Exploring Self-Other Processing in the Psychedelic State

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Ethical review	Not approved
Status	Will not start
Health condition type	Other condition
Study type	Observational non invasive

Summary

ID

NL-OMON53863

Source
ToetsingOnline

Brief title
Psychedelic Self-Other

Condition

- Other condition

Synonym
healthy

Health condition

scientific investigation of healthy subjects

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Leiden
Source(s) of monetary or material Support: Heffter Institute Young Investigator Programme

Intervention

Keyword: Behavioral, Psilocybin truffles, Psychedelic state, Self-Other Processing

Outcome measures

Primary outcome

Behavioural measures: effects of psilocybin-containing truffles on reaction

times, recognition memory, attribution object, valence assessment ("positive*,

negative).

Secondary outcome

Psychometric measures: subjective drug effects as regressors for behavioral and

data.

Study description

Background summary

Psilocybin is a psychedelic compound that naturally occurs in certain species of fungi, and it can be artificially synthesized. At higher doses, both the naturally occurring and synthesized psilocybin can induce mystical experiences that are perceived as being tremendously meaningful and life-changing (Griffiths, Richards, McCann, & Jesse, 2006). Recent clinical studies have demonstrated the psychotherapeutic potential of psilocybin for the treatment of conditions such as depression (Carhart-Harris et al., 2016), end-of-life anxiety (Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016), and substance use disorder and addiction (Bogenschutz et al., 2015; Garcia-Romeu, Griffiths, & Johnson, 2014).

In addition to the therapeutic implications, the reemerging neurocognitive research on psilocybin and other psychedelics using modern neuroimaging modalities has provided us with preliminary insight into the

psychedelic state induced by psilocybin and other psychedelics such as LSD. A set of key findings suggest that the psychedelic state is a more entropic, or more disorganized state compared to the state of wakeful consciousness. Consequently, these findings led to the formulation of an influential hypothesis called the entropic brain hypothesis (Carhart-Harris et al., 2014; Tagliazucchi et al., 2014; Carhart-Harris, 2018). In short, the entropic brain hypothesis proposes that the psychedelic state is a high-entropy state, and this entropic state leads to a richer repertoire of dynamical brain states that are less predictable.

A recent proposal called the REBUS model (Relaxed beliefs under psychedelics and the anarchic brain; Carhart-Harris & Friston, 2019) attempts to integrate the entropic brain hypothesis within the hierarchical predictive processing framework, and thus, provides a unified model of the brain action of psychedelics. Predictive processing is a powerful framework for conceiving the neural mechanisms underlying perception, cognition, and action (Rao & Ballard, 1999; Bubic et al., 2010; Friston,2010). Simply put, predictive processing models describe counter-flowing top-down prediction/expectation signals and bottom-up prediction error signals within the brain*s functional hierarchy. Successful perception, cognition, and action are associated with successful suppression (*explaining away*) of prediction error. According to the REBUS model, via their entropic effect on neural activity, psychedelics work to relax the influence of the highest-level predictions or beliefs in the functional hierarchy of the brain, on lower-level beliefs and percepts. This psychedelic-induced relaxation leads to a dramatic alteration in the dynamics of the brain*s functional hierarchy. Therefore, besides their psychotherapeutic potential, psychedelics are promising and exciting tools for examining the complex neural mechanisms underlying uniquely human cognitive and affective processes in health and disease and, for advancing our understanding of these processes and ultimately, the nature of human consciousness.

One of the most striking and neuroscientifically interesting effects of psychedelics are the radical disruptions of self-related processing and self-consciousness (Huxley, 1954; Leary et al., 1964), including apparently *selfless states* (Lebedev et al., 2015; Nour et al., 2016). These states, instances of *Drug-Induced Ego- Dissolution* (DIED) are characterized by an experienced loss of self and/or loss of self/world(other) boundaries (Millière, 2017; Millière et al., 2018). Furthermore, the evidence suggests that the occurrence of DIED experiences is positively correlated with therapeutic outcomes (Garcia-Romeu et al., 2014; Carhart-Harris and Goodwin, 2017; Roseman et al., 2018; Yaden and Griffiths, 2020). Understanding the mechanisms and principles underlying the DIED experiences is instrumental to understanding the therapeutic effects of psychedelics. Accordingly, this is the aim of this study, as we aim to investigate the effects of psilocybin truffles on self-other processing using a trait-adjective task.

Rationale

Psilocybin is currently one of the most widely investigated substances in both clinical trials (Horton et al., 2021) and fundamental neuroscientific and pharmacological research (de Gregorio et al., 2021). However, nearly all studies investigating psilocybin have done so using the synthetic version and administering it in a controlled, lab environment. As the use of psychedelics, especially psilocybin mushrooms and truffles, is becoming more widespread, both globally and in the Netherlands (Winstock et al., 2022; van Laar & van Miltenburg, 2020), the need for more ecologically valid studies, using natural instead of synthesized products, is becoming more urgent. Furthermore, the importance of context on the effects of psychedelics makes the need for naturalistic study designs even more relevant and necessary (Carhart-Harris et al., 2018). The use of truffles in psychedelic research is still largely unexplored and of scientific and societal interest, due to its high ecological validity and legal status in the Netherlands. So far, the research that explored the use of truffles, did so within the context of microdosing (i.e., a sub-hallucinogenic dose taken every third day) (Prochazkova et al., 2018; Marschall et al., 2021; van Elk et al., 2021) or examined the sub-acute effects of truffles administered in a field-setting (Mason et al., 2019). Accordingly, this study builds on these previous initiatives, by implementing a naturalistic study design and the use of psilocybin-containing truffles as the pharmacological agent of choice instead of the synthetic preparations of psilocybin. Lastly, we intend to increase the reliability and validity of psychedelic research and in the spirit of open science, we will make the data collected in this study available in online repositories for secondary analyses by other researchers.

