De resultaten van hoofdstuk 4 lieten verder zien dat aandachtbias op het gedragsniveau geen voorspeller was van terugval in cocaïnegebruik 3 maanden na de detoxificatie behandeling. Dit is opvallend aangezien de resultaten van hoofdstuk 2 wel aantoonden dat gedragsmatige aandachtsbias een voorspeller is. Een mogelijke verklaring is wellicht dat de relatie tussen aandachtsbias op gedragsniveau en terugval verminderd of verdwijnt als er een grote vertraging zit tussen de meting van aandachtsbias en het

moment van terugval. Het zou kunnen dat hersenactiviteit een meer robuuste meting is van aandachtbias en daarom minder beïnvloed raakt door grote vertragingen tussen de metingen. Deze interpretatie wordt verder ondersteund door de bevinding van hoofdstuk 2 dat aandachtsbias op gedragsniveau wel samenhing met terugval op de korte termijn (eerste week van detoxificatie behandeling) maar niet met terugval op de lange termijn (laatste weken van detoxificatie behandeling).

Zoals eerder genoemd speelt, naast aandachtsbias, cognitieve controle ook een rol bij verslaving. Veel studies hebben aangetoond dat cognitieve controle verminderd is bij drugafhankelijke patiënten en dat dit zijn basis heeft in prefrontale gebieden van het brein (Goldstein en Volkow, 2011). Er zijn heel weinig studies die hebben onderzocht of de verminderde capaciteit van hersengebieden die betrokken zijn bij cognitieve controle voorspellend is voor terugval in druggebruik (Brewer et al., 2008; Paulus et al., 2005).

In **hoofdstuk 5** is onderzocht of foutenverwerking – een indicator van cognitieve controle – voorspellend is voor cocaïnegebruik 3 maanden na detoxificatie behandeling. Om foutenverwerking in de hersenen te meten werden *event-related-potentials* (ERP's) opgenomen met behulp van EEG tijdens het uitvoeren van een snelle reactietijdtaak, de Eriksen flanker taak. ERP's geven de hersenactiviteit weer die te relateren is aan een specifieke gebeurtenis tijdens het uitvoeren van een cognitieve taak. Om te onderzoeken hoe het brein reageert op fouten kijken we specifiek naar die delen in het ERP-signaal waar een fout gemaakt is tijdens de taak. Er verschijnt dan een piek in het signaal dat de *error-related negativity* (ERN) wordt genoemd. De hoogte van de piek geeft aan hoe sterk de ERN is. Hoe sterker de ERN, hoe beter de foutenverwerking in de hersenen. De ERN vindt plaats 25 tot 100 milliseconden na het maken van een fout en omdat dat zo snel is wordt er gesuggereerd dat het de automatische verwerking van een fout weergeeft. De resultaten van hoofdstuk 5 lieten zien dat cocaïne afhankelijke patiënten een lagere ERN hadden dan niet-middelenafhankelijke controles. Nog belangrijker, de resultaten onthulden dat de mate van de ERN voorspellend was voor terugval in cocaïnegebruik, namelijk: patiënten met een lagere ERN gebruikten meer cocaïne in de 3 maanden na de detoxificatie behandeling dan patiënten die een hogere ERN hadden. Met andere woorden, patiënten met een slechtere foutenverwerking in de hersenen zijn vatbaarder voor terugval in cocaïnegebruik. Ook hier gold dat de resultaten overeind bleven zelfs als er gecontroleerd werd voor craving en de ernst van de verslaving, hetgeen suggereert dat de ERN unieke informatie biedt in het identificeren van patiënten die vatbaar zijn voor terugval, al in de eerste week van behandeling.

