

## Exposed

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## **Valorisation addendum**

This section addresses the impact and relevance of the studies described in this dissertation. Outlined are the way these studies are relevant to society, which target groups can benefit and how research findings have been disseminated.

### **Societal relevance**

The acute and long-term consequences of illicit drug use continue to be a matter of global concern (EMCDDA, 2015b; UNODC, 2015). Drugs of abuse negatively impact cognitive performance and behavior, and increase the risk of developing mental disorders and other drug-related problems (EMCDDA, 2015a; Lammers et al., 2014). Likewise, the use of alcohol has been linked to substance related problems such as aggressive behavior and violence (Beck and Heinz, 2013; Duke et al., 2011). Novel psychoactive substances (NPS) that are flooding current drug markets also elicit a high level of public concern (Baumann and Volkow, 2015; EMCDDA, 2015b; UNODC, 2015). Life-threatening toxidromes have been described for NPS, with symptoms varying from agitation, hallucinations, psychosis, violent behaviors to coma. Drug users intoxicated with NPS represent a significant burden to healthcare professionals as adverse medical consequences are common.

One of the aims of this dissertation was to elucidate the effects of alcohol and cannabis intoxication on neurocognition and the interaction with marketing and aggression exposure. It was shown that exposure to alcohol marketing can activate the brain's reward center and potentially reinforce alcohol use (chapter 2). We have also shown that alcohol intoxication is more likely to elicit feelings of aggression (chapter 3). Furthermore, we have shown that portrayal of cannabis use also activates the reward center and that, other than alcohol, cannabis intoxication decreases feelings of aggression (chapter 3). These findings may imply that alcohol or cannabis users, who wish to stay abstinent, can be negatively influenced by alcohol and drug marketing, by reinforcing alcohol and cannabis use, leading to a vicious cycle of drug-taking behavior.

Another aim of this thesis was to study the influence of a frequently abused NPS (i.e. mephedrone) on neurocognitive function in a placebo-controlled setting. Data from

the current NPS study discard the notion that NPS or “legal highs” are safer and milder than traditional illegal drugs, and show that NPS effects on neurocognition can be as detrimental as those caused by alcohol or traditional drugs of abuse. The distinction between “traditional” and “new drugs” is becoming harder to define as NPS are designed to mimic the effects of traditional, scheduled drugs of abuse.

In fact, this was the very first study design ever that obtained medical ethical approval for acute administration of a NPS in a phase 1 study. This study was conducted in close collaboration with the Institut Hospital del Mar d'Investigacions Mèdiques (IMIM) in Barcelona. As such, this study offers a blueprint for future approaches to determine the mechanism of action of NPS, their toxicity profiles and pharmacological routes following acute administration in a controlled setting. Controlled experimental studies with NPS should generally be promoted because these will offer scientific rationales for future political and societal responses to challenges posed by NPS (Green and Nutt, 2014). Response strategies to the influx and use of NPS often involve drug-scheduling, although this approach is not effective and impedes placebo-controlled research with NPS. Ideally, clinical pharmacokinetic and pharmacodynamics information in animals and humans should be obtained before firm conclusions on the harms of these substances can be drawn. NPS research by means of placebo-controlled experimental studies give relevant and objective information about their acute effects on neurocognition, which can aid in education and prevention messages, as well as therapeutic interventions. This has proven to be a challenge in the past since Ethical Review boards often rule that NPS research should follow the same guidelines that have been established for the development of medicinal products (i.e. Good Manufacturing Process (GMP) requirements). The recent ruling of the European Court of Justice that GMP guidelines should not be extended to clinical research on substances of abuse that have no clinical usage is therefore very instrumental in promoting further clinical research on acute and long-term effects of NPS in humans.

## **Target groups**

The findings discussed in this dissertation are relevant to multiple target groups. Firstly, researchers in the field of psychopharmacology can benefit from the information that has been added to the existing knowledge on brain mechanisms underlying the reinforcing effects of alcohol and drug marketing, and the impact of alcohol and cannabis intoxication on different measures of aggression. This thesis also demonstrated that glutamate does not play a major role in MDMA-induced memory. This finding supports previous research showing MDMA induced impairment is primarily caused by 5-HT<sub>2</sub> receptor stimulation (van Wel et al., 2011).

