Psilocybin as a tool for enhanced divergent thinking and positive learning mechanisms

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Primary Objective: to use psilocybin as a research tool in order to enhance divergent thinking, and facilitate relative goal-directed versus habitual behaviour during and after drug intoxication, and to assess whether psilocybin will deter a stress...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON49008

Source
ToetsingOnline

Brief title
Psilocybin as a tool for enhancing cognitive flexibility

Condition

- Other condition

Synonym
n.a.

Health condition

no health condition is being address in the research, and healthy volunteers who have previous experience with psychedelics will be recruited

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: creativity, goal-directed, habit, Psilocybin

Outcome measures

Primary outcome

Divergent thinking will be measured using the picture concept test and the alternate uses test Outcome measures of these tests include fluency, originality, quantity, quality, and flexibility of answers. Behavior switching will be measured via the three-stage instrumental learning task. Outcome measures of this test include accuracy and reaction time.

Secondary outcome

Underlying receptor mechanisms will be assessed via ketanserin. Functional connectivity will be measures via functional magnetic resonance imaging. Neurotransmission and metabolic activity will be measured via proton magnetic resonance imaging. Drug kinetics will be assessed via blood samples. Subjective experience will be assessed via questionnaires (Visual analogue scale, five-dimensional altered states of consciousness, profile of mood states, ego-dissolution inventory, and the persisting effects questionnaire). Neuroendocrine stress markers will be assessed via cortisol concentrations in saliva. Additionally, cognitive and affective empathy will be assessed using the multifacted empathy test.

Study description

Background summary

Psychological disorders as a result of exposure to a traumatic event are common and occur in up to 50% of survivors by the end of the first year. Among these disorders includes posttraumatic stress disorder (PTSD), an anxiety disorder in which an individual*s ability to function is impaired by emotional responses to memories of a traumatic event (Shin & Liberzon, 2010). PTSD is typically a chronic illness associated with high rates of psychiatric and medical comorbidity, disability, suffering, drug abuse, and suicide (Breslau, 2001; Perkonigg, Kessler, Storz, & Wittchen, 2000). However, despite the high incidence and lifetime prevalence rates of PTSD, current treatments such as cognitive behavioural therapy or selective serotonin reuptake inhibitors provide limited effectiveness in treating the disorder, with many people being unresponsive to treatment (Hamner, Robert, & Frueh, 2004; Mithoefer, Wagner, Mithoefer, Jerome, & Doblin, 2011). Thus, there is an urgent need for the development of new, effective treatments.
Suggestions for effective treatments for PTSD include a hypothetical drug that would be capable of enhancing divergent thinking (Sessa, 2011), a cognitive process used to generate as many innovative ideas as possible. Three core networks have been specifically implicated in this process, namely the central executive network, the default mode network, and the salience network (Buckner et al., 2008; Jung et al., 2013; Beaty et al., 2016). These neural networks have all been found to be impaired in patients suffering from PTSD as well as other disorders similarly characterized by maladaptive, habitual behaviours or thought patterns (Chen et al., 2016; Dutta, McKie, & Deakin, 2014; Lanius, Frewen, Tursich, Jetly, & McKinnon, 2015; Posner et al., 2016), suggesting that they underlie these symptoms. Thus, it is suggested that by enhancing divergent thinking, a shift from habitual to goal directed behaviour could be facilitated, and patients would be able to explore alternative solutions for tackling their ingrained problems (Sessa, 2011). However, the mechanisms underlying enhanced divergent thinking are unknown.
A recent study from our lab showed that psychedelics significantly increased divergent thinking after drug intake (Kuypers et al, 2016). Furthermore, imaging studies have shown that the classic psychedelic, psilocybin, promotes a de-synchronization in the default mode network via agonism of the 5-HT2A receptor that is suggested to result in cognitive flexibility and enhanced creative thinking (Carhart-Harris et al., 2012; Carhart-Harris et al., 2014). Additionally, rodent research has shown that low doses of psilocybin facilitate extinction of a conditioned (fear) response (Catlow et al., 2013). Taken together these studies suggest that psilocybin can enhance divergent thinking, which may provide therapeutic potential in facilitating goal directed over habitual behaviour. Principal demonstrations showing that psilocybin facilitates cognitive flexibility would be very

relevant for future support of clinical applications of psilocybin assisted therapy in PTSD patients. As such, psilocybin-assisted psychotherapy may offer a promising option for PTSD patients for whom current options are not effective.