Alle hoofdstukken hebben laten zien dat neurocognitieve metingen adequate voorspellers zijn van terugval in druggebruik, bovenop zelf-gerapporteerde metingen zoals craving. Hoewel craving een centrale rol speelt in verslavingstheorieën laat het huidige onderzoek

zien dat ook impliciete cognitieve processen zeer belangrijk zijn in verslaving en terugval. Het model van Franken (2003) illustreert dat aandachtsbias en zelf-gerapporteerde craving een versterkende relatie hebben die kan leiden tot druggebruik en terugval. Hoewel onderzoek heeft aangetoond dat er inderdaad een relatie bestaat tussen aandachtsbias en craving (Field et al., 2009) hebben wij dit niet kunnen bevestigen met de huidige resultaten. Gezien onze resultaten lijkt het erop dat aandachtsbias onafhankelijk van craving voorspellend is voor terugval. We hebben wel een verband gevonden tussen aandachtsbias en verleiding. Verleiding is sterk gerelateerd aan craving, maar de relatie met aandachtsbias heeft wellicht meer te maken met een ander onderdeel van verleiding, namelijk het uitvoeren van een actie (op het punt staan om te gaan gebruiken) dan met een gevoel van hunkering naar drugs. Tot slot biedt aandachtsbias meer gedetailleerde informatie over de timing van verleidingsmomenten en terugval dan andere metingen.

Klinische toepassingen

Het huidige onderzoek heeft aangetoond dat het mogelijk is om al in de eerste week van de detoxificatie behandeling met behulp van neurocognitieve methoden te identificeren wie het risico loopt om terug te vallen in druggebruik. Hoewel neuroimaging technieken zoals fMRI ons zeer veel informatie opleveren betreffende de relatie tussen hersenfuncties en klinische uitkomsten is het niet realiseerbaar om een MRI-scanner te implementeren in een behandelsetting. Wel kan de informatie van nut zijn voor onderzoek naar farmacologische en neurocognitieve interventies zoals dopamine-manipulatie en aandachtstraining om aandachtsbias te reduceren. Een EEG-apparaat zou echter wel geïmplementeerd kunnen worden in de praktijk aangezien het niet-invasief, minder duur en toegankelijker is dan fMRI. De ERN zou gebruikt kunnen worden om te "screenen" wie vatbaar is voor terugval. De meest toegankelijke techniek om te implementeren in de praktijk is het gebruik van PDA's. PDA's zijn in vergelijking met EEG nog goedkoper en zeer eenvoudig in gebruik. Ze zouden gebruikt kunnen worden om de toeleiding tot verleiding en/of terugval aan te kondigen. Een andere mogelijkheid zou kunnen zijn om een interventie (bijv. aandachtstraining) aan te bieden op de PDA wanneer een patiënt aangeeft dat hij/zij een verleidingsmoment ervaart of om diegene dan meer therapie-tijd aan te bieden.

Beperkingen van het huidige onderzoek en suggesties voor toekomstig onderzoek

Er moet rekening gehouden worden met een aantal beperkingen van het onderzoek bij het interpreteren van de resultaten van dit proefschrift. Ten eerste weten we niet zeker of de neurocognitieve dysfuncties in drugafhankelijke personen direct terugval

veroorzaken of dat er mogelijk nog een derde factor verantwoordelijk is voor dit verband, bijvoorbeeld comorbide psychiatrische stoornissen. Verder beantwoordt dit proefschrift niet of drugafhankelijke personen deze dysfuncties al voor het ontstaan van de verslaving hebben of dat de dysfuncties het gevolg zijn van overmatig druggebruik. Er is wel onderzoek dat heeft laten zien dat de ERN al gereduceerd is in de kinderen van verslaafde ouders, hetgeen suggereert dat een verminderd vermogen in de hersenen om fouten te verwerken wellicht erfelijk is en al voor het ontstaan van een verslaving aanwezig is (Euser et al., 2012). Ten tweede zijn er in dit proefschrift verschillende metingen van terugval gebruikt wat het lastig maakt om de resultaten te vergelijken. In hoofdstuk 2 is er bijvoorbeeld gekeken naar terugval in de eerste week van detoxificatie behandeling en in de 3 weken erna. In hoofdstuk 4 en 5 is terugval alleen op de lange termijn onderzocht, namelijk 3 maanden na de start van behandeling. We weten daarom niet of de neurofysiologische maten van hoofdstuk 4 en 5 ook voorspellers van terugval op de korte termijn zijn. Echter, de EMA methode is een betere methode om uitkomsten op de korte termijn te onderzoeken omdat hiermee cognitieve processen gemeten kunnen worden die afhankelijk zijn van de (wisselende) toestand waarin een persoon verkeerd (bijvoorbeeld aandachtsbias en craving). Neurofysiologische metingen daarentegen zijn wellicht een betere methode om uitkomsten op de lange termijn te meten die meer met de karakteristieken van een persoon te maken hebben en dus minder of niet wisselend van aard zijn (bijvoorbeeld het vermogen om fouten te verwerken). Een derde beperking is dat terugval in hoofdstuk 2 gebaseerd is op zelf-rapportage van de patiënt en dus niet geverifieerd is met een urine controle (wat wel gedaan is in hoofdstuk 4 en 5). Verder is in hoofdstuk 4 en 5 alleen craving in de week voor de behandeling gemeten en niet acute craving, zoals in hoofdstuk 2. Tot slot is er in dit proefschrift geen onderzoek gedaan naar het vermogen om gedrag te inhiberen, wat ook een belangrijk onderdeel van cognitieve controle is.

