

The good, the bad, and the intoxicated

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Impact paragraph

The findings in this thesis suggest that a single dose of cannabis or psilocybin can produce brain changes that can result in acute and persisting (mal)adaptive behavioral consequences. As these substances are used by many, for a myriad of recreational and therapeutic purposes, such findings have a wide societal relevance for a range of target groups, including clinicians, policy-makers, scientists, and users alike.

Potential clinical impact. A growing number of clinical trials are looking at the therapeutic utility of psychedelic substances like psilocybin. Importantly, it has been proposed that the “quality” of the psychedelic experience, and in particular the amount of positively experienced ego dissolution, is an indicator of therapeutic success of the substances^{1,2}. Information from **Chapter 4** provides insight into mechanisms that may underlie the quality of the psychedelic experience, in that it was found that aspects of a “good” and “bad” trip are differentially associated to regional changes in glutamate. It could be proposed that baseline glutamate levels, in combination with baseline functional connectivity³ and personality factors⁴, could be used as individual predictive markers of the quality of the psychedelic experience. Subsequently, a better understanding of individual responses could eventually help doctors evaluate which patients would benefit from psychedelic treatment, and could contribute to a personalized medicine approach within the framework of psychedelic-assisted therapy³.

The increasing trend in the recreational and therapeutic use of cannabis raises concerns about its impairing effects on performance of day-to-day activities. Understanding the neurobiological basis of such effects is essential in the context of therapeutic use of cannabis, as it is often prescribed daily. An example of the potential utility of this information could stem from **Chapter 2**, in that it was found that cannabis did not change the brain or induce impairing behavioral effects until cannabis concentrations surpassed a certain threshold in blood. This combination of brain, behavior, and peripheral (i.e. blood concentration) information could be used to inform clinicians on how to prescribe the substance to maximize efficacy and decrease risk, by, for example, prescribing a dosing-scheme of the drug which does not surpass the peripheral threshold known to be associated with the brain changes underlying unwanted effects.

Potential impact for policy-makers. That said, if such a dosing threshold is surpassed, evidence suggests regular cannabis users develop tolerance to the rewarding and impairing effects of the drug. Findings from **Chapter 2** and **3** provide a possible measurable biomarker of tolerance. By having such an objective tool to quantify a subjective state, future research can systematically study at what dose and use frequency is necessary to produce tolerance. These results can then

provide information on how to assess the safety of cannabis use when performing day-to-day operations, and evaluating impairment in legal settings, by for example taking cannabis use history into account to predict impairing behavioral changes (or lack thereof).

Potential impact for recreational users. Additionally, by extending the investigations above to assess how long it takes for the suggested biomarker of tolerance to disappear (i.e. during abstinence), this information could inform recreational users who view tolerance as unwanted, as to how long and often they should take tolerance breaks for. The latter part of is particular importance, as a risk of the development of tolerance is that it could promote drug addiction¹⁰³.

Potential impact for streamlining future research. Furthermore, a perhaps often overlooked (and underutilized) facet of recreational drug use, is that there are many individuals using these substances, and they are using them for a reason. For example, plant-based psychedelics have been used for potentially thousands of years for healing purposes⁵ and there remains an active culture of self-medication with psychedelics for mental health purposes, and in the facilitation of self-exploration⁶⁻⁹. Thus there is a wealth of information to be gained from recreational users on potential positive and negative effects of these substance. By collecting data from individuals already using these substances (utilizing naturalistic study designs as in **Chapter 5**, or questionnaires, examples of which were not included in this thesis^{6,7,10-12}), one can establish indications of utility of such substances, and further confirm this in clinical or experimental trials. **Chapter 6** is an example of this potential process. It extended the findings from the naturalistic setting suggesting that psilocybin can affect different facets of creativity (**Chapter 5**), and brought it into the lab to replicate, and assess potential underlying biological markers. Findings from **Chapter 6** now suggest that psilocybin can be used as a tool in future studies, to perturb everyday creative thinking, and systematically investigate underlying neural mechanisms of the creative process; a process which has proven to be an elusive aspect of cognition to study for neuroscientists.

Current impact. A great deal of effort was put into disseminating the findings from these chapters amongst both science communicators and the general public. Findings from all chapters have, and continue to be, presented at various international scientific conferences. Additionally, all findings have been shared widely across popular social platforms such as Reddit and Twitter, have been covered by newspapers from around the world, and have been presented at meetings of the general public, ranging from invited lectures with university student groups, to informal presentations in local bars. The findings in **Chapter 4** and **5** have also been ranked in the top 5% of all research outputs scored by Altmetric (368 and 276, accordingly). **Chapter 5** was submitted for the special 50th-anniversary edition of the Journal of Psychoactive Drugs, and quickly became the most-read article in the history of the journal. Additionally, findings from **Chapter 4** were added to

the Wikipedia page of "psilocybin". Due to the potential implications of such findings, and the investment of time, effort, and cost of everyone involved (researchers and participants alike), the dissemination of the findings presented in these chapters with both the scientific community and the general public, will continue to be heavily pursued.

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