

## Exposed

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## Summary

Drugs of abuse such as alcohol, cannabis, cocaine, MDMA and mephedrone are often taken for their pleasurable effects. A great number of legal and illegal drugs of abuse exert their reinforcing effects by either directly or indirectly activating the mesolimbic reward circuitry in the brain. Drugs of abuse have been shown to affect brain functioning, impair neurocognitive performance and alter the interpretation and appraisal of affective cues, such as drug marketing cues, emotional face expressions and aggression cues

Exposure to drug marketing cues can lead to positive expectancies towards drug use and increase the intention to consume. The influence of drug marketing cues can change during intoxication and this may change during intoxication. Similarly, affective cues, such as emotional face expressions, and aggression cues may alter the neurocognitive response to acute drug exposure. Acute drug exposure may impair the recognition of fearful or angry face expressions or increase/decrease aggressive behavior following exposure to aggression cues. It is important to investigate whether interactions between drugs of abuse and affective cues change during acute drug intoxication, possibly leading to an increased motivation to use drugs, increased aggression, and impaired interpretation of emotions in face expressions.

Acute drug experience can also be altered during exposure to multiple drugs. The majority of drug users use multiple drugs during the same episode in order to increase positive or decrease negative effects. Alcohol is the most common used drug in conjunction with others, and can considerably increase the harms and even lead to fatal outcomes. Therefore, it is important to examine the underlying neuropharmacological mechanisms during multiple drug exposure to understand their effects on neurocognitive performance.

The main aim of this dissertation was to investigate interactions between acute drug experiences and exposure to affective cues, and to assess drug interactions during multiple drug exposure. Double-blind placebo-controlled experimental studies were conducted involving administration of a broad range of drugs of abuse, such as alcohol, cannabis, cocaine, MDMA and mephedrone. Neurocognitive performance and subjective effects were measured at peak drug plasma concentrations ( $T_{max}$ ). The studies described in the first three chapters investigated whether brain activity and neurocognitive performance changes during drug intoxication following exposure to drug marketing cues, emotional face cues and aggression cues. The studies in the following chapters assessed whether exposure to one drug would potentiate or block the effects induced by another drug.

The study in Chapter 2 examined the impact of alcohol and cannabis marketing on the reward circuit in alcohol and cannabis users while sober and intoxicated. It was predicted that alcohol and cannabis marketing would increase striatal activation when sober and that reward sensitivity would decrease during alcohol and cannabis intoxication. Heavy alcohol and regular cannabis users participated in a mixed factorial study involving administration of alcohol and placebo in the alcohol group, and cannabis and placebo in the cannabis group. Non-drug users served as between group reference. Brain activation after exposure to alcohol and cannabis marketing movies was measured using fMRI and compared between groups while sober and compared to

placebo while intoxicated. Implicit alcohol and cannabis cognitions were assessed by means of the Single-Category Implicit Association Test (SC-IAT). Alcohol and cannabis marketing significantly increased striatal BOLD activation across all groups while sober. Striatal activation however decreased during intoxication with alcohol and cannabis. Implicit associations with cannabis marketing cues were significantly more positive in alcohol and cannabis users as compared to non-drug using controls. It was concluded that public advertising of alcohol or cannabis use elicits striatal activation in the brain's reward circuit and suggested that reduction of marketing would reduce brain exposure to reward cues that motivate substance use. Conversely, elevated dopamine levels may protect against the reinforcing potential of marketing.

The study in Chapter 3 investigated the acute effects of alcohol and cannabis on subjective aggression in alcohol and cannabis users respectively, following aggression exposure. Drug-free controls served as a reference. It was hypothesized that aggression exposure would increase subjective aggression in alcohol users during alcohol intoxication, whereas it was expected to decrease subjective aggression in cannabis users during cannabis intoxication. Heavy alcohol and regular cannabis users, and controls were included in a mixed factorial study. Alcohol and cannabis users received single doses of alcohol and placebo or cannabis and placebo respectively. Subjective aggression was assessed before and after aggression exposure via the Point-Subtraction Aggression Paradigm (PSAP) and the Single-Category Implicit Association Test. Testosterone and cortisol levels in response to alcohol/cannabis treatment and aggression exposure were recorded as secondary outcome measures. Subjective aggression significantly increased following aggression exposure in all groups while being sober. Alcohol intoxication increased subjective aggression whereas cannabis decreased the subjective aggression following aggression exposure. Aggressive responses during the PSAP increased following alcohol and decreased following cannabis relative to placebo. Changes in aggressive feeling or response were not correlated to the neuroendocrine response to treatments. It was concluded that alcohol facilitates aggression whereas cannabis diminishes aggression in heavy alcohol and