Toekomstig onderzoek zal deze beperkingen in acht moeten nemen en proberen om het anders aan te pakken zoals grootschalig longitudinaal onderzoek, d.w.z. dat je deelnemers op meerdere momenten gedurende een lange periode test om zo uitspraken te kunnen doen over oorzaak en gevolg. Ook is het raadzaam om in terugvalonderzoek meerdere terugvalmetingen te gebruiken, zoals de duur van abstinentie voordat iemand terugvalt, wat bij voorkeur met wekelijkse of zelfs dagelijkse urine controles geverifieerd wordt. Tot slot is het van zowel theoretisch als klinisch belang dat studies die onderzoek doen naar cognitieve en neurobiologische processen bij verslaving rekening houden met de invloed van demografische kenmerken, de ernst van de verslaving en craving, om zodoende een betere uitspraak te kunnen doen over de toegevoegde waarde van neurocognitieve methoden (die relatief "nieuw" zijn). Het zou ideaal zijn als terugvalonderzoek multifactorieel wordt. Dat houdt in dat het risico op terugval wordt onderzocht op meerdere niveaus, zoals (socio)demografisch, psychologisch, fysiologisch

en cognitief. Op deze manier kunnen we een totaalbeeld krijgen van de risicofactoren van terugval. Om dit te bereiken is het echter noodzakelijk dat het onderzoek uitgevoerd wordt met een zeer groot aantal deelnemers.

Hoofdconclusie

Dit proefschrift heeft belangrijke informatie opgeleverd over neurocognitieve mechanismen van drugafhankelijkheid en de relatie met het behandelproces en terugval in druggebruik. Het heeft aan het licht gebracht dat neurocognitieve processen informatie opleveren over vatbaarheid voor terugval bovenop informatie die vergaard wordt door zelf-rapportage, zoals craving. Neurocognitieve metingen kunnen mogelijk al vroeg in de behandeling helpen met de identificatie van patiënten die het risico lopen om terug te vallen en wellicht, met behulp van PDA's, wannneer zij dat risico lopen.

Dankwoord

Het is eindelijk zover, mijn proefschrift is af! Ik had het never nooit zonder de hulp van mijn collega's, familie en vrienden kunnen doen. Hieronder wil ik graag mijn dank uitspreken aan jullie allen.

Allereerst mijn promotor, professor Franken, beste Ingmar. Al vanaf de eerste keer dat ik bij jou solliciteerde wist je mij al goed te begeleiden. Je wees me weliswaar af, maar hebt vervolgens uitgebreid met me gesproken over wat ik moest doen om meer onderzoekservaring op te doen zodat ik uiteindelijk AIO kon worden. Al gauw daarna bood je mij een kans om als onderzoeksassistent aan de slag te gaan, dat een jaar later vervolgd werd met een 4-jarig AIO project. Wat was het een onstuimig project. Maar je was er altijd om me een hart onder de riem te steken. Wanneer het nodig was kon je me ook terecht wijzen, zoals wanneer ik toch echt iets te vaak achter elkaar op reis ging! Maar beste Ingmar, het is gelukkig allemaal goed gekomen. Voor je ligt het resultaat, dit proefschrift. Best mooi, toch? Ingmar jouw talent, kracht en intrinsieke motivatie zijn erg inspirerend. Ik wil je hartelijk bedanken dat je mij hebt opgeleid tot wetenschappelijk onderzoeker. Ik had geen betere leermeester kunnen wensen.