Study objective

Primary Objective: to use psilocybin as a research tool in order to enhance divergent thinking, and facilitate relative goal-directed versus habitual behaviour during and after drug intoxication, and to assess whether psilocybin will deter a stress induced shift from goal directed to habitual behaviour.

Secondary Objective(s): to assess whether enhancement in divergent thinking is mediated by activation at the 5-HT2A receptor (by pretreating individuals with ketanserin), and to assess cortical-subcortical functional connectivity alterations, as well as the relationship between metabolic activity and behavioural outcomes. Furthermore, subjective experience and drug concentration levels will be assessed in relation to the aforementioned variables

Study design

The study consists of two parts, both of which are a double-blind, randomized, placebo controlled, parallel-group design. Part one is a 2 (psilocybin vs placebo) x 2 (Maastricht Acute Stress Test vs. control) design. Participants will receive either a single dose of psilocybin (.17 mg/kg), or placebo, and will experience an incidence of stress induction or a no-stress control manipulation. Part two is a 2 (psilocybin & ketanserin vs placebo & ketanserin) x 2 (Maastricht Acute Stress Test vs. control) design. Participants will receive either ketanserin (60 mg) & placebo or a dose of ketanserin (60mg) & placebo.
For both parts, task performance, brain activity, subjective experience, and blood concentration will be assessed repeatedly throughout a 6 hour time window following drug administration. Participants will then be asked to return one week following administration in order to undergo an incidence of induced stress or a no-stress control manipulation, and to repeat task performance and subjective questionnaires. As it is hypothesized that psilocybin will induce long term changes in behaviour, matched participants will be used.

Intervention

Administration of treatments (see objective of the study and study design), the Maastricht Acute Stress Test, and collection of blood samples each test day to determine treatment concentrations,cortisol, and oxytocin concentrations in blood.

Study burden and risks

Participants will visit our lab four times. The first visit includes a full medical screening by a licensed physician ensuring their safety, which will include a medical history review, a blood sample (12 ml), and an electrocardiogram recording. The second includes a short training session to familiarize them with the testing procedures and the MRI scanner. The third visit will consist of taking the study treatment (psilocybin or placebo if they are in Part 1; or psilocybin & ketanserin or ketanserin & placebo if they are in Part 2), taking 4 blood samples (=75ml in total throughout the entire 7 hour testing day), giving an earwax sample, completing computer tasks inside and outside the magnetic resonance scanner (time in MRI scanner is 60 minutes), and filling out questionnaires. Participants will then return a week later for a follow up visit in which they will undergo a stress or control manipulation, give blood on 4 different occasions (=30 ml in total), and repeat the computer tasks and questionnaires. Over the course of the medical examination and the two test days, participants will give a total of 117 ml of blood. In case they experience complaints, the medical supervisor will be contacted. The total discomfort experienced by the volunteer is minimal when all precautions are taken into account.

Contacts

Public
Universiteit Maastricht

Universiteitssingel 40
Maastricht 6229ER
NL
Scientific
Universiteit Maastricht

Universiteitssingel 40
Maastricht 6229ER
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
* Previous experience with a psychedelic drug, but not within the past 3 months.
* Age between 18 and 40 years
* Free from psychotropic medication
* Good physical health as determined by medical examination and laboratory analysis
* Absence of any major medical, endocrine and neurological condition
* Normal weight, body mass index (weight/height2) between 18 and 28 kg/m2
* Proficient knowledge of the English language, defined as having at least 5 years of English language education (in high school or other education)
* Written Informed Consent

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
* History of drug addiction (determined by the medical questionnaire, drug questionnaire and medical examination)
* Previous experience of serious side effects to psychedelic drugs (anxiety or panic attacks)
* Pregnancy or lactation
* Hypertension (diastolic> 90; systolic> 140)
* Current or history of psychiatric disorder (determined by the medical questionnaire and medical examination)
* Liver dysfunction
* History of cardiac dysfunctions (arrhythmia, ischemic heart disease,*)
* For women: no use of a reliable contraceptive

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	20-07-2017
Enrollment:	120
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ketanserin
Generic name:	Ketanserin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Psilocybin
Generic name:	Psilocybin

Ethics review

Approved WMO

Date:	13-03-2017
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	18-05-2017
Application type:	First submission

Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	19-03-2018
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	30-05-2018
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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
EudraCT	EUCTR2016-005109-38-NL
CCMO	NL60352.068.17