The study described in Chapter 4 was aimed to elucidate the acute effect of cannabis and cocaine on amygdala activation following exposure to affective facial stimuli. It was expected that amygdala reactivity to affective stimuli would decrease during cannabis and cocaine intoxication. Regular drug users, participated in a double-blind, placebo controlled, three-way crossover study. Participants received cannabis, cocaine and placebo, after which brain activity was measured by means of an amygdala reactivity fMRI paradigm. Correlations between brain activity and reaction time during task performance were additionally investigated. Results did not reveal any significant amygdala activation during task performance, but increased activity in occipital and temporal brain regions was found following exposure to affective stimuli. Acute cannabis and cocaine intoxication did not affect amygdala activity. Significant positive and negative correlations between BOLD signals and reaction times were revealed in the right inferior occipital, left inferior frontal operculum, right middle temporal, right superior temporal areas and left amygdala following exposure to threat-related faces during cannabis intoxication. These preliminary findings suggest that amygdala reactivity in regular drug users is not attenuated by cannabis or cocaine intoxication during exposure to affective facial stimuli.

The study in Chapter 5 investigated whether treatment with memantine can prevent MDMA-induced memory impairment in humans. Recreational MDMA users participated in a double-blind, placebo controlled, four-way crossover study. Participants received both pre-treatment (placebo/memantine 20 mg) ( $T_1$ ) and treatment (placebo/MDMA 75 mg) ( $T_2$ ) on separate test days.  $T_1$  preceded  $T_2$  by 120 minutes. Memory function was assessed 90 minutes after  $T_2$  by means of a visual verbal learning task (VVLT), a prospective memory task, the Sternberg memory test and the abstract visual pattern learning task (AVIPALET). Profile of Mood State and psychomotor performance were also assessed to control whether MDMA and memantine interactions would selectively pertain to memory or transfer to other domains as well. MDMA significantly impaired performance in the VVLT and AVIPALET. Pre-treatment with memantine did not prevent MDMA-induced memory impairment in these two tasks. Both positive (vigor, arousal, elation) and negative effects (anxiety) were increased by MDMA. The responses were not altered by pre-treatment with memantine, which had no effect on memory or mood when given alone. These preliminary results suggest that memantine does not reverse MDMA-induced memory impairment and mood in humans.

The study in Chapter 6 was designed to assess the effect of mephedrone alone and after co-administration with alcohol on neurocognitive function. It was hypothesized that mephedrone would improve psychomotor performance but impair memory performance, when administered alone. Neurocognitive performance was expected to be impaired following mephedrone when combined with alcohol. Recreational mephedrone users participated in a double-blind, placebo controlled, four-way crossover study. Participants received single doses of 200 mg mephedrone or placebo combined with 0.8 g/kg alcohol or placebo. Neurocognitive performance was assessed at baseline ( $T_0$ ), at 1 hour ( $T_1$ ) and 4 hours after ( $T_2$ ) mephedrone administration, by means of the Divided Attention Task, Critical Tracking Task, and the Spatial Memory Test. Mephedrone intoxication impaired short-term spatial memory at  $T_1$  and improved critical tracking performance at  $T_2$ . Mephedrone alone did not affect divided attention, but did show an interaction with alcohol on reaction time at  $T_2$ . Reaction time decreased when mephedrone was combined with alcohol as compared to alcohol alone. Alcohol intoxication impaired both short- and long-term spatial memory at  $T_1$  and divided attention at  $T_1$  and  $T_2$ . Critical tracking performance was not affected by alcohol intoxication. The current findings support the hypothesis that mephedrone improves psychomotor performance, impairs spatial memory and does not affect divided attention performance. The effects of mephedrone on cognition are comparable to those elicited by MDMA. Stimulatory effects of mephedrone were not sufficient to compensate for the impairing effects of alcohol on most performance parameters.

Finally, in chapter 7 the key findings of the studies are discussed in a broader perspective and implications and recommendations for future research are provided. Firstly, it was concluded that acute exposure to drugs of abuse can impair the interpretation of affective cues. Secondly, it was shown that neurocognitive performance is differently affected across domains during multiple drug exposure and the degree of drug-drug interaction differed across cognitive domains.