Graag wil ik ook de rest van mijn promotiecommissie bedanken: prof. Jan van Strien, prof. Hans Hovens, prof. Wim van den Brink, prof. Anja Huizink, dr. Andrew Waters, dr. Birgit Mayer en dr. Ben van de Wetering. Ik vind het een eer dat ik met jullie van gedachten mag wisselen over mijn proefschrift. Ben, bedankt voor jouw bijdrage aan de totstandkoming van dit proefschrift.

Andrew, I would like to thank you for all your hard work on the EMA study. You are a talented researcher and I admire your creativity. I appreciate that you are willing to travel to The Netherlands for my PhD defense.

Beste Jan en Liselotte, ik wil jullie graag bedanken voor jullie begeleiding tijdens mijn studententijd op de EUR. Ik heb zeer veel van jullie geleerd en door de onderzoeksstages die ik bij jullie gelopen heb wist ik zeker dat ik wetenschappelijk onderzoeker wilde worden. Ook wil ik jullie bedanken voor alle gezelligheid tijdens uitjes. Liselotte, we moeten maar weer eens een keer een Ladies night houden! Jan, ik hoop dat we dit jaar of volgend jaar weer kunnen swingen onder begeleiding van de SPR band!

Mijn collega's van het Instituut voor Psychologie wil ik uiteraard ook erg bedanken voor de prettige samenwerking. Om te beginnen alle C3-ers en ex-C3-ers: Ali, An, Angela, Anita, Anja, Arjan, Birgit, Colin, Danielle, Elke, Eric, Freddy, Guus, Hans, Ilse, Ivo, Jorg, Katrien, Leonie, Maartje, Marianne, Marien, Marjolein, Marlies, Peter, Renske, Sabine, Susan, Suzanne en Tim, bedankt voor alle leerzame overleggen en praatjes, alle hulp en feedback en voor alle gezelligheid!

Mijn chickies op kamer T12-59 verdienen een extra woord van dank. Anja en Maria, bijna 5 jaar lang hebben wij zij aan zij onze AIO-projecten doorlopen. Lief, leed, alles hebben we gedeeld. Wat mag ik mijzelf gelukkig prijzen met zulke lieve kamergenootjes. Het zit er straks dan toch echt op, we zijn niet langer kamergenootjes. T12-59 zal nimmer meer als een sauna aanvoelen in de winter! Gelukkig zien wij elkaar nog regelmatig, dat moeten we er echt in houden! En ik ben erg blij en trots dat jullie straks achter mij staan als mijn paranimfen. Maria, jouw kracht inspireert mij. Anja, jouw talent is bewonderenswaardig. Jullie zijn the best!

Maartje en Marianne, ook jullie wil ik enorm bedanken voor alle inspiratie en gezelligheid. Jullie zijn zeer getalenteerde onderzoekers en ik voel me vereerd dat ik deel uit mocht maken van de onderzoeksgroep samen met jullie. Maartje, bedankt voor al je mentale en praktische steun tijdens het testen. Jij hebt van erg dichtbij meegemaakt hoe het was en ik had er serieus niet doorheen kunnen komen zonder jouw steun. Je bent een schat! Enne... eigenlijk was het best een leuke studie, toch?

Marianne en Anja, onze reisjes verdienen ook zeker een plaats in dit dankwoord. Wat waren ze fantastisch! Eerst een road-trip door West-USA en daarna een rondreis door delen van Noord-Amerika met aansluitend IJsland. Samen met jullie heb ik prachtige landschappen, onuitstaanbare hittes, kamers met enge beertjes, zoenende cowboys, gierende geisers, babywalvisruggen, hertenkonten en nog veel meer gekke maar vooral mooie dingen gezien en meegemaakt. Ik hoop dat we in de toekomst nog een keer de gelegenheid krijgen om samen een mooie reis te maken. Meiden, bedankt voor jullie liefde en vriendschap.

"Mama" Ilse, Mini-Reshmi is eindelijk klaar met haar proefschrift! Bedankt voor alle peptalks en droge humor-momentjes. Verder wil ik Bruno, Lisa, Inge, Kiki, Noortje en Karin ook graag bedanken voor alle hulp en gezelligheid.

EBL-ers Gerrit-Jan, Christiaan, Marcel, Freek, Jeffrey, Richard, dank jullie wel voor alle hulp in het lab. Ik zal nooit vergeten dat niemand mij durfde te vertellen dat er iets mis was gegaan met de eyetracking data. Dat laat zien hoe begaan jullie met mij waren. Thanks!