Secondly, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and the World Health Organization (WHO) can also benefit from the scientific information presented in this dissertation. The data gathered adds to both international and European databases and contributes to objective risk estimates concerning illicit drug use, which applies to both traditional drugs of abuse as well as NPS. These findings will support policymakers in making informed drug policies and strategies, for example regarding marketing of alcohol and other drugs of abuse.

Our findings on the associations between alcohol and aggression also provide scientific support for the introduction of a new bill to allow alcohol and drug testing in perpetrators of violence, which will come into force in the Netherlands in 2017. The bill provides a legal basis for the deployment of alcohol and drug testing in violent offenders. The results of these tests can be taken into account in the conviction and sentencing stage of the criminal justice process. Our findings support the notion that acute effects of alcohol can induce feelings of aggression, provoked as well as unprovoked. Likewise, the use of stimulant drugs such as cocaine and amphetamine, have also been associated with violence (Hoaken and Stewart, 2003; Lammers et al., 2014; Stoddard et al., 2015; Zhao et al., 2015). The study design employed in the current dissertation to measure alcohol-induced aggression could also be helpful in the development of standardized test batteries

to assess drug-induced aggressive behavior in placebo-controlled studies. A standardized battery will promote to reliably identify aggression-inducing properties of drugs of abuse.

Pharmaceutical industries can also benefit from the current findings in the development of dopaminergic drug targets that increase tonic dopamine levels to help minimize the effects of alcohol and drug marketing by reducing motivation to use drugs. Data presented in chapter 2 demonstrates that high tonic levels of dopamine protect against the reinforcing potential of alcohol and cannabis marketing. This suggests that prescription drugs that increase tonic dopamine levels, such as methylphenidate, may be of prophylactic value to alcohol and cannabis abusers to defy alcohol and cannabis marketing exposure in our society. Likewise, data presented in chapter 3 may indicate novel pharmaceutical indicated for cannabis or cannabinoids. Our finding that cannabis reduces feelings of aggression might spark in interest to develop cannabinoid compounds to treat people with aggressive personalities.

Lastly, the current findings are also interesting to the general population and (potential) drug users who would like to be informed about the health risks of drug use. Different consumption patterns are also associated with different levels and types of harm; and more frequent use (i.e., high doses, concurrent use of other substances) are all linked to elevated health risks.

### **Dissemination and impact**

One of the goals of researchers in the field of psychopharmacology and addiction is to assess the acute and long-term effects of psychoactive substances on neurocognition and mood, and identify factors that make people more susceptible to addictions. The ultimate goal being the translation of experimental findings into practical applications aimed at reducing health risks associated with drug exposure by helping people stay in control of their own behavior. We have taken various efforts to ensure that the knowledge gained from our studies is spread across different target groups. Four out of five studies described in this dissertation have been published in several international journals to spread the findings to the international research community. In addition, most results

have been presented at national and international conferences that hosted many researchers from across the globe. The study in chapter 2 was part of the 'Addictions and Lifestyles In Contemporary Europe Reframing Addiction Project (ALICE RAP)' initiated by the European Commission. ALICE RAP was aimed to stimulate a broad and productive debate on science-based policy approaches to addictions. The findings of chapter 2 have been published on the website of ALICE RAP (<http://www.alicerap.eu/>) and were discussed during a scientific debate, 'the A debate'. The A-debate was an interactive discussion of addiction science (on-site and on-line) featuring scientists, policy actors from national and international organizations and clinical professionals, with the objective of presenting and discussing key research findings that came out of the project.

The findings of chapter 3 have also been covered by highly influential newspapers, such as the 'Washington Post', the 'Portland Press Herald' and 'De Morgen'. This ensured dissemination of the research findings to the general public and science communicators. In September 2016, 2 month after publication, the findings in chapter 3 were mentioned by 11 news outlets, 127 tweeters and 19 Facebook pages, which led to a high Altmetric score of 199 (i.e. in top 5% of all research outputs scored by Altmetric).

Finally, the studies were given more international attention by making most of these publications Open Access. Our future goal is to continue disseminating our research findings by means of (inter)national journal publications, (inter)national conference visits and through websites. In addition, the communication of research findings by means of workshops and public debates in order to provide a more interactive atmosphere will keep the scientific community as well as the general public informed.