Study objective

Accordingly, this study intends to investigate the modulation of self-other processing in the psychedelic state. Specifically, the study has the following key objectives:

(1) To explore the effects of psilocybin-containing truffles on self-other processing

(2) To explore the effects of psilocybin-containing truffles on recognition memory

Study design

The proposed study uses a within-subjects cross-over experimental design. The study consists of a screening session, two online testing sessions that are set at least one week apart from another, post-acute online measures on the next day following each testing session, and one (optional) follow-up exit

interview. Subjects will self-administer/ingest the psilocybin-containing truffles at their homes. We will not instruct the subjects on specific dosing of the truffles and allow them to choose the dose themselves; the dosing options will be either 5 or 10 grams of fresh truffles Subjects will also complete the task once without using any psychoactive substances as the control condition, a week before or after the truffle session, counterbalanced among the subjects to avoid ordering effect. The rationale for keeping the active dose of truffles at or under 10 grams is based on the findings that 10 grams of fresh truffles contain approximately 10 mg of psilocybin, which can be considered a moderate dose (Pellegrini et al., 2012; Passie et al., 2002) and in higher doses, psilocybin has disruptive effects on attention and executive function (Barrett et al., 2018, 2020).

Study burden and risks

The study consists of a 30-minute online screening call and survey, two 30-minute online testing sessions that are set at least one week apart from another, two 30-minute post-acute online measures on the next day following each testing session, and one (optional) follow-up exit interview that will take approximately 15 minutes. During the testing sessions, subjects will complete several questionnaires and an online cognitive task that will take approximately 30 minutes. During the post-acute sessions, in a similar manner, subjects will complete several questionnaires, open questionnaires, and an online task for 30 minutes. The subjects will ingest small and small-to-medium doses of psilocybin-containing truffles, which will induce mild cognitive and perceptual effects. The outcomes of the study will provide important new insight into the acute psychological effects of psilocybin-containing truffles used in naturalistic settings.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

18-40 years old;

Physically and mentally healthy;

Right-handed;

Normal, or corrected-to-normal vision;

Good command of the English language;

Prior experience with a hallucinogenic drug (i.e., the subject must have taken a serotonergic hallucinogen, such as psilocybin, LSD, DMT or ayahuasca at least 5 times) without an adverse event;

Capable of giving informed consent;

Providing informed consent prior to the study as documented by signature;

Willing to refrain from drinking alcohol up within 24 hours before each experimental session, willing to refrain from caffeine within 3 hours before each experimental session, and willing to refrain from nicotine during each experimental session;

Willing to refrain from consuming psychoactive substances, except caffeine, alcohol and nicotine, two weeks before enrolling in the study and for the remainder of the study;

Have a family member or friend (the responsible other) with prior experience with a hallucinogenic drug, who they can rely on for support in case they

encounter challenging experiences or after-effects during or following the experimental session.

Agree to refrain from operating a vehicle on the evening of the experimental session;

Agree to eat only a light snack within 4 hours before taking part in each experimental session.

Exclusion criteria

Have a current psychiatric diagnosis, a lifetime history of bipolar affective disorder type 1, or a history of a primary psychotic disorder assessed via the Mini International Neuropsychiatric Interview (MINI);

Have one or several current neurological disease(s) or long-term adverse consequences resulting from a previous neurological disease;

Have one or more immediate family members with a current or previously diagnosed bipolar affective disorder type 1 or primary psychotic disorder;

Any subject presenting suicide risk, as determined through the screening and responses to C-SSRS will be excluded. Exclusion criteria include the following:

History of a suicide attempt within the last 10 years

Suicidal ideation (a score of 1 or greater) within the past year;

Have a medically significant condition which renders them unsuitable for the study (e.g., diabetes, severe cardiovascular disease, hepatic or renal failure etc.);

Weigh less than 45 kg;

Significant history of head trauma, premature birth, learning disabilities, neurological or psychiatric illness;

Are not able to give adequate informed consent;

Heart arrhythmia or hypertension;

Use of antidepressants or psychotropic medication;

Are pregnant, nursing, or can become pregnant and not willing to practice an

effective means of birth control;

Have no prior experience with a serotonergic hallucinogenic drug (e.g., LSD, magic mushrooms or truffles, DMT, ayahuasca);

Have previously experienced an adverse response to a serotonergic hallucinogenic drug;

Have any current moderate or severe alcohol use disorder or substance use disorder based the results of the MINI;

Smoking more than five cigarettes a day - to avoid nicotine withdrawal effects during the experimental session;

Use of any substance with activity on the serotonergic system, including antidepressants, lithium, 5-HTP, and St. John*s Wort, is prohibited for 5 half-lives of the medication or active metabolite prior to the experimental Session.

Study design

Design

Study type: Observational non invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	55
Type:	Anticipated

Ethics review

Not approved

Date:	04-05-2023

Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL83310.058.22