Dames van het secretariaat: Mirella, Hanny, Angelique, Iris. Zonder jullie zou Psychologie echt nergens zijn. Jullie verrichten zwaar werk en ik heb daar bewondering voor. Mirella, wil je Hans namens mij bedanken? Zijn bijdrage aan het onderzoek is zeer waardevol geweest.

Ik wil ook graag alle leden van de fMRI (nu AMBER) meeting op het Erasmus MC bedanken voor alle leerzame en interessante meetings. Marion, bedankt voor je bijdrage aan dit proefschrift. Rebecca en Carolina, bedankt voor alle "troubleshooting" tijdens het scannen. Dat geldt uiteraard ook voor Gavin.

Lisa, Jeffrey, Radha, Yavuz, Alexandra en Biling, bedankt voor jullie assistentie (en vooral flexibiliteit!) bij de uitvoering van het onderzoek. Mede dankzij jullie is het toch nog gelukt om alle data voor het einde van mijn promotietraject te verzamelen. Mijn dank is groot!

Graag wil ik ook de medewerkers van de detox afdeling bij Bouman GGZ bedanken. Jullie hebben een zeer grote bijdrage geleverd aan de uitvoering van het onderzoek en sommigen van jullie zijn zelfs de scanner in gegaan als deelnemers van de controlegroep. Jullie inzet waardeer ik enorm maar bovenal waardeer ik jullie warme onthaal elke keer als ik weer op de detox afdeling aan kwam. Uiteraard wil ik ook de patiënten die mee hebben gedaan aan het onderzoek bedanken. Het was een zeer bijzondere ervaring om samen met jullie dit onderzoek in te vullen en ik heb er veel van geleerd. Jullie motivatie en interesse voor dit onderzoek heeft mij geïnspireerd om het werk hierin voort te zetten. Samen kunnen we eruit komen. Dank jullie wel.

Ook mijn nieuwe collega's van de Academische Werkplaats wil ik graag noemen. Theo, Arne en Floor, ik ben zeer enthousiast om de komende jaren samen met jullie aan dit grootschalige onderzoek te werken. Theo en Arne, bedankt dat jullie mij hebben aangenomen in team RAFT (gelukkig maar, anders was het team AFT of FAT). Ik wil jullie ook bedanken voor alle begrip en ruimte die jullie mij hebben gegund voor het afronden van dit proefschrift. Floor, wat ben ik blij met jou als kersverse collega. Je bent lief, gezellig en zeer punctueel! Het feit dat jouw lunch-dip pas verschijnt wanneer die van mij afgelopen is geeft aan hoe goed wij op elkaar aansluiten. Ik kan niet wachten totdat wij als *echte* post-docs aan de slag kunnen met het 5-jaren plan. Collega's en deelnemers van De Nieuwe Kans: bedankt voor jullie interesse in hersenonderzoek!

Mijn collega's zijn zeer waardevol geweest in de totstandkoming van dit proefschrift, maar ik had het uiteraard niet zonder mijn familie en vrienden kunnen doen. Daarom wil ik nu graag de ruimte nemen om jullie uitgebreid te bedanken.

Ik begin met mijn vriendinnen. Lieve Thirsa en Gillian, jullie hebben altijd naast me gestaan tijdens mijn onderzoeksproject. Gilly, jij hebt zelfs letterlijk naast me gezeten tijdens het scannen! Thirrie, je staat altijd voor me klaar, no matter what. Jullie liefde heeft mij sterk gehouden, ik ben jullie zeer dankbaar daarvoor. Sam, jij zorgt er altijd voor dat ik mijn nodige ontspanning krijg. Bedankt voor alle gezellige etentjes, stedentripjes en party-hardy avonden! Maar bovenal bedankt voor jouw interesse, medeleven en begrip. Hetzelfde geldt voor Sanne en Joanne, thanks lieve meiden! Sanne, ook jij hebt letterlijk bijgedragen aan mijn onderzoek. Je was zelfs bereid om twee keer de scanner in te gaan voor mij, erg lief van je! Ook bedankt voor je hulp en bemoedigende woorden tijdens het schrijven. Elaine, jij hebt ook twee keer de scanner getrotseerd voor mij, many thanks! Tot slot wil ik de rest van mijn middelbare schoolvriendinnen ook bedanken, in het bijzonder

Rezvan, want zonder jou had ik nooit zo'n fantastische nieuwe baan gevonden waarin ik mijn werk als onderzoeker kan voortzetten.

