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HOT TOPICS

Does the trip matter? Investigating the role of the subjective effects of psychedelics in persisting therapeutic effects

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Neuropsychopharmacology (2023) 48:215–216; https://doi.org/10.1038/s41386-022-01424-z

Given the demonstrated promise of psychedelics (especially so-called classic or serotonergic psychedelics such as psilocybin and LSD) for the treatment of mood, anxiety, and substance use disorders, there is now exploding interest in identifying the mechanisms underlying their clinical effects [1]. While psychedelics are best known for their mind-altering intense acute effects on perception, cognition, affect, and frequently include mystical, self-transcendent, or out-of-body experiences [1], an important outstanding question is whether these characteristic acute subjective effects are necessary for the longer-lasting clinically therapeutic effects. There are clear correlations between psychedelic experiences and therapeutic responses [2]; though it is possible that these are not necessary for the clinical effects [3]. Identified alternative possible mechanisms for treatment effects include through various serotonin receptors and the induction of structural and functional plasticity in several affective brain regions. However, the use of active placebos in clinical trials and the key experiment (referred to by Yaden and Griffiths as a "critical test" [2]) in which psychedelics are given to patients under anesthesia are important approaches to examine the potential causal role of the subjective conscious experience in the clinical efficacy of psychedelics.

To address the role of acute subjective effects in the persisting clinical effects of psilocybin, recent studies explored if activation of serotonin 2A receptor (5-HT_{2A}R) is required for its antidepressant-like behavioral effects in mice, given that 5-HT_{2A}R binding is necessary for the subjective experience in humans [1]. Some may argue that the demonstration of an antidepressant-like effect of psilocybin in mice is evidence enough that acute subjective effects are not required for persisting behavioral effects [4, 5]. Hesselgrave et al. further showed that the effects of psilocybin on increasing social reward and sucrose preference in mice were not blocked by coadministration of ketanserin, a 5-$HT_{2A/2C}$R antagonist [4], suggesting that 5-HT_{2A}R activation and by extension, the acute subjective experience is not required for these persisting behavioral effects. However, the blockade of 5-HT_{2A}R by ketanserin was incomplete as measured by residual headtwitches, a common behavioral readout for 5-HT_{2A}R activation and hallucination-like effects in rodents. Though headtwitches did not correlate with remaining antidepressant effects, it is possible that headtwitches are not an accurate litmus of acute subjective effects of psychedelics in mice. Interestingly, the effects of psilocybin on hippocampal plasticity were also not blocked by ketanserin administration [4]. Shao et al. also demonstrated that some of the neuroplastic effects of psilocybin were intact with blockade of psilocybin binding to 5-$HT_{2A/2C}$R with ketanserin. These results show that acute effects of psilocybin associated with their hallucinogenic properties can be dissociated from the drugs neuroplastic properties in mice. Clinical studies co-administering psychedelics with the bendodiazepine Midazolam (to block memories of the experience) or Propofol (to block the acute subjective experience entirely) could be informative.

Overall, psychedelics like psilocybin are actively being tested in clinical trials at a high cost of monitoring the psychedelic experience during treatment. In addition, extensive resources are supporting the development of non-subjective psychedelics [6]. For these reasons, additional studies are needed to assess the causal role of the acute subjective effects in the persisting therapeutic benefits of psychedelics.

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ACKNOWLEDGEMENTS

We thank Roland Griffiths, Peter Tse, Nathan Heller, and Sixtine Fleury for their helpful discussions. KMN is supported by NIMH (R01MH126178). Support for DBY through the Johns Hopkins Center for Psychedelic and Consciousness Research was provided by Tim Ferriss, Matt Mullenweg, Blake Mycoskie, Craig Nerenberg, and the Steven and Alexandra Cohen Foundation.

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Published online: 18 August 2022

AUTHOR CONTRIBUTIONS

KMN and DBY wrote, edited, and approved the final version of this paper.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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