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## Is impulsivity a treatable risk factor of cocaine addiction?

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2018

### **document version**

Publisher's PDF, also known as Version of record

[Link to publication in VU Research Portal](#)

### **citation for published version (APA)**

Broos-Boersma, N. (2018). *Is impulsivity a treatable risk factor of cocaine addiction?* [, Vrije Universiteit Amsterdam].

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# SUMMARY

People suffering from cocaine dependence have an excessive interest in the acute rewarding effects of the drug despite the long term harmful personal as well as social consequences. This indicates poor decision making skills and this might lead to the high and chronic risk to relapse. Therefore, there is a great interest in the relationship between cocaine addiction and decision making skills, such as impulsivity. Previous research identified that patients with cocaine dependence are on average more impulsive than healthy controls. Notably, until now there is no registered (pharmacological) treatment to prevent relapse to cocaine addiction. On the other hand, there are clinically approved drugs that alleviate impulsive behavior. Therefore, it is of great interest to investigate whether there is a causal relation between impulsive behavior and the sensitivity to relapse. Causality could imply the opportunity to treat the risk to relapse via a reduction in impulsive behavior. Therefore, the leading question of my thesis is: Is impulsivity a treatable risk factor of cocaine addiction?

In **chapter 2**, I showed that impulsivity is not a unitary construct, but can be viewed as an umbrella term including a range of separate behavioral phenomena. In the current thesis, I focus on impulsive decision making and impulsive action. Impulsive decision making refers to the extreme preference for the short term benefits despite long term drawbacks. Impulsive action refers to the inability to await the appropriate time and situation to act. Using a cross-species translational and within-subjects approach, I showed that impulsive decision making and impulsive action were unrelated both in humans and in rats. Additionally, in humans a self-report measure of impulsivity was not related to any of the behavioral measures of impulsivity. In rats, the pharmacological effects of amphetamine and atomoxetine (ATO) on the two impulsivity paradigms were not related. Based on these observations the role of impulsive decision making and impulsive action in cocaine intake and cocaine seeking during abstinence was investigated in separate experiments. Additionally, these results stress the importance of clearly defining the separate aspects of impulsive behavior in psychiatric disorders.

Cocaine dependent patients display relatively high levels of impulsive decision making. Interestingly, the level of impulsive decision making does not differ between current cocaine users and users that are abstinent for one month. Additionally, although several cognitive deficits observed in cocaine users deteriorate by increasing cocaine consumption and improve by reducing consumption, this is not the case for impulsive decision making. These results seem to indicate that impulsive decision making is a pre-existing vulnerability factor, which is not affected by cocaine consumption. However, it is also possible that cocaine consumption has long-lasting effects on impulsive decision making that do not recover with abstinence. My

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Summary

experiments described in **chapter 3** suggest the former explanation: Impulsive decision making appeared to be a highly stable trait since it was not affected by cocaine taking or seeking and impulsive decision making did not predict cocaine taking. Nonetheless, *trait* impulsive decision making strongly predicted cocaine seeking during abstinence and the sensitivity to context-induced relapse. Consequently, an acute pharmacological treatment protocol was used in a within-subjects design, using the same drug challenge in both the impulsive decision making and the relapse model. The clinically-relevant drug, methylphenidate, and the DA D1 antagonist, SCH-23390, showed opposing effects in these two tasks: Methylphenidate decreased impulsive decision making and increased relapse responding. On the other hand, SCH-23390 increased impulsive decision making and decreased relapse responding. Importantly, the change in impulsivity was unrelated to the change in relapse propensity. Thus, this suggests that temporary impulsive decision making *state* did not alter cocaine seeking. However, since *trait* impulsivity was found to predict the risk to relapse, it might be possible to prevent relapse by reducing *trait* impulsivity.

In **chapter 4**, I used a sub-chronic ATO treatment protocol to induce a long-lasting change in impulsive decision making. After acquiring stable levels of impulsive decision making and three weeks of cocaine self-administration, animals were treated daily for 20 days with the norepinephrine (NE) reuptake inhibitor ATO or its vehicle (saline) during abstinence from cocaine self-administration. I observed that sub-chronic treatment with ATO clearly reduced context-induced reinstatement. However, ATO had no additional effect on reinstatement of cocaine-seeking behavior when it was combined with extinction training. In contrast to the predictions, impulsive decision making was not affected by daily injections of ATO. Importantly, although ATO did not reduce impulsive decision making in animals with a cocaine history, it seems a promising drug to prevent relapse of cocaine seeking.

Cocaine dependent patients show increased levels of impulsive action. Additionally, preclinical studies in rats have determined that *trait* impulsive action has no effect on basal cocaine intake, but does predict compulsive cocaine taking. However, from these observations it is difficult to determine whether the elevation of impulsive action is a pre-existing vulnerability factor or a drug-induced consequence. In **chapter 5**, I showed that impulsive action was transiently altered by the intake of cocaine. Subsequently, when animals were challenged with acute injections of cocaine and the pharmacological stressor yohimbine, both drugs increased impulsive action and relapse propensity. Yet, the magnitude of these effects did not correlate. Therefore, in line with the results on impulsive decision making (chapter 3), this observation suggests that although impulsive action and relapse can be modulated in the same direction within individuals, these effects appear not to be directly coupled. This is in line with clinical studies showing that the level of impulsive action determined at the start of treatment is not predictive of treatment outcome in cocaine dependent subjects. In addition, in ADHD patients

suffering from cocaine or nicotine dependence, methylphenidate improves clinical symptoms of ADHD, but has no effect on cocaine or nicotine use or craving. Given that impulsive action primarily relates to compulsive cocaine intake rather than abstinence and relapse, reducing impulsive action might reduce the risk to start taking drugs or the transition from regular drug use to addiction.

To conclude, the current studies show a clear relationship between impulsivity and cocaine taking and seeking. However, alterations of impulsive behavior did not relate to alterations in cocaine seeking. In my opinion this indicates that the relationship between impulsivity and cocaine addiction is not causal, but there is a common cause of both behaviors. For example, there are several overlapping genetic markers and environmental risk factors, such as childhood trauma, playing an important role in both impulsive and addictive behavior. In addition, environmental enrichment and cognitive interventions, such as training of working memory or cognitive control, have positive effects on impulsivity as well as addiction. Therefore, it might be valuable to train high risk individuals beforehand to cope with potential impulses and to avoid situations at high risk of drug use. Further research into the neurobiological basis of and the psychological and social influences on impulsivity and addiction remains of great importance.

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Summary