Ook Sidney's familie ben ik erg dankbaar. Frank en Linda, jullie steun en liefde betekent veel voor mij. Duane, Miran en kleine tjing-pang-lao Manoah, ik heb eindelijk weer tijd voor jullie! We gaan alle schade inhalen. De rest van de familie, tante Cynthia en de Metselaars, wil ik ook bedanken. In het bijzonder wil ik Ali en Marlon bedanken voor hun deelname aan mijn onderzoek (als controle proefpersonen!). Dat was me wat hè? Maar zie hier het resultaat. Ik hoop dat jullie het dat waard vonden, ik in ieder geval wel!

Familie Marhe en familie Benie, bedankt voor al jullie trots! Nana en adjie, jullie hebben mij altijd geleerd om door te zetten, zo zijn jullie zelf ook. Ik ben erg blij dat ik jullie kleindochter ben en hoop dat ik jullie trots heb gemaakt. Rack en Kim, thanks voor alle steun die jullie mij bieden en uiteraard ook bedankt voor de gezellige sushi-avonden! Oom Shaam, Tante Bhartie, Bharat, Viresh, Priya, Ravi, Bhartie, Aman, Amisha, Tante Nal, Devika, Oom Raj en tante Urmila, bedankt dat jullie zo dicht aan mijn zijde hebben gestaan! Tante Bhartie, ook u hebt deelgenomen aan mijn onderzoek als controleproefpersoon. Bedankt voor uw interesse, vertrouwen en steun. Het betekent heel veel voor mij. Familie Marhe is echt teveel om op te noemen, dus dat doe ik maar onder 1 noemer. Thanks!

Lieve mama, papa en Pol, ik weet eigenlijk niet waar ik moet beginnen met het uitspreken van mijn dank voor jullie. Mijn dank is zo groot dat ik er bijna geen woorden voor heb. Mama en papa, zonder jullie had ik dit ECHT niet gekund. Jullie staan altijd voor mij klaar en hebben mij altijd in mijn waarde gelaten (althans, na de puberteit haha). Bedankt voor jullie onvoorwaardelijke vertrouwen in mij. Dat is voor mij essentieel geweest. Mama, bedankt voor alle last-minute correcties aan mijn proefschrift. Papa, thanks voor alle bemoedigende woorden zoals "kom op, doorzetten Loes, je kan het!". Dat heeft echt geholpen! Pol, bedankt dat je altijd naar mijn gezondheid vraagt en erop let dat ik niet teveel van mezelf verg. Alledrie bedankt voor jullie steun en goede zorg.

Last but not least, degene die al bijna 5 jaar aan mijn zijde staat en mijn promotietraject dus van zeer dichtbij heeft meegemaakt. Lieve SiD, bedankt voor je geduld en ongeduld met mij. Elke keer als ik "midden in een zin" zat liet je me ook lekker alleen met mijn zin (soms met enige irritatie, maar dat mag). En als er weer eens een deadline op springen stond kon je mij ook goed pushen. Ik ben je ook eeuwig dankbaar voor al het werk dat je verricht hebt om dit proefschrift mooi te maken, terwijl je ook je afstudeerscriptie moest schrijven. Het is zwaar geweest, maar straks kunnen we onze boeken en computers eindelijk van de eettafel halen en… eten! Nog even doorbijten en dan kunnen we echt gaan genieten: Budapest, Suriname/Indonesië, LowLands, of gewoon lekker ouderwets bankhangen.
Ik verheug me erop!

Curriculum Vitae

Reshmi Marhe was born in Paramaribo, Suriname, on March 23rd, 1984. In 1988 she moved to The Netherlands with her family. After completing secondary education (VWO) at the Comenius College in Capelle a/d IJssel (near Rotterdam), she started studying Psychology at the Erasmus University Rotterdam. In 2006, she obtained her Bachelor's degree in Biological and Cognitive Psychology and in 2007 she received her Master's degree in Biological and Cognitive Psychology. From September 2007 to August 2008 she worked as a research assistant at the Institute of Psychology, Erasmus University Rotterdam where she started a project on the assessment of implicit and explicit drug-related cognitions in an ecological momentary assessment setting. In September 2008, she was able to continue and extend this research in a PhD program of which the results are described in this thesis. The studies in this project focused on neurocognitive predictors of relapse in heroin and cocaine use and were supervised by Professor Ingmar H. A. Franken. All studies described in this thesis were conducted in close collaboration with addiction treatment center Bouman GGZ, Rotterdam. During her PhD, she participated in the education program of the Dutch-Flemish post-graduate school "Experimental Psychopathology". She was also engaged in teaching several (clinical) psychology bachelor and master courses, she supervised research projects of bachelor and master students, and (guest) lectured on clinical subjects. Furthermore, she reviewed empirical articles for international journals. In October 2012, she started working at the Department of Child and Adolescent Psychiatry, VU University Medical Center, Duivendrecht as a PostDoc and project coordinator of the *Academische Werkplaats bij De Nieuwe Kans* in Rotterdam, a rehabilitation/ forensic program for young adults.

Publications

International peer-reviewed papers

Marhe, R., Waters, A. J., Van de Wetering, B. J. M., & Franken, I. H. A. (2013) Implicit and explicit drug-related cognitions during detoxification treatment are associated with drug relapse: An Ecological Momentary Assessment study. *Journal of Consulting and Clinical Psychology, 81*(1), 1-12.

Waters, A. J., Marhe, R., & Franken, I. H. A. (2012). Attentional bias to drug cues is elevated before and during temptations to use heroin and cocaine. *Psychopharmacology, 219*(3), 909-921.

Marhe, R., Luijten, M., Van de Wetering, B. J. M., Smits, M., & Franken, I. H. A. (2013). Individual differences in anterior cingulate activation associated with attentional bias predicts cocaine use after treatment. *Neuropsychopharmacology,* published online ahead of print Jan 30. doi: 10.1038/npp.2013.7.

Marhe, R., Van de Wetering, B. J. M., & Franken, I. H. A. (2013). Error-related brain activity predicts cocaine use after treatment at 3-month follow-up. *Biological Psychiatry,* published online ahead of print Jan 29. doi: 10.1016/j.biopsych.2012.12.016.

Manuscript in preparation

Field, M, Marhe, R., & Franken, I. H. A. Introduction to the psychological construct and clinical relevance of attentional bias. *Invited review for CNS Spectrums*.

Invited presentations

Marhe, R., Franken, I. H. A., & Waters, A. J. (2008). Implicit and explicit drug-related cognitions in an ecological momentary assessment setting. *European Neuropsychopharmacology, 8*(4), S538, presented in Barcelona, Spain.

Marhe, R., Franken, I. H. A., & Waters, A. J. (2009). Implicit and explicit drug-related cognitions in an ecological momentary assessment setting. *Forum Alcohol en Drugs Onderzoek; FADO*, Utrecht.

Marhe, R., Franken, I. H. A., & Waters, A. J. (2010). Associations between implicit and explicit drug-related cognitions and relapse: An ecological momentary assessment study. *NIDA International Forum: Drug Abuse Research, Policy, and the Public Good & the Annual Meeting of CPDD*, Scottsdale, Arizona, US.

Marhe, R., Waters, A. J., Van de Wetering, B. J. M., & Franken, I. H. A. (2010). Implicit and explicit drug-related cognitions predict relapse in heroin and cocaine: An ecological momentary assessment study. *Forum Alcohol en Drugs Onderzoek; FADO*, Utrecht.

Marhe, R., Van de Wetering, B. J. M., & Franken, I. H. A. (2011). Reduced error processing in cocaine dependent patients in the first week of detoxification treatment: An ERP study. *Forum Alcohol en Drugs Onderzoek; FADO*, Utrecht.

Marhe, R., Van de Wetering, B. J. M., & Franken, I. H. A. (2011). Reduced error processing in cocaine dependent patients in the first week of detoxification treatment: An ERP study. *Society for Psychophysiological Research (SPR), 51st Annual meeting*, Boston, Massachusetts, US.

Marhe, R., Van de Wetering, B. J. M., & Franken, I. H. A. (2012). Error-related brain activity predicts cocaine use after treatment at 3-month follow-up. *Donders Discussions*, Nijmegen.